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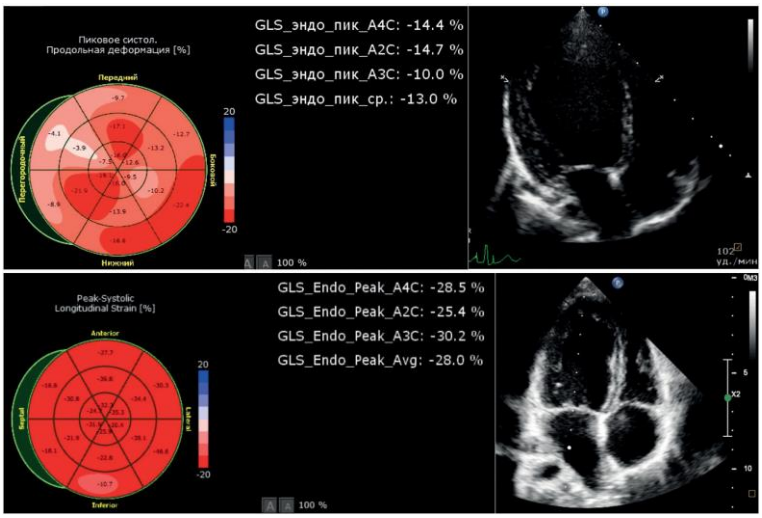

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CONTENT

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RELATIONSHIP BETWEEN EPICARDIAL ADIPOSE TISSUE CHARACTERISTICS MEASURED BY MULTIDETECTOR COMPUTED TOMOGRAPHY AND BLOOD BIOMARKERS IN PATIENTS WITH ATRIAL FIBRILLATION

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Aim. To evaluate the association of computed tomography measurements (volume and density) of epicardial adipose tissue (EAT) with the blood concentration of adipokines, proinflammatory cytokines and catecholamines in patients with atrial fibrillation (AF).

Methods. We included 32 patients (median age 58.5 (52.5; 64.0); 18 men) with AF scheduled for radiofrequency ablation. All patients underwent multispiral computed tomographic coronary angiography and segmentation of the EAT. In addition, the concentration of adiponectin, leptin, resistin, interleukins 1b, 6, 8 and methanephrine in the blood was determined by enzyme immunoassay.

Results. A negative correlation was established between the volume and the density of EAT ($r = -0.5$, $p<0.05$). The X-ray density of EAT negatively correlated with the concentration of methanephrine ($r = -0.4$) and leptin ($r = -0.4$), and positively correlated with the concentration of interleukin-8 ($r=0.36$). In addition, the duration of AF was negatively correlated with the density of EAT ($r=-0.42$, $p<0.05$) and positively correlated with the concentration of blood methanephrine ($r=0.34$, $p<0.05$). No associations were found between the volume of EAT and the studied blood biomarkers.

Conclusion. The results of the study showed an association between EAT X-ray density and the concentration of leptin, interleukin-8 and metanephrine in AF patients.

Key words: atrial fibrillation; epicardial adipose tissue; computed tomography; X-ray density; metanephrine; blood biomarkers

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In recent years, increasing attention has been paid to the potential use of morphometric parameters of epicardial adipose tissue (EAT), as assessed by various imaging modalities (echocardiography, computed tomography), as markers of coronary artery (CA) atherosclerosis progression and predictors of adverse cardiovascular events [1-3]. In addition, several studies have demonstrated an association between the volume or density of EAT and the risk of developing and maintaining atrial fibrillation (AF) [4, 5]. This association is thought to stem, on the one hand, from the capacity of EAT to produce a range of biologically active substances that contribute to "metabolic inflammation" and exert deleterious effects on myocardial tissue, and, on the other hand, from the ability of EAT to infiltrate and electrically uncouple myocardial fibres [4-6].

It has also been suggested that EAT exerts proarrhythmic effects through modulation of autonomic regulation of the heart. In particular, reduced heart rate variability and turbulence have been observed in patients with a higher EAT volume [7, 8]. At the same time, A.B. Romanov et al., using a novel scintigraphic technique, demonstrated a positive correlation between the volume of peri-atrial adipose tissue and sympathetic ganglionic activity in the atria [9]. A possible explanation for these findings lies in endogenous adipokine stimulation and increased catecholamine concentrations in both EAT and the peripheral blood of patients with AF. However, the exact mechanisms through which EAT influences myocardial function and contributes to AF pathogenesis remain unclear, warranting further investigation.

The aim of the present study was to evaluate the association between computed tomography (CT)-derived characteristics of epicardial adipose tissue (volume and density) and the concentrations of adipokines, proinflammatory cytokines, and catecholamines in the blood of patients with atrial fibrillation.

METHODS

A total of 32 patients (median age 58.5 [52.5; 64.0]; 18 men) with atrial fibrillation (AF) were prospectively enrolled in the study. These patients were undergoing evaluation at the Department of Surgical Treatment of Complex Cardiac Rhythm Disorders and Cardiac Pacing, and had been scheduled for radiofrequency catheter ablation (RFCA) for AF. The indications for RFCA were determined in accordance with current guidelines for the diagnosis and management of arrhythmias [10]. Prior to the intervention, all patients underwent a full standard clinical and instrumental evaluation, as well as multislice CT-CA tomography coronary angiography (MSCT-CA) to exclude obstructive atherosclerotic lesions of the coronary arteries.

Before performing MSCT-CA, blood samples were collected to determine the concentrations of adipose tissue-related hormones (adiponectin, leptin, resistin), proinflammatory cytokines (interleukins 1β, 6, and 8), and metanephrine.

Inclusion criteria for the study group were as follows:

- Age over 18 years, regardless of sex;
- AF refractory to antiarrhythmic drug therapy;
- Written informed consent to participate in the study.

Exclusion criteria included:

- History of myocardial revascularisation;
- Myocarditis or cardiomyopathies;
- Coronary artery stenosis >50%;
- Congenital or acquired heart defects;
- Chronic heart failure (NYHA class > II);
- Presence of thrombus in the left atrium or other heart chambers;
- Inability to undergo contrast-enhanced cardiac CT;
- Diabetes mellitus;
- Hyperthyroidism or hypothyroidism;
- Grade III or IV obesity;
- Grade III arterial hypertension;
- Presence of other arrhythmias (e.g., sick sinus syndrome, tachyarrhythmias, WPW syndrome).

The clinical characteristics of the study group are presented in Table 1.

In addition to the main study group, a control group was formed, consisting of 20 individuals without rhythm disturbances who underwent MSCT-CA to exclude coronary atherosclerosis.

Inclusion criteria for the control group:

- Age between 18 and 50 years;
- No signs of atherosclerotic coronary artery disease on MSCT-CA;
- Informed consent to participate in the study.

Exclusion criteria:

- History of cardiac rhythm or conduction disturbances, or other confirmed cardiovascular diseases;
- Body Mass Index (BMI) >28;
- Endocrine disorders.

All control group participants were invited for blood sampling three days after MSCT-CA. The clinical characteristics of the control group are provided in Table 2.

It is important to note that statistically significant differences in age and BMI were observed between the study and control groups ($p<0.05$). This precluded a meaningful statistical comparison of radiological parameters between the groups. However, due to the absence of established reference values for EAT volume and density, the control group data were used as approximate reference values.

MSCT-CA

At the time of the scan, all patients were in sinus rhythm with a heart rate of 50-65 beats per minute. MSCT-CA was performed using a 64-slice CT scanner (GE Discovery NM/CT 570c, GE Healthcare, Milwaukee, WI, USA) in accordance with the standard protocol outlined in the Recommendations for Coronary CT Angiography [11]. The study consisted of two scanning phases: a non-contrast phase (calcium scoring) and a contrast-enhanced phase. The acquired data was reconstructed and analyzed using the Advantage Workstation 4.6 (GE Healthcare).

EAT segmentation

EAT segmentation was conducted on the non-contrast ECG-synchronized 3D DICOM image series (calcium scoring phase), which were exported into the 3D Slicer software application (Boston, MA, USA) [12]. Segmentation of EAT (see Figure 1) was performed manually using a variable-sized tool across slices, within the adipose tissue density range from -190 to -30 Hounsfield Units (HU), from the bifurcation of the pulmonary trunk to the apex of the heart [13]. Using the SlicerRadiomics module (version 4.10.2), the total EAT

Table 1.
Clinical characteristics of patients with atrial fibrillation (n=32)

Indicator	Value
Age, years*	58.5 (52.5; 64.0)
Sex, male, n (%)	18 (56.3)
Body mass index*	29.0 (24.9; 33.1)
Disease duration, months*	24.0 (9.0; 60.0)
Hypertension, n (%)	28 (87.5)
Coronary atherosclerosis[#], n (%)	14 (43.8)
Ischaemic heart disease, n (%)	14 (43.8)
Diabetes mellitus, n (%)	6 (18.8)
Smoking, n (%)	8 (25.0)
Paroxysmal AF, n (%)	21 (65.6)
Non-paroxysmal[$] AF, n (%)	11 (34.4)
Chronic heart failure, n (%)	12 (37.5)
LV EF, %*	66.5 (64.0; 68.0)
LV end-diastolic volume, mL*	97.0 (88.5; 107.0)
LV end-systolic volume, mL*	33.5 (28.0; 38.0)
Left atrial volume, cm^3*	116 (94.7;138.0)

Note: here and below, * - data are presented as Me (Q1; Q3); n - number of patients; [#] - without significant luminal stenosis; AF - atrial fibrillatijn; LV - left ventricular; EF - ejection fraction; .

volume and mean EAT density within the segmented volume were calculated.

Laboratory methods

To assess biomarker concentrations, whole blood samples were collected from patients included in the study. Samples were centrifuged at 3,000 rpm to separate blood components and plasma. The plasma was then frozen and stored at -25 °C. After thawing, concentrations of omentin (RayBiotech, China), leptin (DBC, Canada), resistin (BioVendor, USA), adiponectin (BioVendor, USA), interleukins IL-1β, IL-6, IL-8 (Vector-BEST, Russia), and metanephrine (Labor Diagnostika Nord, Germany) were measured in the plasma using enzyme-linked immunosorbent assay (ELISA). Optical density measurements, calibration curve construction, quantitative analysis, and data processing were performed using the Infinite F50 microplate reader and Magellan Tracker software (Austria).

Statistical analysis

Statistical analysis was conducted using STATISTICA 12.0 (StatSoft Inc., Tulsa, OK, USA). The Shapiro-Wilk test was used to assess the normality of data distribution. For variables that did not follow a normal distribution, the results were expressed as median (Me) and interquartile ranges (25th and 75th percentiles). The Mann-Whitney U test was applied to assess the statistical significance of intergroup differences for independent samples. Correlation between quantitative and categorical variables was analysed using Spearman's rank correlation coefficient.

RESULTS

According to radiological assessment, patients with AF had a median EAT of 141.0 cm³ (IQR: 113.3-187.5) and a median EAT density of -81 HU (IQR: -88.5 to -75.5). In the control group, the EAT volume was significantly lower at 107.5 cm³ (IQR: 86.9-126.1; $p < 0.05$), while the EAT density was significantly higher at -74 HU (IQR: -78 to -73; $p < 0.05$) compared to the study group. However, these differences are likely attributable to substantial clinical and instrumental disparities between the groups, particularly in terms of age and BMI. Nevertheless, a negative correlation between EAT volume and density was identified in both groups ($r = -0.5$, $p < 0.05$).

Table 2.

Clinical characteristics of patients in the control group (n=20)

Indicator	Value
Sex male, n	15
Age, years*	33 (35; 40)
BMI*	24,1 (26,2; 27,5)
Pre-test probability of CAD, %*	8 (5; 12)

As shown in Table 3, patients with AF exhibited elevated levels of proinflammatory interleukins and plasma metanephrine. Leptin levels in the study group exceeded the reference range by 30%, while adiponectin concentrations were significantly lower than in the control group. In the AF group, EAT density showed a negative correlation with plasma metanephrine ($r = -0.4$) and leptin ($r = -0.4$), and a positive correlation with interleukin-8 concentration ($r = 0.36$) (see Table 4). No statistically significant correlations between EAT density and biomarkers were observed in the control group. Moreover, EAT volume was not associated with any of the studied biomarkers in either group.

When stratifying patients by AF subtype (persistent vs. paroxysmal), those with persistent AF exhibited significantly greater left atrial volumes (112.0 cm³ [IQR: 83.0-143.1] vs. 107.0 cm³ [IQR: 80.0-127.0]) and EAT volumes (147.4 cm³ [IQR: 110.4-214.8] vs. 144.8 cm³ [IQR: 110.4-196.0]). No significant differences were observed between subgroups in terms of EAT density or biomarker concentrations. Correlation analysis further revealed that AF duration was negatively associated with EAT density ($r = -0.42$, $p < 0.05$) and positively associated with plasma metanephrine levels ($r = 0.34$, $p < 0.05$).

DISCUSSION

To date, numerous studies, including meta-analyses, have demonstrated a direct association between EAT volume and the risk of AF, independent of BMI [6]. Several studies have shown that the volume of EAT and periatrial fat is associated with an increased risk of AF recurrence following RFCA [6]. Moreover, it has been demonstrated that patients with persistent AF have a larger volume of pericardial fat than those with paroxysmal AF [14, 15]. Our findings were consistent with these reports: EAT volume was significantly higher in the AF group compared to the control group, and among AF patients, those with persistent AF had greater EAT volume than those with paroxysmal AF.

In recent years, increasing attention has been paid to the radiological density of EAT [16, 17], which is believed

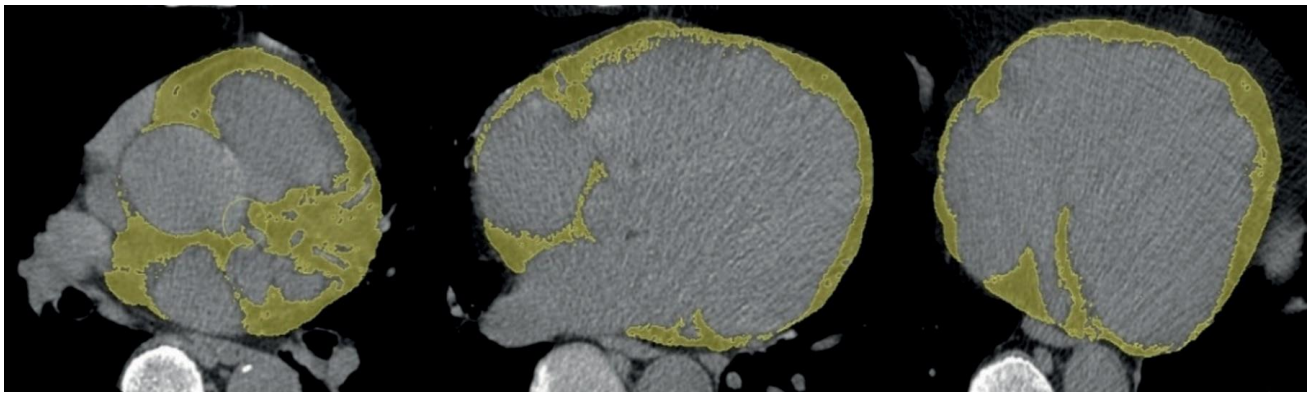

Figure 1. Segmentation of epicardial adipose tissue on non-contrast heart CT images (epicardial adipose tissue highlighted in yellow).

to reflect the structural and functional state of adipose tissue. A study by J.E. Lake et al. (2019) demonstrated that CT images of adipose tissue composed of larger adipocytes exhibit lower radiodensity compared to fat tissue composed of smaller, poorly differentiated adipocytes [18]. Other factors that influence this parameter include inflammation and subsequent fibrosis of the adipose tissue, which may lead to increased radiodensity [19].

Findings on EAT radiodensity in AF patients have varied across studies [14, 16, 17]. For instance, A.T. Huber et al. (2024) reported significantly lower EAT radiodensity in patients with persistent AF compared to those with paroxysmal AF [16]. Conversely, M. Nodera et al. (2024) found higher EAT radiodensity in AF patients compared to controls, which differs from our results [17]. Nevertheless, the latter study also identified a negative correlation between EAT volume and radiodensity, consistent with our data [17]. These discrepancies may be explained by differences in clinical and instrumental characteristics of the study populations, variations in the methodology for EAT measurement, and potential differences between total EAT density and periatrial fat density [17].

It is important to note that periatrial adipose tissue is in close anatomical proximity to the atrial myocardium and pulmonary vein ostia, making it particularly relevant for investigating both the mechanisms of arrhythmogenesis and predictors of post-ablation AF recurrence. It has been shown that the thickness and radiodensity of periatrial fat are more strongly associated with arrhythmia recurrence after catheter ablation than the same parameters measured in total EAT. However, given that the primary aim of our study was to assess the effects of circulating blood biomarkers, which act systemically, total EAT was chosen as the object of investigation.

Recent studies have demonstrated that local tissue-level proinflammatory and profibrotic cytokines and chemokines in EAT are associated with both EAT fibrosis and atrial myocardial fibrosis in AF patients [20]. In addition, certain circulating proinflammatory cytokines, such as interleukin-6, have been linked to myocardial inflammation and AF recurrence after RFA [21].

A number of other circulating biomarkers - including leptin, adiponectin, and resistin - have also been implicated in the development and maintenance of AF [22]. In this context, our findings of elevated circulating levels of proinflammatory cytokines and leptin, along with decreased adiponectin levels in AF patients compared to controls, are in full agreement with the existing literature.

To our knowledge, there are currently no published studies directly comparing EAT radiodensity with circulating biomarkers in patients with AF. However, the positive correlation identified in our study between EAT radiodensity and serum interleukin-8 levels aligns with previous findings demonstrating a positive association between inflammation and fibrosis within EAT and increased tissue radiodensity [20].

The observed inverse correlation between circulating leptin levels and EAT radiodensity in AF patients may be attributed to adipocyte hypertrophy and increased intracellular lipid droplet accumulation under conditions of hyperleptinaemia. However, a study by O.A. Koshelskaia et al. (2023) did not establish a link between serum leptin concentrations and adipocyte hypertrophy in histological EAT samples. This may be due to the fact that samples were collected from patients with advanced coronary atherosclerosis and markedly elevated baseline leptin levels [23].

It is well known that one of the central mechanisms in the pathogenesis and progression of AF is autonomic imbalance and sympathetic overactivity [7]. Several studies using myocardial scintigraphy with ^123I-metaiodobenzylguanidine have demonstrated that increased sympathetic nervous system activity is associated with a higher risk of AF recurrence after RFA [24-26]. In the study by F. Polat and A.L. Ko (2023), urinary metanephrine levels were significantly higher in patients with AF compared to controls [27]. Similarly, our study showed higher circulating metanephrine concentrations in AF patients than in those without arrhythmia. Moreover, we observed a positive correlation between metanephrine levels and arrhythmia duration, and a negative correlation between metanephrine levels and EAT

Table 3.

Blood biomarkers in patients with atrial fibrillation and in the control group

Indicator	AF group (n=32)	Control (n=20)	p-value
Leptin (ng/mL)	14.18 (4.69; 24.31)	Норма менее 11.1	<0.05
Resistin (ng/mL)	3.75 (3.15; 4.55)	3.62 (3.12; 4.25)	ns
Adiponectin (μg/mL)	5.29 (3.79; 8.76)	11.59 (10.63; 13.21)	<0.05
Interleukin-6 (pg/mL)	1.99 (1.64; 2.49)	1.50 (0.45; 1.91)	<0.05
Interleukin-1β (pg/mL)	2.20(1.57; 2.96)	1.80 (0.95; 2.19)	<0.05
Interleukin-8 (pg/mL)	3.94 (3.5; 6.91)	3.38 (2.45; 4.10)	<0.05
Metanephrine (pg/mL)	28.8 (21.44; 49.3)	18.75 (9.9; 20.74)	<0.05

Note: Here and below: ns - no statistically significant differences.

Table 4.

Correlations between radiological characteristics of epicardial adipose tissue and blood biomarkers in patients with atrial fibrillation

Biomarker	EAT Volume	p-value	EAT Density	p-value
Leptin (ng/mL)	0.33	ns	-0.4	<0.05
Resistin (ng/mL)	-0.01	ns	0.2	ns
Adiponectin (μg/mL)	0.13	ns	0.06	ns
Interleukin-6 (pg/mL)	-0.01	ns	0.25	ns
Interleukin-1β (pg/mL)	-0.16	ns	-0.06	ns
Interleukin-8 (pg/mL)	-0.3	ns	0.36	<0.05
Metanephrine (pg/mL)	-0.01	ns	-0.4	<0.05

Note: EAT - epicardial adipose tissue.

radiodensity. A plausible pathophysiological explanation may involve increased adrenergic activation of ganglionated plexi embedded in EAT, potentially due to elevated catecholamine content in hypertrophied fat tissue or alterations in calcium ion flux [28, 29]. An additional mechanism of systemic sympathetic activation in our AF cohort may be hyperleptinaemia [30], which also demonstrated a negative association with EAT radiodensity.

Study limitations

This study has several limitations. First, the relatively small sample size may affect the generalisability of our findings. Second, the inclusion of a few patients with diabetes mellitus may have influenced results. However, we were unable to identify any reports in the available literature specifically addressing the impact of diabetes on EAT radiodensity.

CONCLUSION

The results of this study demonstrated an association between the radiodensity of epicardial adipose tissue and serum concentrations of leptin, interleukin-8, and metanephrine in patients with AF. These findings are consistent with previous hypotheses suggesting that EAT may exert an activating effect on the sympathetic ganglia located within it and may also contribute to the systemic inflammatory response characteristic of this arrhythmia. Given that cardiac CT is a widely available and accurate imaging modality routinely performed in patients with cardiovascular disease, radiological parameters of EAT - such as its volume and density - appear to be promising tools for risk stratification in AF patients prior to catheter ablation.

REFERENCES

1. Gaborit B, Sengenes C, Ancel P, et al. Role of Epicardial Adipose Tissue in Health and Disease: A Matter of Fat? *Compr Physiol.* 2017;7(3): 1051-1082. https://doi.org/10.1002/cphy.c160034.

2. Iacobellis G. Epicardial fat links obesity to cardiovascular diseases. *Prog Cardiovasc Dis.* 2023;78: 27-33. https://doi.org/10.1016/j.pcad.2023.04.006.

3. Mustafina IA, Dolganov AA, Kutlubaev M.., Zagidullin NSh. The relationship of epicardial adipose tissue and metabolic syndrome. *"Arterial'naya Gipertenziya" ("Arterial Hypertension").* 2023;29(2)186-193. (In Russ.). https://doi.org/10.18705/1607-419X-2023-29-2-186-193.

4. Conte M, Petraglia L, Cabaro S, et al. Epicardial Adipose Tissue and Cardiac Arrhythmias: Focus on Atrial Fibrillation. *Front Cardiovasc Med.* 2022;9: 932262. https://doi.org/10.3389/fcvm.2022.932262.

5. Ernault AC, Meijborg VMF, Coronel R. Modulation of Cardiac Arrhythmogenesis by Epicardial Adipose Tissue: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2021;78(17): 1730-1745. https://doi.org/10.1016/j.jacc.2021.08.037.

6. Mustafina IA, Ionin VA, Dolganov AA, et al. Role of epicardial adipose tissue in the development of cardiovascular diseases. *Russian Journal of Cardiology.* 2022;27(1S): 4872. (In Russ.). https://doi.org/10.15829/1560-4071-2022-4872.

7. Plotnikova IV, Afanasiev SA, Perevoznikova YuE, et al. The effect of the autonomic nervous system on the formation of cardiac arrhythmias in childhood (review). *Siberian Journal of Clinical and Experimental Medicine.* 2023;38(2): 23-29. (In Russ.). https://doi.org/10.29001/2073-8552-2023-38-2-23-29.

8. Balcioğlu AS, Çiçek D, Akinci S, et al. Arrhythmogenic evidence for epicardial adipose tissue: heart rate variability and turbulence are influenced by epicardial fat thickness. *Pacing Clin Electrophysiol*. 2015;38(1): 99-106. https://doi.org/10.1111/pace.12512.

9. Romanov A, Minin S, Nikitin N, et al. The relationship between global cardiac and regional left atrial sympathetic innervation and epicardial fat in patients with atrial fibrillation. *Ann Nucl Med.* 2021;35(10): 1079-1088. https://doi.org/10.1007/s12149-021-01643-2.

10. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J.* 2021;42(5): 373-498. https://doi.org/10.1093/eurheartj/ehaa612.

11. Abbara S, Blanke P, Maroules CD, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: A report of the society of Cardiovascular Computed Tomography Guidelines Committee: Endorsed by the North American Society for Cardiovascular Imaging (NASCI). *J Cardiovasc Comput Tomogr*. 2016;10(6): 435-449. https://doi.org/10.1016/j.jcct.2016.10.002.

12. Prokop M, Galansky M., et al. Spiral and Multislice Computed Tomography of the Body. *Thieme*. 2003. https://doi.org/10.1055/b-0034-79234.

13. Chernina VY, Pisov ME, Belyaev MG, et al. Epicardial fat Tissue Volumetry: Comparison of Semi-Automatic Measurement and the Machine Learning Algorithm. *Kardiologiia.* 2020;60(9): 46-54. (In Russ.). https://doi.org/10.18087/cardio.2020.9.n1111.

14. Ciuffo L, Nguyen H, Marques MD, et al. Periatrial Fat Quality Predicts Atrial Fibrillation Ablation Outcome. *Circ Cardiovasc Imaging.* 2019;12(6): e008764. https://doi.org/10.1161/CIRCIMAGING.118.008764.

15. Al Chekakie MO, Welles CC, Metoyer R, et al. Pericardial fat is independently associated with human atrial fibrillation. *J Am Coll Cardiol.* 2010;56(10): 784-8. https://doi.org/10.1016/j.jacc.2010.03.071.

16. Huber AT, Fankhauser S, Wittmer S, et al. Epicardial adipose tissue dispersion at CT and recurrent atrial fibrillation after pulmonary vein isolation. *Eur Radiol.* 2024;34(8): 4928-4938. https://doi.org/10.1007/s00330-023-10498-2.

17. Nodera M, Ishida T, Hasegawa K, et al. Epicardial adipose tissue density predicts the presence of atrial fibrillation and its recurrence after catheter ablation: three-dimensional reconstructed image analysis. *Heart Vessels.* 2024;39(8): 696-705. https://doi.org/10.1007/s00380-024-02384-8.

18. Lake JE, Moser C, Johnston L, et al. CT Fat Density Accurately Reflects Histologic Fat Quality in Adults With HIV On and Off Antiretroviral Therapy. *J Clin Endocrinol*

Metab. 2019;104(10): 4857-4864. https://doi.org/10.1210/jc.2018-02785.
19. Takahashi N, Abe I, Kira S, et al. Role of epicardial adipose tissue in human atrial fibrillation. *J Arrhythm*. 2023;39(2): 93-110. https://doi.org/10.1002/joa3.12825.
20. Ishii Y, Abe I, Kira S, et al. Detection of fibrotic remodeling of epicardial adipose tissue in patients with atrial fibrillation: Imaging approach based on histological observation. *Heart Rhythm O2.* 2021;2(4): 311-323. https://doi.org/10.1016/j.hroo.2021.05.006.
21. Sazonova SI, Ilushenkova JN, Batalov RE, et al. Plasma markers of myocardial inflammation at isolated atrial fibrillation. *J Arrhythm.* 2018;34(5): 493-500. https://doi.org/10.1002/joa3.12083.
22. Tarasova IV, Vertkin AL. The role of epicardial adipose tissue in the development of atrial fibrillation: a literature review. *Lechaschi Vrach.* 2024;7(27): 17-22. (In Russ.). https://doi.org/10.51793/OS.2024.27.7.002.
23. Koshelskaya OA, Naryzhnaya NV, Kologrivova IV, et al. Correlation of epicardial adipocytes hypertrophy with adipokines, inflammation and glucose and lipid metabolism. *Siberian Journal of Clinical and Experimental Medicine.* 2023;38(1): 64-74. (In Russ.). https://doi.org/10.29001/2073-8552-2023-38-1-64-74.
24. Sazonova SI, Varlamova JV, Nikitin NA, et al. Cardiac ^{123}I-mIBG scintigraphy for prediction of catheter ablation outcome in patients with atrial fibrillation. *J Nucl Cardiol.* 2022;29(5): 2220-2231. https://doi.org/10.1007/s12350-021-02658-y.
25. Akutsu Y, Kaneko K, Kodama Y, et al. Iodine-123 mIBG Imaging for Predicting the Development of Atrial Fibrillation. *JACC Cardiovasc Imaging*. 2011;4(1): 78-86. https://doi.org/10.1016/j.jcmg.2010.10.005.
26. Arimoto T, Tada H, Igarashi M, et al. High washout rate of iodine-123-metaiodobenzylguanidine imaging predicts the outcome of catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol.* 2011;22(12): 1297-304. https://doi.org/10.1111/j.1540-8167.2011.02123.x.
27. Polat F, Ko AL. Comparison of Patients with Atrial Fibrillation Without Structural Heart Disease and Normal Population In Terms of Urine Catecholamines. *Turk Kardiyol Dern Ars.* 2023;51(3): 168-173. English. https://doi.org/10.5543/tkda.2022.16281.
28. Kanorskii SG. Epicardial Adipose Tissue and Cardiac Arrhythmias. *Cardiac Arrhythmias.* 2022;2(2): 5-18. https://doi.org/10.17816/cardar107112.
29. Losik DV, Nikitin NA, Minin SM, et al. The role of epicardial adipose tissue and autonomic nervous system in pathophysiology of cardiac arrhythmias. *Patologiya krovoobrashcheniya i kardiokhirurgiya = Circulation Pathology and Cardiac Surgery.* 2021;25(3): 27-33. (In Russ.). https://doi.org/10.21688/1681-3472-2021-3-27-33.
30. Jijihiya KM, Kade AH, Zanin S A, et al. Leptin and arterial hypertension in metabolic syndrome. *The successes of modern natural science*. 2013;7: 159. (In Russ.).

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SAFETY OF OUT-OF-HOSPITAL INITIATION OF FLECAINIDE IN PATIENTS WITH ATRIAL AND VENTRICULAR ARRHYTHMIAS AND STRUCTURALLY NORMAL HEART

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Aim. This study aimed at investigating the safety of out-of-hospital initiation of flecainide in patients presenting with atrial or ventricular arrhythmias and structurally normal heart.

Methods. Patients were followed 1 week, 1 month and 2 months after drug initiation either in person or through phone interviews and were asked to report symptoms suggestive of sustained arrhythmia, syncope, aborted sudden death and/or emergency room (ER) visits. QRS duration and QTc intervals were measured in a 12-lead ECG at each follow up. Patients were asked to fill out a treatment satisfaction questionnaire for medication (TSQM), four weeks after drug initiation.

Results. The mean patient age was 48.5 ± 15.7 years, 36 patients (52%) were females. The most frequent presenting arrhythmia was premature ventricular contractions in 34 (45.3%) patients followed by paroxysmal atrial fibrillation in 22 (29.3%) patients. There was a significant increase in the mean QRS duration (89.9 ± 6.8 msec vs 91.1±7 msec, P <0.001) and the mean QTc interval (417.4 ±10.6 msec vs 418 ± 10.4 msec, P = 0.025) at 1 week compared to baseline. Only one patient (1.3%) had a clinically significant (more than 25%) increase in the QRS duration requiring drug discontinuation. There was no reported life-threatening ventricular arrhythmia, syncope, ER visits or aborted sudden cardiac death. There was 6.7% incidence of cardiac adverse events including conduction system abnormalities and atrial flutter, 4% of patients experienced non-resolving extracardiac manifestations. The overall drug discontinuation rate was 10.7%. The mean TSQM score for effectiveness domain was 70.4 ± 23.8 while the mean of the side effects domain was 94.3 ± 14.6, that of convenience domain was 65.2 ± 10.5 and that of global satisfaction was 72.8 ± 21.8.

Conclusion. Out-of-hospital initiation of flecainide is safe and thus feasible, there was no reported documented or suspected life-threatening ventricular arrhythmias. Cardiac and extracardiac adverse events requiring drug discontinuation was effectively detected through clinical and ECG outpatient follow up.

Key words: flecainide; antiarrhythmic; IC; structurally normal heart; safety

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Flecainide is a class Ic antiarrhythmic drug that inhibits sodium channels, reducing cardiac cell excitability and conduction velocity [1, 2]. Flecainide also blocks ion flow across the sarcoplasmic reticulum, influencing calcium dynamics and stabilizing cardiac electrical activity [3, 4].

Flecainide has multiple indications supported by recent research, among the most common indications are restoration and maintenance of sinus rhythm in patients with atrial fibrillation and control of symptomatic frequent premature ventricular beats [5-8]. However, despite its benefits, flecainide's ability to delay cardiac conduction and hence enhancing spatial heterogeneities of electrical restitution, particularly in patients with structural heart disease, can lead to proarrhythmic side effects [6]. This was evident in the cardiac arrhythmia suppression trial (CAST) study that showed increased mortality in post myocardial infarction (MI) patients receiving class Ic antiarrhythmic drugs [9]. This study paved the way for contraindicating

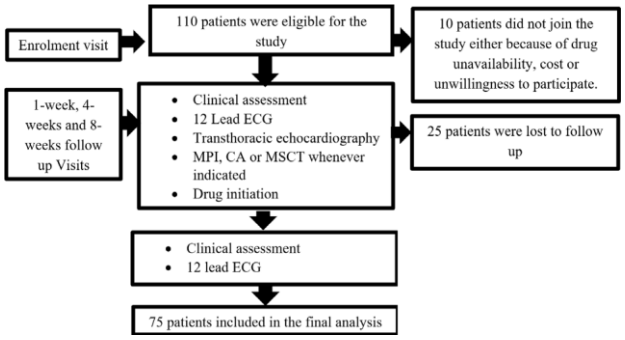

Fig. 1. Study design flow chart.

class Ic antiarrhythmic drugs in post MI patients and for extrapolating this practice to all patients with structural heart disease despite the lack of strong clinical evidence to support this practice. More recently, this dogma has been challenged by studies that support the safety of flecainide in subsets of patients with structural heart disease [10, 11].

The proarrhythmic effect of class Ic AAD tends to cluster shortly after drug initiation [12, 13], thus it is common practice to routinely hospitalize patients for drug initiation under continuous electrocardiographic surveillance. The low incidence of serious pro-arrhythmia in this patient population makes the cost-effectiveness of this practice controversial [14]. Although an expert opinion has suggested that outpatient drug initiation in patients without structural heart disease is safe, no prospective data currently exists to support this opinion [15]. We thought to test the safety of out-of-hospital initiation of flecainide in patients with atrial and ventricular arrhythmias and structurally normal heart.

Table 1.

Baseline characteristics and the presenting arrhythmia in the study population (N=75)

Baseline characteristics	Value
Age, years (Mean±SD)	48.5 ± 15.7
Male, n (%)	36 (48)
Female, n (%)	39 (52)
Diabetes Mellitus, n (%)	5 (6.7)
Hypertension, n (%)	25 (33.3)
Smoking, n (%)	2 (2.7)
Dyslipidemia, n (%)	3 (4)
Presenting Arrhythmia	
Paroxysmal AF, n (%)	22 (29.3)
Atrial flutter, n (%)	3 (4)
Atrial tachycardia, n (%)	4 (5.3)
Premature atrial contractions, n (%)	6 (8)
Premature ventricular contractions, n (%)	34 (45.3)
AVRT, n (%)	2 (2.7)
Combined arrhythmia, n (%)[$]	4 (5.3)

Note: here and below, AVRT - accessory pathway mediated atrioventricular recurrent tachycardia; [$] - paroxysmal AF with PVCs or PACs with PVCs.

METHODS

This study adopted a prospective single-arm experimental protocol, included patients above 18 years old who presented with atrial or ventricular arrhythmia to a specialized arrhythmia clinic affiliated to a tertiary referral hospital. The presenting arrhythmia included atrial fibrillation, atrial tachycardia, premature atrial beats, accessory pathway medicated tachycardia, sustained ventricular tachycardia and premature ventricular beats (PVCs). All patients had to have structurally normal heart and thus were considered candidates for flecainide therapy at the discretion of the treating physician. The heterogeneity of the presenting arrhythmia is thought not to preclude final analysis, since the primary endpoint is a safety endpoint related to the tested drug and the lack of underlying structural heart disease rather than the presenting arrhythmia. The study was conducted during the period from October 2021 to June 2023. The study protocol was approved by the local Research Ethics Board of the hospital to which the clinic conducting the study is affiliated.

Patients were considered to have normal heart based on normal physical examination, normal ECG, normal echocardiography, and no clinical suspicion of coronary artery disease (CAD). If suspected, CAD was ruled out through myocardial perfusion imaging, multi-slice computed tomography coronary angiography, or coronary angiography based on the judgment of the treating physician. Patients were excluded from the study if they have structural heart disease (significant left ventricular hypertrophy, ischemic heart disease, reduced systolic function, and significant valvular heart disease), significant kidney disease (CKD EPI<30 mL/min/1.73 m^2) or significant bradyarrhythmia (sinus node or atrioventricular node diseases).

Study flowchart is displayed in Figure 1, on the day of initiating therapy, all patients were interviewed to obtain baseline demographic data (age and gender), risk factors for CAD such as diabetes mellitus, hypertension, smoking, and dyslipidemia and any reported symptoms that raises suspicion of CAD. General and local cardiac examination were performed. Baseline 12-lead electrocardiography was obtained for calculation of baseline QRS and QTc duration [QT interval was corrected to the heart rate using Bazett's formula [16]] and exclusion of any sinus node or AV node diseases. Baseline echocardiography was performed to exclude structural heart disease.

Table 2.

Post-hoc pairwise comparison between baseline and follow-up values of the QRS width and QT interval in the study population

Items (Mean ± SD)	Baseline	1-week	4-weeks	8-weeks	P-value
QRS width (msec)	89.9±6.8	91.1±7	91.2±7	91.9±8.2	<0.001*
% of increase	0 (0,4.7) 2.3±5.7				
Pairwise comparisons: P1<0.001* P2<0.001* P3<0.001* P4=0.321 P5=0.134 P6=0.118					
QT interval (msec)	417.4±10.6	418±10.4	418.9±9.9	418.9±9.9	<0.001*
% of increase	0 (0,0.7) 0.4±0.6				
Pairwise comparisons: P1=0.02* P2<0.001* P3<0.001* P4<0.0018* P5<0.001* P6=1.000					

Note: * - significant P value. P1(baseline vs 1-week), P2 (baseline vs 4-weeks), P3 (baseline vs 8-weeks), P4 (1 week vs 4-weeks), P5 (1-week vs 8-weeks), P6 (4-weeks vs 8-weeks).

Flecainide was administered out of hospital at a dose of 50 mg twice daily and was uptitrated, if needed, to 100 mg twice daily at the 1-week visit based on improvement of symptoms and the first follow up ECG. Patients were followed up at 1-week, 4-weeks and 8-weeks, either in person or through telephonic interviews. Each follow up visit, patients were evaluated for symptoms suggestive of aggravation of the presenting arrhythmia or development of new arrhythmia including syncope, aborted sudden cardiac death and/or emergency room (ER) visits. Twelve-lead electrocardiography was reviewed, at each follow up, with emphasis on calculation of the QRS duration and QTc duration. Holter was requested if clinically indicated.

Treatment Satisfaction Questionnaire for Medication (TSQM version 1.4-IQVIA) was sent for patients to fill out at the 4-weeks follow up to evaluate patients' satisfaction. A license agreement was obtained from the company that owns the copyright. The TSQM has 14 questions and encompasses four domains: Effectiveness, Convenience, Side Effects, and Global Satisfaction. We adhered to the standard guidelines for implementing TSQM, including administering it in the respondents' native language thus the Arabic version was utilized [17], allocating enough time for the completion of the TSQM and ensuring that the font size of the TSQM text was sufficient for easy readability. The responder was required to indicate their degree of satisfaction or dissatisfaction with the drug for each item. This was done by inserting a single tick mark next to the answer that best matched their personal experiences, based on the previous 4 weeks. We categorized the responses to the Questions of each domain as "highly satisfied," "satisfied," "neutral," "dissatisfied," or "highly dissatisfied" based on the Likert scale.

The four previously mentioned domains of the TSQM were calculated. The scores for each domain are calculated by summing the TSQM items within each domain and then converting the combined score into a numerical value between 0 and 100, the higher being the better. The TSQM itself doesn't typically have a universal or standardized cutoff point to determine a threshold for treatment satisfaction.

The primary endpoint of this study was symptoms suggestive of life threatening proarrhythmia and clinically relevant ECG changes necessitating drug termination. Secondary objectives included investigating minor adverse events that does not necessitate drug termination, patient satisfaction according to the TSQM and flecainide efficacy in controlling atrial and ventricular arrhythmias.

Statistical analysis

The study sample size at an effect size of 0.25 based on the difference from constant (binomial test, one sample case) with two-tailed calculation and a constant proportion of 50%, at alpha error of 0.05, and a power of 95%. We found that the sample size was 65 patients then we calculated a 20% dropout. The analysis was conducted using Statistical Package for Social Science (SPSS v. 27) on Windows. Quantitative variables that follow a normal distribution are often stated using the mean and standard deviation (SD), whereas non-parametric distributions are expressed using the median and interquartile range. The qualitative variables were represented using numerical values in the form of numbers (No.) and percentages (%). Chi-squared test (or Fisher's exact) was used to detect the difference in both groups regarding the categorical variables. Comparison between 2 subgroups regarding normally distributed scale variables was done by T-test and that of not normally distributed was done using the Mann-Whitney U test. Comparison between 3 subgroups regarding normally distributed scale variables was done by One-Way ANOVA and that of not normally distributed was done using the Kruskal Wallis test. The significance of the results was assessed in the form of a P-value when it was < 0.05.

RESULTS

Baseline characteristics of the study population

One hundred fifteen patients assessed for eligibility to our study, 5 patients were excluded because of not meet-

Table 3.

Clinical predictors of flecainide adverse events

Risk factors	No adverse events (n=59)	Adverse events (n=16)	P-value
Age (Median [IQR])	48 (37,57)	53 (40,65)	0.295 (MW)
Male, n (%)	29 (49.2)	7 (43.8)	0.908 (MW)
Diabetes Mellitus, n (%)	5 (8.3)	0 (0.0)	0.128
Hypertension, n (%)	21 (35.0)	4 (26.7)	0.540
Smoking, n (%)	2 (3.3)	0 (0.0)	0.341 (FET)
Dyslipidemia, n (%)	1 (1.7)	2 (13.3)	0.100 (FET)
Paroxysmal AF, n (%)	19 (32.2)	3 (18.8)	0.178
Paroxysmal atrial flutter, n (%)	3 (5.0)	0 (0.0)	
Atrial tachycardia, n (%)	3 (5.0)	1 (6.3)	
PACs, n (%)	5 (8.4)	1 (6.3)	
PVCs, n (%)	25 (42.4)	9 (56.3)	
AVRT, n (%)	2 (3.4)	0 (0.0)	
PFCs and PVCs, n (%)	1 (1.7)	0 (0.0)	
Paroxysmal AF and PVCs, n (%)	1 (1.7)	2 (12.5)	
Flecainide dose 50 mg BD, n (%)	18 (30.5)	3 (18.8)	0.440
Flecainide dose 100 mg BD, n (%)	41 (69.5)	13 (81.3)	
Baseline QRS width (Median [IQR])	90 (85,95)	85 (85,90)	0.295
Baseline QT width (Median [IQR])	410 (410,428)	415 (410,430)	0.829

Note: AF - atrial fibrillation; PACs - premature atrial contractions; PVCs - premature ventricular contractions; IQR - interquartile range; FET - Fisher exact test; MW - Mann Whitney U test

ing the inclusion criteria, 10 patients couldn't initiate flecainide either because of availability or cost limitations, 25 patients were lost to follow-up, and thus 75 patients were included in the final analysis. Mean age was 48.5±15.7 years, 36 patients (48%) were males. Five (6.7%) patients were diabetic and 25 (33.3%) were hypertensives. The most common presenting arrhythmia was PVCs in 34 (45.3%) patients followed by paroxysmal atrial fibrillation (PAF) in 22 (29.3%) patients. Following the first follow up visit, 54 (72%) patients were maintained on 100 mgs flecainide twice daily dosing, while 21 (28%) patients were maintained on 50 mgs twice daily dosing. Baseline characteristics of the study population is shown in Table 1.

Electrocardiographic data

The mean baseline QRS width was 89.9±6.8 msec while the mean baseline QTc interval was 417.4±10.6 msec. There was a significant increase in the mean QRS duration (89.9 ± 6.8 msec vs 91.1±7 msec, P <0.001) and the mean QTc interval (417.4 ±10.6 msec vs 418 ± 10.4 msec, P = 0.025) at the 1-week follow up compared to baseline, however, there was no further increment in the QRS duration beyond the first follow up visit Table 2.

At the end of follow up, 54 (72%) had no change of QRS duration, 4 (5.3%) had to < 5% QRS prolongation, 15 (20%) patients had 5-10 % QRS prolongation, only one (1.3%) patient had 10-25% QRS prolongation and only one (1.3%) patient had > 25% QRS prolongation requiring discontinuation of the drug (44.5% increment from baseline). Fifty-three (70.7%) of patients that had no change in QTc interval from baseline and 22 (29.3%) of patients less than 5% QT prolongation from baseline.

Proarrhythmia, side effects, efficacy and patients' satisfaction

There were no reported symptoms suggestive of aggravation of the presenting arrhythmia or development of life-threatening arrhythmia including syncope, aborted sudden cardiac death and/or ER visits. Two patients (2.7%) developed complete right bundle branch block, 1 patient (1.3%) developed asymptomatic tri-fascicular block, 1 patient (1.3%) developed marked PR prolongation, and 1 (1.3%) patient developed asymptomatic transient (30 seconds) atrial flutter with 1:1 atrioventricular conduction documented in a Holter monitor. The most common extracardiac side effects were blurred vision in 3 (4%) patients, insomnia in 2 (2.7%) patients and gastrointestinal symptoms in 2 (2.7%) patients, dizziness in 2 (2.7%) patients, other less common non-cardiac adverse effects occurred in 2 (2.7%) patients including weight gain and eyelid tremors. The drug was discontinued in eight (10.7%) patients due to adverse effects, in 5 (6.6%) patients due to cardiac adverse effects (conduction system abnormalities and atrial flutter) and in 3 (4%) patients due to blurring of vision and insomnia. The occurrence of adverse events was independent of the patients' baseline characteristics, the presenting arrhythmia, baseline QRS and QTc duration and flecainide dose Table 3.

Table 4 shows the efficacy of flecainide evidenced by reduction of the arrhythmia burden reduction in patients who underwent follow up Holter monitor at the discretion of the treating physician. The mean effectiveness domain of the TSQM score was 70.4 ± 23.8 while the mean side effects' domain was 94.3±14.6, that of the convenience domain was 65.2±10.5, and that of global satisfaction was 72.8±21.8. There was no statistically significant difference between in all domains of the TSQM comparing atrial to ventricular arrhythmias Table 5.

Table 4.

Efficacy of flecainide evidenced by arrhythmia burden in patients undergoing Holter monitor before and 8-weeks after therapy

Presenting arrhythmia	Number of patients	Baseline	At follow up	P-value
PVCs	22	13.5% (8.2-20.5)	5% (1-5)	0.001
PACs	3	10% (3.310)	10% (1-10)	0.656
Paroxysmal AF	9	9/9 (100%)	2/9(22.2%)	0.001
Atrial flutter	2	2/2 (100%)	0/2 (0%)	0.083
Atrial tachycardia	2	2/2 (100%)	0/2 (0%)	0.083

Note: data represented by percentage (%) median (Interquartile range) for PVCs and PACs and by for number of episodes for paroxysmal AF, atrial tachycardia and flutter episodes.

Table 5.

TSQM score based on the type of presenting arrhythmia

TSQM Domain	Presenting Arrythmia[#]		P-value
	Atrial (n=35)	Ventricular (n=34)	
Effectiveness (Mean ± SD)	64.6±22.1	67.1±24.3	0.704
Side effects (Mean ± SD)	95.7±11.9	94.2±14.5	0.215
Convenience (Mean ± SD)	74.3±10	73.9±11.3	0.993
Global satisfaction (Mean ± SD)	62.3±21.1	63.2±23.2	0.902

Note: [#] - excluding patients with accessory pathway medicated tachycardia and patients with combined arrhythmia.

DISCUSSION

Flecainide is a class Ic antiarrhythmic drug that blocks sodium channels. The drug is effective for the treatment of both atrial and ventricular arrhythmias [5-8]. There has been reports about increased mortality in post MI patients [9], this raised concerns about its safety in patients with structural heart disease and led to the common practice of initiating it in-hospital in many centers worldwide even in patients with structurally normal heart [13, 18-20]. This prospective single-arm cohort study explored the safety of outpatient initiation of flecainide in patients with apparently structurally normal hearts in patients presenting with atrial or ventricular arrhythmia.

The present study found a statistically significant increase in the QRS duration and QTc interval at the 1-week follow up visit of drug initiation compared to baseline. There were no reported symptoms suggesting life-threatening

ventricular arrhythmia, including syncope, aborted SCD and/or ER visits. There was 6.7% incidence of cardiac adverse events including conduction system disease and atrial flutter, 4% of patients experienced non-resolving extracardiac manifestations. The overall drug discontinuation rate was 10.7%.

To our knowledge, the current study is the first that investigates the safety of out-of-hospital initiation of flecainide as long-term therapy in patients with structurally normal hearts. There was no life-threatening pro-arrhythmia, cardiac and extracardiac side effects requiring drug discontinuation were detected through scheduled follow up visits thus proving the safety and feasibility of this approach. One study, investigated the use of flecainide as an out-of-hospital, pill in the pocket therapy in 165 patients and reported that 12 (7%) patients had drug adverse effects, one 1(0.6%) patient and atrial flutter with rapid ventricular response and the rest of the adverse effects were non cardiac including nausea, asthenia and vertigo, thus advocating for the drug safety in the out-of-hospital setting. However, this study investigated a pill-in-the-pocket single dose approach rather than initiation of long-term therapy [21].

Previous studies reported a multitude of side effects associated with flecainide, with comparable incidences to those in our study. In patients without structural heart disease, flecainide is relatively well-tolerated, with dizziness (15-20%) and visual abnormalities such as blurred vision and difficulty focusing (up to 15%) being the common adverse effects [22] A comparative study by Tamargo et al. noted adverse effects like angina symptoms (1%), hypotension (0.8%), diarrhea (0.7%), headache (2.0%), and nausea (1.6%) [19]. Central nervous system side effects such as dizziness, visual disturbances, headache, and nausea are frequent, though severe central nervous system toxicity is rare [23]. In a study by Oudijk et al., negative inotropic effects occurred in 2 to 5% of patients [24]. In this study, none of the baseline clinical and electrocardiographic characteristics, flecainide dose or the presenting arrhythmia correlated with the occurrence of adverse events. In one study conducted in the pediatric population, younger age and lighter weight were associated with higher plasma concentrations of flecainide, potentially increasing the risk of adverse effects, this was likely because of significantly less mean age and body weight in this pediatric patient group [25].

Study limitations

The present study is limited by being a single-arm non-randomized cohort study thus future randomized controlled studied is needed to further investigate this research question. The relatively short time of follow up is another limitation which may result in underreporting of some of the drug adverse events particularly the extracardiac manifestations. A third limitation is the relatively high drop-out rate in follow up (25 out of 100 patients), this is more likely to be explained by logistic factors that hinders communication due to continuous relocation and change of medical facilities characteristic to this young active population rather than being related to life threatening events, particularly that the rest of the cohort showed no life threatening events.

CONCLUSION

In conclusion, this study demonstrates the safety and feasibility of out-of-hospital initiation of flecainide in patients with structurally normal hearts presenting with atrial or ventricular arrhythmias. Consistent with existing literature, flecainide prolonged the QRS complex and the QT interval at drug initiation, however, there was no report of any symptoms suggesting life-threatening ventricular arrhythmia. Drug adverse effects that warranted discontinuation were around 10.7% and were effectively detected through clinical and ECG outpatient follow up.

REFERENCES

1. Ramos E, O'Leary ME. State-dependent Trapping of Flecainide in the Cardiac Sodium Channel. The Journal of Physiology. 2004;560(1): 37-49. https://doi.org/10.1113/jphysiol.2004.065003.

2. Yang P, Moreno JD, Miyake CY et al. ''In Silico'' Prediction of Drug Therapy in Catecholaminergic Polymorphic Ventricular Tachycardia. The Journal of Physiology. 2015;594(3): 567-93. https://doi.org/10.1113/JP271282.

3. Bannister ML, MacLeod KT, George CH. Moving in the Right Direction: Elucidating the Mechanisms of Interaction Between Flecainide and the Cardiac Ryanodine Receptor. British Journal of Pharmacology. 2021;179(11): 2558-63. https://doi.org/10.1111/bph.15718.

4. Thireau J, Pasquié J-L, Martel E et al. New Drugs vs. Old Concepts: A Fresh Look at Antiarrhythmics. Pharmacology & Therapeutics. 2011;132(2): 125-45. https://doi.org/10.1016/j.pharmthera.2011.03.003.

5. Ruskin JN, Camm J, Dufton D et al. Orally inhaled flecainide for conversion of atrial fibrillation to sinus rhythm: INSTANT phase 2 trial. JACC: Clinical Electrophysiology. 2024;10(6): 1021-1033. https://doi.org/10.1016/j.jacep.2024.02.021.

6. Hauguel-Moreau M, Guedeney P, Dauphin C et al. Flecainide to Prevent Atrial Arrhythmia after Patent Foramen Ovale Closure, the AFLOAT Study: A Randomized Clinical Trial." Circulation. 2024;150(21). https://doi.org/10.1161/CIRCULATIONAHA.124.071186.

7. Bertels A., Kammeraad AE, van Geloven N et al. ECTOPIC trial: The efficacy of flecainide Compared To metOprolol in reducing Premature ventrIcular Contractions: A randomized open-label crossover study in pediatric patients. Heart Rhythm. 2025;22(2):536-543.https://doi.org/10.1016/j.hrthm.2024.07.111.

8. Soroosh K, Sayegh M, Ibrahim R et al. The feasibility and safety of flecainide use among patients with varying degrees of coronary disease.Clinical Electrophysiology. 2023;9: 1172-1180. https://doi.org/10.1016/j.jacep.2022.12.021.

9. Echt DS, Liebson PR, Mitchell LB et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. The New England journal of medicine. 1991;324(12): 781-8. https://doi.org/10.1056/NEJM199103213241201.

10. Moffett BS, Valdés SO, Lupo PJ et al. Flecainide Use in Children With Cardiomyopathy or Structural Heart Disease. Pediatric Cardiology. 2014;36(1): 146-50. https://doi.

org/10.1007/s00246-014-0978-3.
11. Maura ZM, Wolfes J, Schleberger R et al. Use of class IC antiarrhythmic drugs in patients with structural heart disease and implantable cardioverter defibrillator. Clinical Research in Cardiology. 2024: 1-9. https://doi.org/10.1007/s00392-024-02394-6.
12. Alboni P, Botto GL, Boriani G et al. Intravenous Administration of Flecainide or Propafenone in Patients With Recent-Onset Atrial Fibrillation Does Not Predict Adverse Effects During 'Pill-in-the-Pocket' Treatment. Heart. 2010;96(7): 546-9. https://doi.org/10.1136/hrt.2009.187963.
13. Kartalis A, Afendoulis D, Voutas P et al. Acute Management of Paroxysmal Atrial Fibrillation With Intravenous Flecainide Plus Oral Beta-Blockers. International Journal of Translational Medicine. 2024;4(2): 334-41. https://doi.org/10.3390/ijtm4020021.
14. Basza M, Maciejewski C, Bojanowicz W et al. Flecainide in clinical practice. Cardiology journal. 2023;30(3): 473-82. https://doi.org/10.5603/CJ.a2023.0018.
15. Zimetbaum PJ, Schreckengost VE, Cohen DJ et al. Evaluation of outpatient initiation of antiarrhythmic drug therapy in patients reverting to sinus rhythm after an episode of atrial fibrillation. American Journal of Cardiology. 1999;83(3): 450-2. https://doi.org/10.1016/s0002-9149(98)00885-6.
16. Bazett's formula - QT interval corrected. In: Gilbert-Kawai ET, Wittenberg MD, editors. Essential Equations for Anaesthesia: Key Clinical Concepts for the FRCA and EDA. Cambridge: Cambridge University Press; 2014.
17. Atkinson MJ, Sinha A, Hass SL et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health and quality of life outcomes. 2004;2:1-13. https://doi.org/10.1186/1477-7525-2-12.
18. Tamargo J, Capucci A, Mabo P. Safety of flecainide. Drug safety. 2012;35(4): 273-89. https://doi.org/10.2165/11599950-000000000-00000.
19. Tamargo J, Heuzey JYL, Mabo P. Narrow Therapeutic Index Drugs: A Clinical Pharmacological Consideration to Flecainide. European Journal of Clinical Pharmacology. 2015;71(5): 549-67. https://doi.org/10.1007/s00228-015-1832-0.
20. Hill AC, Silka MJ, Bar-Cohen Y. A Comparison of Oral Flecainide and Amiodarone for the Treatment of Recurrent Supraventricular Tachycardia in Children. Pacing and Clinical Electrophysiology. 2019;42(6): 670-7. https://doi.org/10.1111/pace.13662.
21. Alboni P, Botto GL, Boriani G et al. Intravenous administration of flecainide or propafenone in patients with recent-onset atrial fibrillation does not predict adverse effects during 'pill-in-the-pocket' treatment. Heart (British Cardiac Society). 2010;96(7): 546-9. https://doi.org/10.1136/hrt.2009.187963.
22. Frendl G, Sodickson A, Chung MK et al. 2014 AATS Guidelines for the Prevention and Management of Perioperative Atrial Fibrillation and Flutter for Thoracic Surgical Procedures. Journal of Thoracic and Cardiovascular Surgery. 2014;148(3): e153-e93. https://doi.org/10.1016/j.jtcvs.2014.06.036.
23. Ting S, Lee D, MacLean D, Sheerin N. Paranoid Psychosis and Myoclonus: Flecainide Toxicity in Renal Failure. Cardiology. 2008;111(2): 83-6. https://doi.org/10.1159/000119694.
24. Oudijk MA, Ruskamp JM, Ambachtsheer BE et al. Drug Treatment of Fetal Tachycardias. Pediatric Drugs. 2002;4(1):49-63. https://doi.org/10.2165/00128072-200204010-00006.
25. Thomas SAL, Ferguson RL, Wilson DG. Flecainide Administration in Children: Dosage, Drug Levels, and Clinical Effect. Cardiology in the Young. 2022;33(10): 2072-7. https://doi.org/10.1017/S1047951122003729.

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COMPARATIVE ASSESSMENT OF CARDIAC ARRHYTHMIAS AND CLINICAL AND ECONOMIC ANALYSIS USING REMOTE TELEMETRY IN ELDERLY AND SENILE PATIENTS FOLLOWING DUAL-CHAMBER PACEMAKER IMPLANTATION

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Aim. To compare the frequency and timing of cardiac arrhythmia detection and conduct a clinical and economic analysis of remote telemetry (RT) in elderly and senile patients following dual-chamber pacemaker (PM) implantation compared to in-person clinical follow-up over a 12-month period.

Methods. A prospective study was conducted involving 92 patients (50% female), with a mean age of 71,5 years. The intervention group (n=39) was monitored remotely using the Medtronic CareLink Network, USA, with patients transmitting data monthly for one year. The control group (n=53) underwent in-person clinical follow-ups at one month and one year post-implantation. The groups were comparable in age, sex, clinical diagnoses, and complications (p>0,05). A cost-effectiveness analysis (CEA) was performed, and the cost-effectiveness ratio (CER) was calculated.

Results. No statistically significant differences were observed between the experimental and control groups in the frequency of cardiac arrhythmias. However, significant differences were found in the timing of arrhythmia detection (p<0,001), with earlier detection in the experimental group. According to the results of the clinical and economic cost-effectiveness analysis, the CER value for the remote monitoring method (33226,30 [33226,30; 33226,30]) is statistically significantly lower than the similar coefficient for in-person diagnostics (373542,00 [3735,42; 373542,00]).

Conclusion. The use of RT in elderly and senile patients following dual-chamber PM implantation did not show a statistical difference in arrhythmia detection rates. However, cardiac arrhythmias were diagnosed earlier in the experimental group. The cost-effectiveness analysis demonstrated that RT requires lower financial costs to achieve a unit of effectiveness compared to in-person monitoring.

Key words: clinical and economic analysis; pacemaker; remote telemetry.

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There is a steady global increase in the number of patients with cardiovascular implantable electronic devices (CIEDs), such as pacemakers (PMs), implantable cardioverter-defibrillators (ICDs), and cardiac resynchronisation therapy (CRT) devices. In Russia, in 2022, antiarrhythmic devices were implanted in 53,486 patients across 211 medical institutions (compared to 50,646 in 2021), with an overall growth of 36.4% in CIED implantations from 2013 to 2022 [1]. The implantable systems themselves are becoming more sophisticated, requiring more time for evaluation due to the presence of a complex microcomputer that assesses both the device's function and the detection of rhythm disturbances in patients.

Following the implantation of dual-chamber P in adult patients, it is recommended to conduct two follow-up tests within six months and then at least once annually [2].

In recent decades, telemedicine has increasingly been used for monitoring patients with CIEDs. The COVID-19 pandemic accelerated this trend, prompting both patients and healthcare professionals to adopt new means of communication [3]. The review of data obtained through remote telemetry (RT) allows for the evaluation of virtually all detected arrhythmias, comparable to in-clinic follow-up assessments of PM function. RT enables the quantification of ventricular and supraventricular ectopic beats, while intracardiac electrograms (IEGMs) provide differential diagnosis between supraventricular tachycardia (SVT) and ventricular tachycardia (VT), as well as the detection of atrial fibrillation (AF) or atrial flutter (AFL). V. Russo et al. (2022) demonstrated that RT leads to a shorter interval between the occurrence of atrial high rate episodes (AHREs) and clinical evaluation by a physician compared to in-clinic monitoring [4].

The ASSERT study (2017) established that prolonged AHREs are significantly associated with an increased risk of acute cerebrovascular events (stroke) or

systemic embolism [5]. In such patients, anticoagulant therapy reduces the risk of thromboembolic complications compared to aspirin, albeit with an increased risk of serious bleeding [6].

RT also offers advantages in the detection and assessment of clinical events [4, 7, 8] compared to conventional clinic visits. The TRUST study demonstrated a nearly 50% reduction in clinic workload (mainly due to the elimination of routine, non-contributory device checks) without compromising patient safety, as well as a reduction in the average time to evaluate clinically significant events to 3 days [9].

There are also studies demonstrating the economic efficiency of RT compared to in-person follow-up [10, 11]. For instance, the PONIENTE study revealed significant healthcare cost savings (for both patients and institutions) [12]. However, according to researchers, over five years of follow-up, RT in elderly patients with pacemakers may prove to be a more expensive alternative to clinic-based monitoring.

The Norwegian NORDLAND study, published in 2022, indicated that total costs per patient monitored via RT were higher, though the difference was not statistically significant [13]. No comparable studies conducted in Russia were found in the available literature. Nevertheless, despite the advantages of remote PM monitoring, in real-world Russian clinical practice, in-person visits to healthcare institutions remain predominant for the assessment of pacemaker function.

Study aim: To compare the frequency and timing of arrhythmia detection and to conduct a clinical and economic analysis of remote telemetry in elderly and senile patients after dual-chamber pacemaker implantation, in comparison with conventional in-clinic follow-up over a 12-month period.

METHODS

The present study is a prospective, single-centre investigation that included 92 patients (aged 60 to 88 years) following initial dual-chamber PM implantation at the Department of Surgical Treatment of Complex Cardiac Arrhythmias and Cardiac Pacing. The indications for pacemaker implantation were second- or third-degree atrioventricular block and sick sinus syndrome with clinical manifestations.

Inclusion criteria were as follows: age 60 years or older; no documented history of tachyarrhythmias; no ongoing antiarrhythmic therapy; indication for dual-chamber PM implantation; the patient's (or caregiver's) ability to understand instructions for remote data transmission and willingness to comply with them.

Exclusion criteria included: presence of a PM model incapable of recording and storing intracardiac electrograms (IEGM); severe or decompensated somatic comorbidities; thyroid dysfunction; documented episodes of tachyarrhythmias; and ongoing antiarrhythmic therapy.

Withdrawal criteria were: patient refusal to continue participation in the study and the presence of marked cognitive impairment.

Table 1.

Clinical and demographic characteristics of the patients included in the study

Parameter	Test Group (n=39)	Control Group (n=53)	p-value
Age, years	71.1±6.9	71.8±8.4	0.406
Male sex, n (%)	18 (46.2)	28 (52.8)	0.406
Female sex, n (%)	21 (53.8)	25 (47.2)	
Body mass index, kg/m^2	28.2 (25.7-30.9)	27.2 (24.2-30.1)	0.207
Body surface area, m^2	1.9 (1.82-2.04)	1.9 (1.86-1.97)	0.857
Indications for pacemaker implantation, n (%)			
Atrioventricular block	23 (59.0)	37 (69.8)	0.292
Sick sinus syndrome	16 (41.0)	16 (30.2)	
Comorbidities, n (%)			
Cardiac arrhythmia	38 (97.4)	52 (98.1)	1
Stable angina pectoris	4 (10.3)	10 (18.9)	0.251
History of myocardial infarction	6 (15.4)	10 (18.9)	0.654
Hypertension	39 (100)	51(96.2)	0.259
CHF	39 (100)	53 (100)	
Class I	2 (5.1)	9 (17)	0.202
Class II	14 (35.9)	20 (37.7)	
Class III	23 (59)	25 (47.1)	
Class IV	0 (0)	0 (0)	
CVA	3 (7.7)	2 (3.7)	0.648
Diabetes mellitus	11 (28.2)	9 (17)	0.204

Note: CHF - Chronic Heart Failure; CVA - cerebrovascular accident

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee (Protocol No. 9 dated 11 March 2024). All patients provided written informed consent for participation in the study and for the surgical intervention.

All patients received dual-chamber PMs equipped with IEGM recording capabilities. After enrolment, patients were divided into two groups. The intervention group (n = 39) was provided with a MyCareLink patient monitor (Model 24950, USA) to enable remote data transmission. These patients submitted data monthly via the Medtronic CareLink server for one year following implantation. The control group (n = 53) was monitored in the clinic one month and then one year after surgery. The intervention and control groups were comparable in terms of age, sex, nosological categories, and clinical-demographic characteristics. The results are presented in Table 1.

Statistical Analysis

Statistical processing of the data and graphical presentation of the results were performed using Statistica 13.0 (StatSoft Inc., USA, licence No. AX003J-115213FAACD-X), SPSS Statistics 20 (IBM SPSS, USA), GraphPad Prism 9.0 (GraphPad Software, USA), and Microsoft Office XP (Microsoft, USA). For quantitative data, the distribution pattern was assessed using the Shapiro-Wilk test, while homogeneity of variances was evaluated using Levene's test.

Variables with a distribution deviating from normal (nonparametric data) were analysed using the Kruskal-Wallis test. Dunn's test was used for multiple comparisons, and the Mann-Whitney U test was employed to compare nonparametric quantitative variables between two independent groups. For qualitative dichotomous variables, comparisons between independent groups were performed using the two-sided Fisher's exact test.

Differences were considered statistically significant at $p < 0.05$. For quantitative variables with a non-normal distribution, the median (Median) and interquartile range (lower quartile; upper quartile) were calculated. For qualitative dichotomous variables, frequencies (%) were reported [14].

Cost-effectiveness clinical and economic analysis

For the purposes of this study, a cost-effectiveness analysis (CEA) was performed, along with the calculation of the cost-effectiveness ratio (CER), to assess whether the costs of remote versus in-clinic monitoring over a 12-month period were justified by their clinical effectiveness, and to determine the more economically favourable approach, defined as the one with the lower CER value.

The CER (reflecting the cost per unit of effectiveness) was calculated using the following formula:

$CER = DC / Ef,$

where DC represents direct costs, and Ef denotes the monitoring effectiveness.

The lower the CER value, the lower the cost per unit of effectiveness, thus indicating a more economically advantageous method of patient follow-up [15].

For the purpose of this analysis, the primary criterion for clinical effectiveness was the timely detection of rhythm disturbances (AHREs, AF, atrial flutter, supraventricular tachycardia, or ventricular tachycardia) in both the remote monitoring and control groups.

Detection of the rhythm disorder within the same calendar month in which it occurred was considered to reflect 100% detection effectiveness (1.0). If the event was detected after the month in which it occurred, effectiveness was reduced to 1% (0.01) for the purpose of analysis, as the use of zero values was not permitted within the model.

The CEA included only those patients in both the remote and control groups who experienced a detected arrhythmia over the 12-month observation period. In cases where a single patient experienced multiple rhythm disturbances, each event was evaluated separately. For the CEA calculations, the sample included all such events: n = 53 for the control group and n = 39 for the remote monitoring group. When converting days to months for analytical purposes, a uniform 30-day month was assumed.

Sources of Cost Data for Detection

The cost of the equipment used for remote patient monitoring was obtained from Medtronic and amounted to 30,000 RUB per patient. According to standard practice in the Ryazan region, in-person follow-up involves a patient visiting a general practitioner (GP) for an electrocardiogram (ECG) and referral to a cardiologist at the Ryazan Regional Cardiology Dispensary, where the device follow-up is conducted. Notably, this follow-up service is not reimbursed under the regional compulsory health insurance fund (TFOMS). All visits to medical facilities are free of charge for patients.

According to TFOMS reimbursement rates: one GP consultation is valued at 744.20 RUB; one cardiologist consultation at 954.42 RUB; fn ECG at 169.09 RUB. Thus, the total cost of an in-person monitoring episode reimbursed by TFOMS amounts to 3,735.42 RUB.

According to our institutional data, the time required to review a single remote transmission (including completion of electronic medical records and patient communication) averages 30 minutes. Under the remote monitoring (RM) protocol used in this study, 11 transmissions were conducted per patient (one per month), with the estimated cost per transmission at 293.30 RUB (data from the Regional Clinical Cardiology Dispensary, Ryazan). Therefore, the total remote monitoring cost per patient amounted to 3,326.30 RUB.

Table 2.

Detected arrhythmias

	Control Group (n=53)	Test Group (n=39)	p-value
AHRE, n (%)	25 (47,2)	15 (38,5)	0,438
AF, n (%)	10 (18,9)	3 (7,7)	0,226
AFL, n (%)	3 (5,7)	0	0,261
SVT, n (%)	8 (15,1)	11 (28,2)	0,130
VT, n (%)	11 (20,7)	11 (28,2)	0,463

Note: AHRE - atrial high rate episodes; AF - atrial fibrillation; AFL - atrial flutter; SVT - supraventricular tachycardia; VT - ventricular tachycardia.

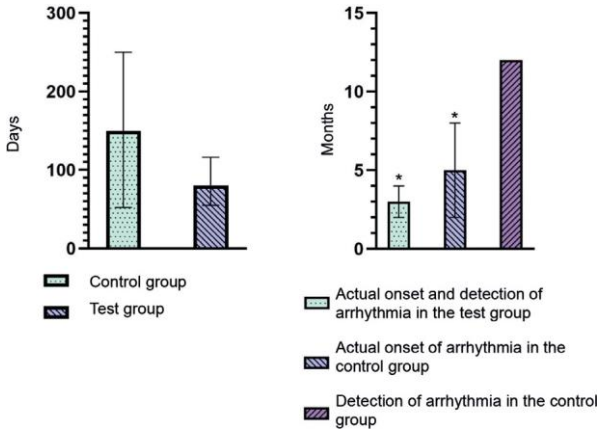

Figure 1. Left: Actual onset of arrhythmia episodes (Median [Q1; Q3] in days, p = 0.077). Right: Comparison of actual onset and detection time of arrhythmias in the intervention and control groups (Median [Q1; Q3] in months, *p < 0.05 compared to detection time in the control group). See text for details.

Sensitivity Analysis of the Cost-Effectiveness Analysis

To evaluate the robustness of the cost-effectiveness analysis results, a deterministic one-way sensitivity analysis was performed. This assessed the impact of varying the cost estimates for both remote and in-clinic monitoring by ±10%, simulating plausible real-world fluctuations in healthcare expenditure. The analysis revealed how such changes in cost assumptions would affect the cost-effectiveness ratio (CER) values and, consequently, the comparative economic preference for either monitoring strategy [16].

RESULTS

In both the intervention and control groups, no statistically significant differences were observed in the incidence of rhythm disturbances, including AHREs ($p = 0.438$), AF ($p = 0.226$), atrial flutter (AFL) ($p = 0.261$), SVT ($p = 0.130$), and VT ($p = 0.463$) (Table 2).

Similarly, there were no significant differences between the groups regarding the actual time to onset of rhythm disturbances measured in days from the beginning of the study ($p = 0.077$) (Fig. 1). However, in the control group, there was a statistically significant delay ($p < 0.001$) between the actual month of rhythm disturbance onset and the month of its detection, with detection occurring considerably later than the event itself.

In contrast, in the remote monitoring group, arrhythmias were detected in the same month as their actual occurrence, resulting in a significantly shorter detection latency compared to the control group ($p < 0.001$) (Fig. 2). Consequently, the groups differed significantly in terms of detection efficiency ($p < 0.001$) (Table 3).

The CEA demonstrated that the CER for remote monitoring was statistically significantly lower than that for conventional in-clinic monitoring ($p < 0.001$) (Fig. 3). This indicates a higher economic value for remote monitoring in terms of cost per timely detection. The findings were further confirmed by deterministic one-way sensitivity analysis, which also showed a statistically lower CER for remote monitoring ($p < 0.001$), demonstrating the robustness of the results.

Each patient in the intervention group underwent 11 scheduled remote transmissions. However, considering that the majority of rhythm disturbances (AHRE, AF, AFL, SVT, VT) in the remote group occurred during months 2, 3, and 4, an alternative transmission schedule was evaluated for potential optimisation. This hypothetical schedule included transmissions in months 1, 2, 3, 4, 6, 8, 10, and 12.

Under this modified scheme, although a slight decrease in diagnostic efficiency was observed (based on the original clinical effectiveness metric), the intervention group remained significantly more effective than the control group in detecting arrhythmias in a timely manner ($p < 0.001$) (Table 3).

Furthermore, even with the reduced number of transmissions, the CER for remote monitoring remained significantly lower than that of in-clinic follow-up ($p = 0.041$) (Fig. 4). These findings were likewise confirmed by the sensitivity analysis.

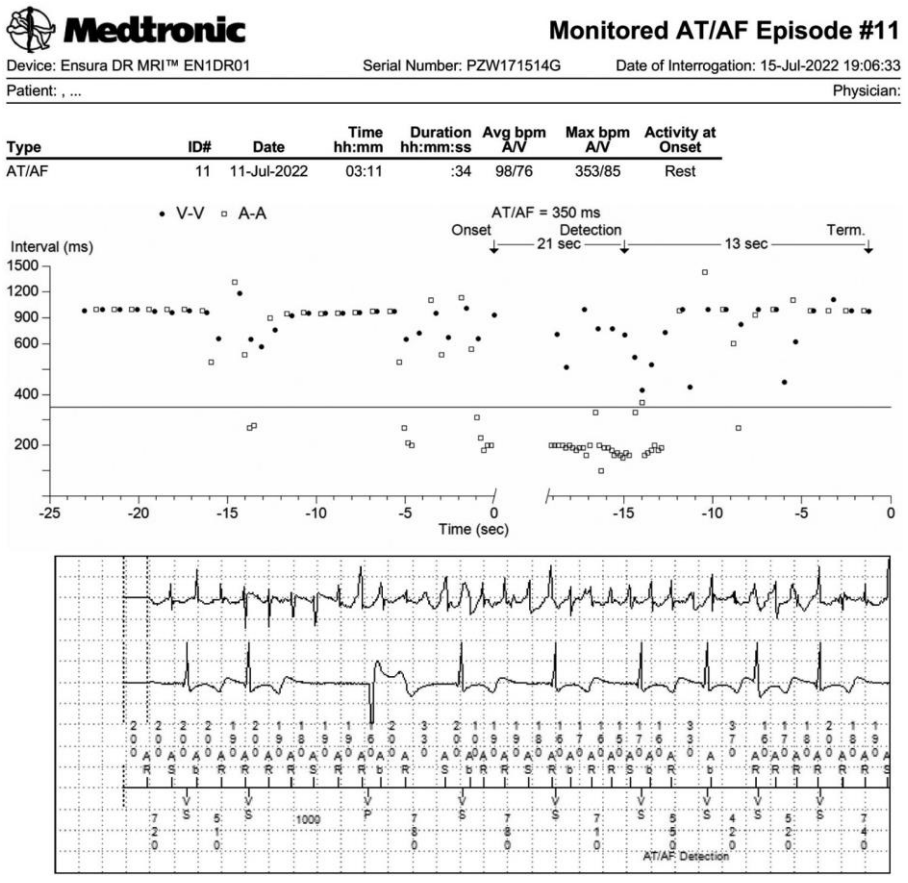

Figure 2. Episode of AHREs in the intervention group: registered on 11 July 2022 and detected on 15 July 2022.

Table 3.

Detection of arrhythmias in the month of their onset, n (%)

Match between month of arrhythmia detection and actual onset	11 Transmissions			Transmissions in 1, 2, 3, 4, 6, 8, 10 and 12 Months		
	Control Group (n=53)	Test Group (n=39)	p-value	Control Group (n=53)	Test Group (n=39)	p-value
Coincide	15 (28.3)	39 (100)	p<0.001	15 (28.3)	34 (87.18)	p<0.001
Do not coincide	38 (71.7)	0 (0)		38 (71.7)	5 (12.82)	

DISCUSSION

According to the results of our study, no significant difference was observed in the frequency of arrhythmia detectionbetween remote telemetry and conventional in-clinic monitoring among elderly patients following dual-chamber pacemaker implantation. These findings are consistent with those reported by A.S. Menezes Junior et al. (2023), who demonstrated that among patients followed up either remotely or in person over a 12-24 month period after pacemaker implantation, atrial tachyarrhythmias were more frequently identified via remote telemetry (OR = 1.22, 95% CI: 1.01-1.48, p = 0.04), whereas no statistically significant differences were found between groups in all-cause mortality, stroke, cardiovascular hospitalisations, or quality of life [17].

Conversely, J. Jiang et al. (2023) found that the detection of AHREs in patients with implanted ICD or CRT devices was associated with more than a twofold increased risk of cardiovascular events and all-cause mortality [18]. It is important to note that the methods used to detect arrhythmias (in-clinic follow-up or remote monitoring) do not influence the occurrence of rhythm disturbances themselves. If an arrhythmic episode occurs, it can be identified by either method - the key difference lies in the timing of detection.

Due to the limited sample size and relatively short follow-up period of the present study, it did not assess endpoints such as mortality, hospitalisation rates for acute coronary syndromes or cerebrovascular events, or their associations with AHREs or remote telemetry.

While remote monitoring was initially considered more critical for patients with ICD or CRT devices - particularly due to risks such as inappropriate shocks or the early detection of ineffective heart failure therapy [10, 19, 20] - recent data underscore its relevance for patients with implanted pacemakers as well. For example, the COMPASS trial reported significantly fewer hospitalisations due to atrial arrhythmias and strokes in the remotely monitored group ($p < 0.05$) [21], while the REFORM study demonstrated a 63.2% reduction in clinic visits among patients receiving remote follow-up [11].

Despite early expectations, randomised controlled trials and meta-analyses evaluating the impact of remote monitoring on overall survival have been largely neutral, although they have consistently shown a reduction in planned hospital visits and associated costs [10, 22]. In the present study, the number of in-person clinic visits among the remote monitoring group was reduced by at least 39 consultations, equivalent to a cost saving of 72,840 RUB.

Some studies have reported improved survival outcomes in patients with implanted devices who underwent remote follow-up [23]. Consistent with prior findings [4, 8], our results demonstrated that arrhythmias were detected significantly earlier in patients from the remote monitoring group.

To our knowledge, no cost-effectiveness studies evaluating remote monitoring in patients with pacemakers have been conducted in Russia. However, a study by Japanese researchers found that remote telemetry was more cost-effective than in-clinic monitoring in this patient population, particularly among those with a CHA_2DS_2-VASc score ≥3, where the benefits of earlier detection and management are likely to be more pronounced [24].

To date, only international publications have evaluated the effectiveness of hybrid monitoring (a combination of remote and in-clinic follow-up). For instance, a joint statement by the Canadian Cardiovascular Society and the Canadian Heart Rhythm Society recommends that, in clinically stable patients, routine in-person follow-up visits should alternate with remote data transmissions via RM) in a 1:1 ratio [25]. However, it is emphasised that clinics should adopt a more flexible and individualised approach, with the 1:1 ratio serving as a general guideline.

In their 2018 study, M. Wah et al. assessed the cost-effectiveness of hybrid monitoring (alternating remote and in-clinic visits at a 1:1 ratio) and found that, among patients with implanted pacemakers, this model was less costly (yielding an additional cost saving of USD 2,370 per patient) and more effective (with a gain of 0.12 quality-adjusted life years) compared to in-clinic follow-up alone [11]. Moreover, public reimbursement for remote monitoring could result in USD 14 million in savings over five years [11]. Similar findings were reported in a study by F.J. García-Fernández et al. (2019), further supporting the cost-effectiveness of hybrid follow-up [26].

Thus, remote monitoring should not fully replace in-person follow-up, but rather serve as a complementary approach, particularly in large, sparsely populated regions of Russia where RM holds significant potential.

An Italian study involving 209 patients with dual-chamber pacemakers compared the cost and effective-

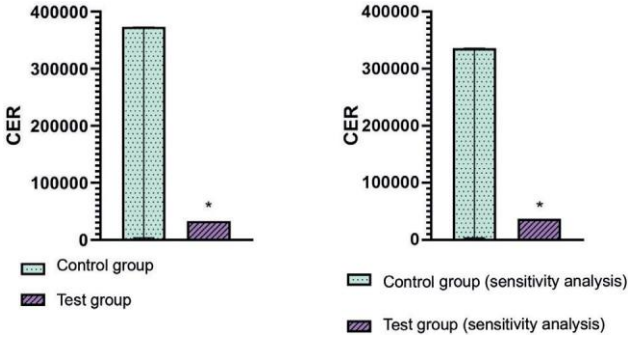

Figure 3. Cost-effectiveness analysis (left) and sensitivity analysis (right) for the scenario with 11 transmissions. *p < 0.05 compared to the control group.

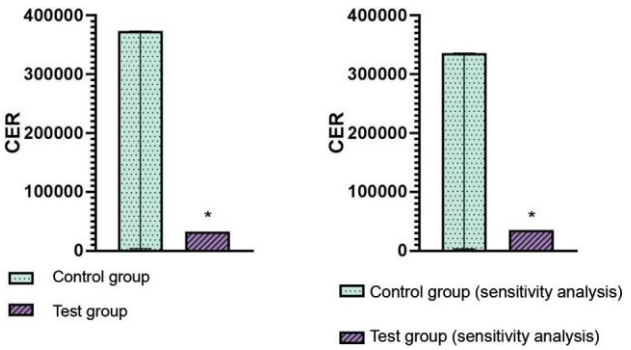

Figure 4. Cost-effectiveness analysis (left) and sensitivity analysis (right) for the scenario with transmissions performed in months 1, 2, 3, 4, 6, 8, 10, and 12. *p <0.05 compared to the control group.

ness of RM versus standard in-clinic follow-up. Annual per-patient costs were significantly lower in the RM group (€56.87 ± 80.22) compared to the standard care group (€169.49 ± 80.22; $p < 0.001$). Hospitalisations in the RM group were reduced by 58.78%, contributing further to cost savings, while quality of life did not differ between the two groups [27].

South Korean researchers calculated the average cost of medical care per minute over a 12-month period before and after the implementation of RM by dividing total healthcare expenditures by the total time spent delivering care per patient. The introduction of RM resulted in a 44% reduction in per-minute medical care costs ($p < 0.001$) [28].

According to the American College of Cardiology and HRS consensus on remote monitoring of CIEDs, data transmission should be performed at least every four months [29]. Current Russian guidelines do not address age-specific considerations or the need for more frequent transmissions in older patients. However, this appears particularly relevant given the higher comorbidity burden and cardiovascular risk in the elderly, warranting more frequent monitoring.

It should be noted that many economic evaluations do not account for the initial costs of implementing RM systems (e.g., equipment purchase) [13]. Moreover, important factors such as patient travel costs, lost workdays, and fall-related risks in the elderly were not included in this study due to the complexity of quantifying such variables and the potential to overburden the design. Nonetheless, future Russian studies should address these aspects as they appear highly relevant and timely.

The RM schedule proposed in this study (months 1, 2, 3, 4, 6, 8, 10, and 12 post-implantation) may contribute to future research evaluating the clinical and economic value of RM in patients with dual-chamber pacemakers in Russia.

While RM may offer a cost-effective solution for most clinics, its feasibility must be assessed locally. For example, RM-enabled devices are used in 58.5% of cases in North and South America, but less than 6% in Asia, likely due to regulatory and economic factors [31]. International data on the cost-effectiveness of RM in pacemaker patients remains inconsistent [13]. However, the present single-centre study demonstrated that RM is economically more viable, a conclusion further supported by deterministic one-way sensitivity analysis.

The lack of clear reimbursement criteria for physicians remains a barrier to the widespread adoption of this promising approach in routine Russian practice. Meanwhile, financial incentives have been shown to increase RM uptake [32]. Further studies are needed to maintain a balance between the increased workload for healthcare providers and the clinical and economic benefits of remote monitoring.

Study Limitations

Clinical effectiveness was assessed based on a surrogate endpoint, without consideration of final clinical outcomes. As the criterion for clinical effectiveness of patient monitoring, the timely detection of arrhythmias (AHRE, AF, AFL, SVT, VT) in the intervention and control groups was used. Detection was regarded as timely if the month of actual onset of the arrhythmia coincided with its identification. A discrepancy between the actual onset and detection of arrhythmia was interpreted as an almost complete loss of diagnostic effectiveness.

The study did not include an evaluation of other economic factors that could have influenced the overall results (e.g. transportation costs, loss of income due to hospital visits, and similar indirect expenses).

Information on the cost of the equipment required for remote monitoring was provided by the manufacturer, Medtronic, USA.

The sample size was determined based on the availability of MyCareLink monitors (model 24950, USA) for remote data transmission, due to existing logistical constraints at the time that prevented expansion of the study cohort.

CONCLUSION

The use of remote monitoring in elderly patients following dual-chamber pacemaker implantation over a one-year period did not reveal statistically significant differences in the incidence of arrhythmias. However, arrhythmias were detected at significantly earlier stages in the intervention group. The cost-effectiveness analysis conducted demonstrated that RM is associated with lower financial costs per unit of effectiveness compared to conventional in-clinic follow-up.

REFERENCES

1. Golukhova EZ, Milievskaya EB, Filatov AG, et al. Arrhythmology - 2022. Heart rhythm and conduction disorders. Moscow: A.N. Bakulev National Medical Research Center for Cardiovascular Surgery, Ministry of Health of the Russian Federation; 2023. 148 p. (In Russ). ISBN: 978-5-7982-0452-6.

2. Revishvili ASh, Artyukhina EA, Glezer MG, et al. Clinical practice guidelines for Bradyarrhythmias and conduction disorders. *Russian Journal of Cardiology*. 2021;26(4): 4448. (In Russ.). https://doi.org/10.15829/1560-4071-2021-4448.

3. Suran M. Increased Use of Medicare Telehealth During the Pandemic. *JAMA*. 2022;327(4): 313. https://doi.org/10.1001/jama.2021.23332.

4. Russo V, Rapacciuolo A, Rago A, et al. Early evaluation of atrial high rate episodes using remote monitoring in pacemaker patients: Results from the RAPID study. *J. Arrhythmia*. 2022;38(2): 213-220. https://doi.org/10.1002/joa3.12685.

5. Van Gelder IC, Healey JS, Crijns HJGM. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J.* 2017;38(17)1339-1344. https://doi.org/10.1093/eurheartj/ehx042.

6. Healey JS, Lopes RD, Granger CB, et al. ARTESIA Investigators. Apixaban for Stroke
Prevention in Subclinical Atrial Fibrillation. *The New England Journal of Medicine*. 2024; 390(2): 107-117. https://doi.org/10.1056/NEJMoa2310234.

7. Crossley GH, Boyle A, Vitense H, et al. The CONNECT (Clinical Evaluation of Remote Notification to Re-

duce Time to Clinical Decision) trial: The value of wireless remote monitoring with automatic clinician alerts. *J Am Coll Cardiol.* 2011;57(10): 1181-1189. https://doi.org/10.1016/j.jacc.2010.12.012.
8. Saxon LA, Hayes DL, Roosevelt GF, et al. Long-term outcome after ICD and CRT implantation and influence of remote device follow-up: The ALTITUDE survival study. *Circulation*. 2010;122(23): 2359-2367. https://doi.org/10.1161/CIRCULATIONAHA.110.960633.
9. Varma N, Epstein AE, Irimpen A, et al. Efficacy and safety of automatic remote monitoring for implantable cardioverter-defibrillator follow-up: The lumos-t safely reduces routine office device follow-up (TRUST) trial. *Circulation.* 2010;122(4): 325-332. https://doi.org/10.1161/CIRCULATIONAHA.110.937409.
10. Klersy C, Boriani G, De Silvestri A, et al. Effect of telemonitoring of cardiac implantable electronic devices on healthcare utilization: A meta-analysis of randomized controlled trials in patients with heart failure. *Eur J Heart Fail*. 2016;18(2): 195-204. https://doi.org/10.1002/ejhf.470.
11. Vania Costa, Man Wah Yeung, Jenny Gilbert, et al. Remote monitoring of implantable cardioverter-defibrillators, cardiac resynchronization therapy and permanent pacemakers: A health technology assessment. *Ont Health Technol Assess Ser*. 2018;18 (7): 1-199.
12. Lopez-Villegas A, Catalan-Matamoros D, Musso ER, et al. Effectiveness of pacemaker tele-monitoring on quality of life, functional capacity, event detection and workload: The PONIENTE trial. *Geriatr. Gerontol. Int.* 2016;16(11): 1188-1195. https://doi.org/10.1111/ggi.12612.
13. Lopez-Villegas A, Catalan-Matamoros D, Peiro S, et al. Cost-utility analysis of telemonitoring versus conventional hospital-based follow-up of patients with pacemakers. The NORDLAND randomized clinical trial. *PLoS One*. 2020;15(1): 1-17. https://doi.org/10.1371/journal.pone.0226188.
14. Kalinin RE, Suchkov IA, Uporov MM, et al. Effectiveness of Different Treatment Tactics of Superficial Thrombophlebitis of Lower Limbs (with Development of Mathematical Model for Prediction of Therapeutic Effectiveness). *IP. Pavlov Russ Med Biol Herald.* 2023;31(4): 535-550. (In Russ). https://doi.org/10.17816/PAVLOVJ192535.
15. Yagudina RI, Kulikov AYu, Metelkin IA. Methodology of cost-effectiveness analysis in conducting pharmacoeconomic studies. *Pharmacoeconomics*. 2012;5(4): 3-8. (In Russ.).
16. Yagudina RI, Serpik VG, Kulikov AYu. *Pharmacoeconomics: theory and practice.* 2014;2(1): 5-20. (In Russ). https://doi.org/10.30809/phe.1.2014.47
17. Menezes Junior AS, Rivera A, Ayumi Miyawaki I, et al. Long-Term Remote vs. Conventional Monitoring of Pacemakers: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Curr Cardiol Rep*. 2023;25(11): 1415-1424. https://doi.org/10.1007/s11886-023-01963-x.
18. Yee R, Verma A, Beardsall M, et al. Canadian Cardiovascular Society/Canadian Heart Rhythm Society joint position statement on the use of remote monitoring for cardiovascular implantable electronic device follow-up. *Can J Cardiol.* 2013;29(6): 644-51. https://doi.org/10.1016/j.cjca.2012.11.036.
19. Guédon-Moreau L, Lacroix D, Sadoul N, et al. A randomized study of remote follow-up of implantable cardioverter defibrillators: Safety and efficacy report of the ECOST trial. *Eur Heart J*. 2013;34(8): 605-614. https://doi.org/10.1093/eurheartj/ehs425.
20. Ferrick AM, Raj SR, Deneke T, et al. 2023 HRS/EHRA/APHRS/LAHRS expert consensus statement on practical management of the remote device clinic. *Hear Rhythm*. 2023;20(9): e92-e144. https://doi.org/10.1016/j.hrthm.2023.03.1525.
21. Mabo P, Victor F, Bazin P, et al. A randomized trial of long-term remote monitoring of pacemaker recipients (The COMPAS trial). *Eur Heart J*. 2012;33(9): 1105-1111. https://doi.org/10.1093/eurheartj/ehr419.
22. Parthiban N, Esterman A, Mahajan R, et al. Remote Monitoring of Implantable Cardioverter-Defibrillators: A Systematic Review and Meta-Analysis of Clinical Outcomes. *J. Am. Coll. Cardiol*. 2015;65(24): 2591-2600. https://doi.org/10.1016/j.jacc.2015.04.029.
23. Kolk MZH, Narayan SM, Clopton P, et al. Reduction in long-term mortality using remote device monitoring in a large real-world population of patients with implantable defibrillators. *Europace. Oxford University Press*. 2023;25(3): 969-977. https://doi.org/10.1093/europace/euac280.
24. Kawakami H, Saito M, Fujisawa T, et al. A cost-effectiveness analysis of remote monitoring after pacemaker implantation for bradycardia in Japan. *J Cardiol*. 2023;82(5): 388-397. https://doi.org/10.1016/j.jjcc.2023.06.003.
25. Jiang J, Mi L, Chen K, Hua W, Su Y, Xu W, Zhao S, Zhang S. Association of Device-Detected Atrial High-Rate Episodes With Long-term Cardiovascular and All-Cause Mortality: A Cohort Study. Can J Cardiol. 2024;40(4): 598-607. https://doi.org/10.1016/j.cjca.2023.12.007.
26. García-Fernández FJ, Asensi JO, Romero R, et al. Safety and efficiency of a common and simplified protocol for pacemaker and defibrillator surveillance based on remote monitoring only: A long-term randomized trial (RM-ALONE). *Eur Heart J*. 2019;40(23): 1837-1846. https://doi.org/10.1093/eurheartj/ehz067.
27. Ricci RP, Vicentini A, D'Onofrio A, et al. Economic analysis of remote monitoring of cardiac implantable electronic devices: Results of the Health Economics Evaluation Registry for Remote Follow-up (TARIFF) study. *Hear Rhythm*. 2017;14(1): 50-57. https://doi.org/10.1016/j.hrthm.2016.09.008.
28. Bae H, Hwang Y. Economic Evaluation of Remote Monitoring for Implantable Cardiac Devices: Evidence from a Remote-Care Study. *Clinicoecon Outcomes Res*. 2024;16 September: 697-705. https://doi.org/10.2147/CEOR.S478089.
29. Slotwiner D, Varma N, Akar. JG, et al. HRS expert consensus statement on remote interrogation and monitoring for cardiovascular implantable electronic devices. *Hear Rhythm. Elsevier*. 2015;12(7): e69-e100. https://doi.org/10.1016/j.hrthm.2015.05.008.
30. Lopez-Villegas A, Leal-Costa C, Perez-Heredia M, et al. Knowledge update on the economic evaluation of pacemaker telemonitoring systems. *Int. J. Environ. Res. Public Health*. 2021;. 18 (22):12120. https://doi.org/10.3390/ijerph182212120.

31. Varma N, Kondo Y, Park SJ, et al. Utilization of remote monitoring among patients receiving cardiac resynchronization therapy and comparison between Asia and the Americas. *Hear Rhythm O2*. 2022;3(6): 868-870. https://doi.org/10.1016/j.hroo.2022.06.013.

32. Vandenberk B, Ferrick N, Wan EY, et al. Determinants of global cardiac implantable electrical device remote monitoring utilization - Results from an international survey. *Cardiovasc. Digit. Heal. J*. 2024;5(3): 141-148. https://doi.org/10.1016/j.cvdhj.2024.03.003.

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ATRIAL FIBRILLATION DETECTION USING MACHINE LEARNING ALGORITHM FROM SINGLE LEAD ELECTROCARDIOGRAMS

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Aim. Atrial fibrillation (AF) represents one of the most critical cardiac arrhythmias, as it significantly increases the risk of stroke. Its detection is particularly challenging due to the unpredictable nature of its episodes.

Methods. This study proposes a low-complexity algorithm, enabling integration into embedded devices for real-time AF episode detection. The proposed method integrates non-linear, time-domain and frequency-domain features extracted from electrocardiogram signals with The LightGBM algorithm (an extension of decision tree algorithm) is used to classify and detect AF.

Results. The model was trained using the MIT-BIH AF Database (MIT-AFDB), achieving sensitivity (*Se*), specificity (*Sp*), accuracy rates (*Acc*), precision (*PPV*), F1-score and AUC of 0.9838, 0.9690, 0.9748, 0.9543, 0.9688 and 0.9957, respectively. We also performed 10-fold cross-validation on this dataset. The obtained values for *Se*, *Sp*, *Acc*, *PPV*, F1-score, and AUC were, respectively, 0.9837 ± 0.0020, 0.9701 ± 0.0021, 0.9755 ± 0.0007, 0.9559 ± 0.0029, 0.9696 ± 0.0008, and 0.9959 ± 0.0002. This indicates that the model achieves good performance compared to current studies in AF recognition and detection.

Conclusions. The experimental results demonstrate that the model achieves high performance in the classification and detection of AF episodes. Furthermore, the model is suitable for integration into real-time arrhythmia detection systems.

Key words: electrocardiogram; atrial fibrillation; heart rate variability; QT interval variability; power spectrum; machine learning

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Atrial fibrillation (AF), a life-threatening cardiac arrhythmia, has shown a significant global burden, with its prevalence rising from 33.5 million cases in 2010 to 59 million in 2019. Projections estimate a twofold to threefold increase by 2050, particularly among high-risk populations such as hypertensive and diabetic patients. AF is characterized by uncoordinated atrial electrical activity, leading to thrombus formation and elevated stroke risk [1]. Clinically, AF is categorized into paroxysmal, persistent, and permanent subtypes, with the latter posing significant management challenges due to irreversible rhythm disturbances.

Current diagnostic methods, including Holter monitoring, exhibit limitations in detecting transient AF episodes, underscoring the need for advanced monitoring systems. Recent advancements in wearable devices and artificial intelligence have enhanced real-time AF detection; however, demonstrating their effectiveness in detecting short AF episodes lasting less than 30 seconds remains a challenging problem. These AF episodes have the potential to develop into longer, more persistent episodes, which are more difficult to restore to normal sinus rhythm (NSR). Electrocardiogram (ECG)-based machine learning models leverage AF-associated markers, such as RR interval irregularity and fibrillatory wave morphology, to improve classification accuracy. Prior studies have employed Markov chains, spectral analysis, and entropy metrics on RR intervals [2-4], while others have integrated atrial activity frequency features [5, 6]. Deep learning approaches, in which convolutional neural networks (CNNs) are used to automatically extract features with filters that have been investigated in recent years, have also been explored. In study [7], the authors used segments comprising 30 RR intervals from the MIT-AFDB, combining CNN and Long-Short Term Memory (LSTM) networks to extract high-level features for the classification of AF and NSR. The model achieved sensitivity and specificity of 98.98% and 96.95%, respectively. In study [8], the authors used segments with a duration of 750 ms - comprising 250 ms before the R peak and 500 ms after the R peak - as input data for a machine learning model employing a hybrid CNN-LSTM network to classify AF and other cases, achieving sensitivity and specificity of 97.87% and 99.29%, respectively. Additionally, some models transform biosignal data

into 2D images, which are then fed into CNNs to recognize AF and NSR, as demonstrated in studies [9, 10]. However, these models require large amounts of input data and powerful computational resources that, in some cases, exceed those available on conventional computing devices.

The development of algorithms that utilize the selection of pathological features from ECG signals based on time-domain and frequency-domain characteristics is of considerable significance. These models facilitate a reduction in the number of input features and require less training data compared to deep learning models, making them more suitable for real-time applications. In this study, we propose a method that incorporates time-domain features, nonlinear features of heart rate variability (HRV), and the morphological characteristics of atrial activity in cases of AF and NSR, along with frequency-domain features for the identification and detection of AF episodes. The model was developed using the MIT-AFDB and validated on the SHDB-AF Database (SHDB-AF). Furthermore, the implementation of the LightGBM algorithm enhances the model's applicability in real-time systems for AF recognition and detection.

METHODS

Outline of proposed method

In this study, we propose a methodology that incorporates HRV, time- and frequency-domain features alongside a machine learning model to classify and detect AF using ECG signals. The feature set construction process in the proposed algorithm consists of the following steps: signal preprocessing, which includes signal selection, filtering, and analysis; computation of HRV features in the time domain; calculation of frequency-domain features; construction of the machine learning model; and evaluation of its performance.

The classification and detection algorithm are designed for single-channel ECG signals. To compute time-domain and frequency-domain features, the ECG signal first undergoes noise filtering. Subsequently, feature extraction is performed by isolating characteristic waves of the ECG signal, including the QRS complex, P wave, and T wave. HRV features, encompassing time-domain and nonlinear characteristics, are identified. Additionally, atrial waveform morphology features in cases of AF and NSR are determined through QT intervals on the ECG signal. Frequency-domain features are extracted by analyzing the peak energy spectral distribution under varying conditions. Finally, the LightGBM algorithm is utilized to classify ECG signals into two categories: AF and non-AF.

Signal preprocessing

Elimination of baseline drift noise was achieved using a median filter [11]. Following the removal of baseline drift, a Savitzky-Golay smoothing filter was applied for mitigating high-frequency noise [12]. Both the median filter and the Savitzky-Golay filter preserve the morphology of the ECG signal, ensuring that the original signal characteristics remain unchanged. After denoising the ECG signal, premature ventricular complexes and premature atrial complexes were removed based on the length of the RR interval. Detection is based on the criterion that the distance from the R peak of abnormality to the preceding R peak is less than 0.8 times the average RR interval.

ECG signals were subsequently segmented, including QRS complexes and T-wave endpoints. Detection of QRS complexes was performed using the Pan-Tompkins algorithm [13]. This algorithm identifies QRS complexes through filtering and thresholding techniques for locating R-peaks. Positions of the Q and S waves were determined relative to the R-wave positions. Identification of T-wave positions was carried out using the Zhang algorithm, which leverages the convexity or concavity of the T-wave [14].

The primary advantage of these waveform segmentation algorithms lies in their low computational complexity and high effectiveness in detecting ECG waveforms. Thus, they are well-suited for real-time analysis and recognition of ECG signals.

Heart rate variability features

AF is characterized by irregular RR intervals. Consequently, HRV features play a crucial role in detecting AF. In this study, statistical features of RR intervals, including the mean, range, and dispersion, were utilized as inputs for the machine learning model. These parameters are defined by Eq. (1), (2), and (3), as follows.

$$RR_{mean} = \frac{\sum_{i=1}^{N_b} RR_i}{N_b} \quad (1)$$

$$dRR = RR_{max} - RR_{min} \quad (2)$$

$$dispRR = \sqrt{\frac{\sum_{i=1}^{N_b} (RR_i - RR_{mean})^2}{N_b - 1}} \quad (3)$$

The non-linear features of HRV analyzed include the SD1 and SD2 parameters derived from the Poincaré plot, and the ellipse area defined by the SD1 and SD2 axes. These parameters provide insights into HRV, with SD1 reflecting short-term variability and SD2 representing long-term variability. The irregularity of RR intervals is evident in the scattergram of RR intervals, distinguishing cases of AF from NSR. The SD1 and SD2 values and area of ellipse are calculated using Eq. (4), (5) and (6), respectively.

$$SD_1 = \sqrt{\frac{Var(RR_{n+1} - RR_n)}{2}} \quad (4)$$

$$SD_2 = \sqrt{\frac{Var(RR_{n+1} + RR_n)}{2}} \quad (5)$$

$$Area_{SD} = \pi SD_1 SD_2 \quad (6)$$

where the *Var* functions correspond to the variance function of the respective variable of the function.

Time-domain features

In the case of patients with AF, small-amplitude atrial *f* waves with varying frequencies and shapes appear on the ECG signal. The QT interval is the wave interval measured from the end of the T wave to the start of the QRS complex (QRS onset). These points are determined using the algorithms mentioned above. Subsequently, the synchronization of the signal intervals is performed using interpolation methods to assess the variability of the QT interval in both AF and NSR cases.

Due to changes in the relative position of the Q wave with respect to the R peak, the position of the P wave peak

in some cases also changes within the analysis window. Therefore, when synchronizing the QT intervals in the case of NSR, we account for the position of the P wave peak. The probability of detecting the P peak is expressed through the following conditions: (i) the P peak appears within 180 ms before the R peak and (ii) the amplitude of the P wave is not less than 0.02 times the average amplitude of the R wave in the signal analysis window. If P peaks satisfying both of two conditions (i) and (ii), the QT intervals within the analysis window are synchronized through interpolation using three points of the largest QT interval: the endpoint of T wave, the QRS onset point, and the peak of the QT interval or the P wave peak. In the opposite case, the QT intervals are synchronized through interpolation using only the endpoint of T wave and the QRS onset points of the largest QT interval. The feature used to determine the presence of the P wave on the QT interval is defined by Eq. (7), (8) and (9), as follows.

$$\overline{TQ} = \frac{\sum_{i=1}^{N_b} TQ_i}{N_b} \quad (7)$$

$$D_e = \frac{\|TQ_i - \overline{TQ}\|}{\|TQ_i\|} \quad (8)$$

$$Var_{De} = \frac{N_{D_e \geq D_{th}}}{N_b} \quad (9)$$

where, *TQi* represents the QT intervals in the monitored signal segment after synchronization, $\overline{TQ}$ is the average value of the *TQi* intervals, $N_{De \geq Dth}$ is the number of D_e values greater than a specified threshold D_{th} (in this study, D_{th} is empirically determined to be 0.8), N_b is the number of QT intervals after excluding premature ventricular beats and premature atrial beats, and || || denotes the length of a vector.

Frequency-domain features

In this study, the power spectral distribution is utilized as a feature for identifying and classifying AF and NSR. The power spectrum is computed using a method that eliminates spectral leakage at the main spectral peaks of the signal's power spectrum. This approach enables the identification of peak distribution based on clear separation in the signal's power spectrum. The process involves multiplying the signal with appropriate windows. It can be observed that, in the case of NSR, the power spectral peaks are evenly distributed due to the stability of the ECG signal. Assume a sequence of spectral peaks $\{f_i^{PS}\}$ is obtained, where *i = 1,2,...M +1*, and *M + 1* represents the number of spectral peaks within the frequency range [0,15 Hz]. The frequency-domain feature is defined as the variance of the sequence $\delta_i^{PS} = f_{i+1}^{PS} - f_i^{PS}$, for $1 \leq i \leq M$, as determined by Eq. (10).

$$\sigma_p^{PS} = Var(\delta_i^{PS}) = \sqrt{\frac{1}{M-1}\sum_{i=1}^{M}(\delta_i^{PS} - \overline{\delta^{PS}})^2} \quad (10)$$

where, $\overline{\delta^{PS}}$ represents the mean value of the sequence δ_i^{PS}.

The distribution of peaks is determined based on the power spectrum of the signal, independent of the detection of the ECG's R peak. Therefore, this approach is particularly beneficial in scenarios where the signal remains stable during NSR but is affected by noise, especially when the R peak has a lower amplitude compared to other waveform peaks. In such instances, we determine the variability values of the non-linear HRV features similarly to those defined in Eq. (4), (5), and (6). Variations in the peak spectral distribution are calculated according to Eq. (11), (12), and (13) as follows.

$$\sigma_{SD1} = \sqrt{\frac{Var(\delta_{n+1}^{PS} - \delta_n^{PS})}{2}} \quad (11)$$

$$\sigma_{SD2} = \sqrt{\frac{Var(\delta_{n+1}^{PS} + \delta_n^{PS})}{2}} \quad (12)$$

$$Area_\sigma = \pi \sigma_{SD1} \sigma_{SD2} \quad (13)$$

Building machine learning model for classification

ECG database

The MIT-AFDB comprises 25 records, each containing two ECG signals recorded over durations ranging from 6 to 10 hours at Beth Israel Hospital in Boston. The signals were sampled at a frequency of 250 Hz with an analog-to-digital converter (ADC) resolution of 12 bits. The dataset provides annotations for episodes of AF, NSR, and non-AF arrythmias, including atrial flutter (AFL). Notably, most AF cases in this dataset are classified as paroxysmal AF (PAF) [2, 15]. Apart from recordings 00735m and 03665m, which are unavailable, the remaining recordings were utilized for training and evaluating the machine learning model. The SHDB-AF (Saitama Heart Database Atrial Fibrillation) is an open-source ECG recording database from Japan, consist- ing of 100 patients with PAF [15, 16]. The recordings were collected over approximately 24 hours between November 2019 and January 2022. Data acquisition was performed us- ing a Holter monitor with a sampling frequency of 125 Hz, recording two leads per session according to the CC5 and NASA configurations. The recordings in the database un- derwent preprocessing to remove baseline wander and high- frequency noise and were subsequently unsampled to 200 Hz. The dataset includes five classified rhythm types: AFIB (atrial fibrillation), AFL (atrial flutter), AT (atrial tachycardia),

Table 1.

Classification Features

Feature	Description
RRmean	Mean of RR intervals
dRR	Range of RR intervals
dispRR	Dispersion of RR intervals
SD_1	Short-term variability of HRV
SD_2	Long-term variability of HRV
$Area_{SD}$	Area of the ellipse defined by SD1 and SD2
Var_{De}	Variability of TQ intervals
σ_p^{PS}	Dispersion of ECG signal power spectrum peaks
σ_{SD1}	Modified SD1 of ECG signal power spectral peaks
σ_{SD2}	Modified SD2 of power spectral peaks
$Area_\sigma$	Modified of area of the ellipse defined by SD1 and SD2 of power spectral peaks

PAT (other supraventricular tachycardias), NOD (intranodal tachycardias), and N (other rhythms, including NSR).

Classification

We used the MIT-AFDB dataset to train the model. Signal segments were extracted from record 1 for each patient, after which these segments were translationally shifted by q = 300 steps, corresponding to approximately one cardiac cycle at a sampling frequency of 250 Hz. The signals were filtered to remove noise, and features were computed as described in the preceding sections and shown in the Table 1. A total of 685,771 samples were obtained using this method, including 272,032 AF samples and 413,739 non-AF samples.

In this study, the LightGBM algorithm was employed to construct the model. LightGBM is a gradient boosting framework based on decision tree algorithms, designed to enhance model performance and reduce memory usage while effectively handling large-scale data. It incorporates several novel techniques, including Gradient-based One-Side Sampling, which selectively retains cases with steep gradients during training to optimize both memory usage and training time. The advantages of this algorithm include rapid training speed, high training efficiency, robust performance with imbalanced data, ease of parameter tuning, and a reduced risk of overfitting [17].

RESULTS

The MIT-AFDB dataset was partitioned into training and testing sets in a 70%:30% ratio. The computing system utilized comprised an Intel Core i7 12700K CPU (5.2 GHz), a 12 GB GPU (Nvidia GeForce RTX 3060), and 32 GB of RAM. The confusion matrix and ROC curve based on the MIT-AFDB are presented in Fig. 1. The sensitivity (*Se*), specificity (*Sp*), accuracy (*Acc*), precision (*PPV*), F1 score, and AUC are 0.9838, 0.9690, 0.9748, 0.9543, 0.9688, and 0.9957, respectively. We also conducted 10-fold cross-validation. The average values of *Se*, *Sp*, *Acc*, *PPV*, F1 score, and AUC are 0.9837 ± 0.0020, 0.9701 ± 0.0021, 0.9755 ± 0.0007, 0.9559 ± 0.0029, 0.9696 ± 0.0008, and 0.9959 ± 0.0002, respectively. A comparative table and distribution of model metrics across the cross-validation folds are illustrated in Fig. 2.

The model was additionally validated on the SHDB-AF. Segments with a length of 15 seconds were extracted using a sliding window with a step size of 240 samples, corresponding to 1.2 seconds at a sampling frequency of 200 Hz. The total number of samples is 6,740,673, of which 1,201,561 are labeled as AF and the remaining 5,539,112 as non-AF, which were used for model testing. The confusion matrix and ROC curve for the SHDB-AF are presented in Fig. 3. The model performance metrics, including *Se*, *Sp*, *Acc*, *PPV* (Positive Predictive Value) and *FPR* (False Positive Rate), in Table 2 and the ROC curve (AUC = 0.9503) on the SHDB-AF indicate that the proposed model can effectively operate on unseen data.

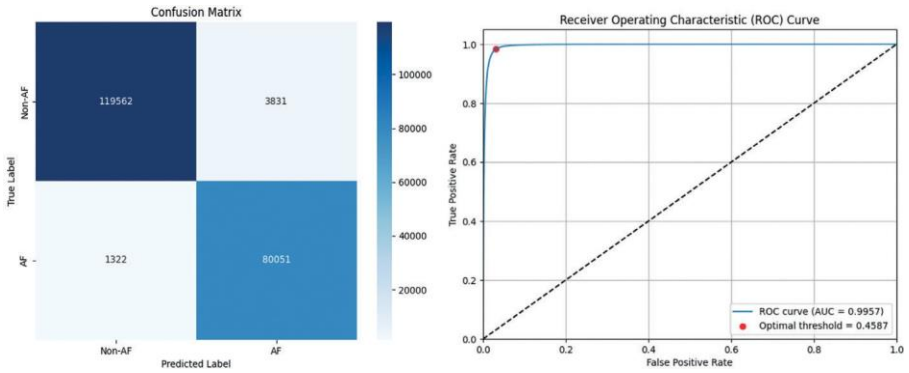

Fig. 1. Confusion matrix for AF classification and AUC curve with MIT-AFDB.

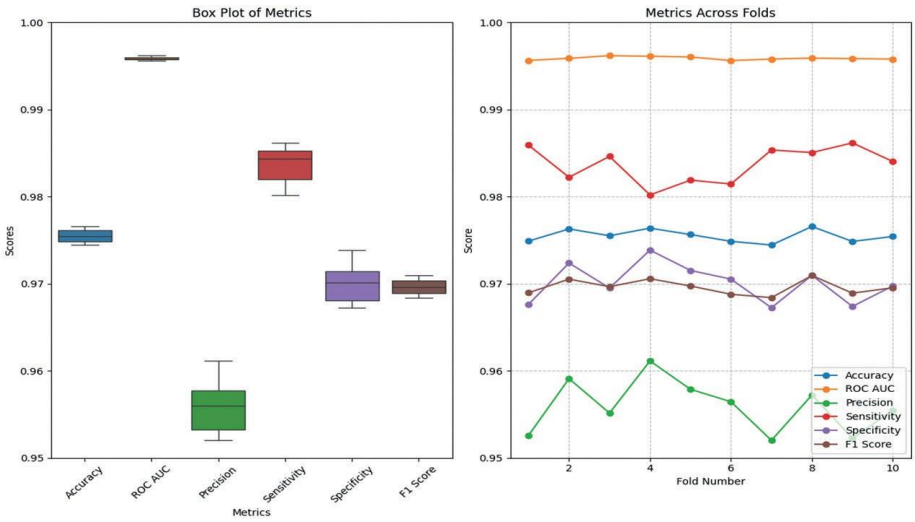

Fig. 2. Model performance metrics across folds in a 10-fold cross-validation of the MIT-AFDB.

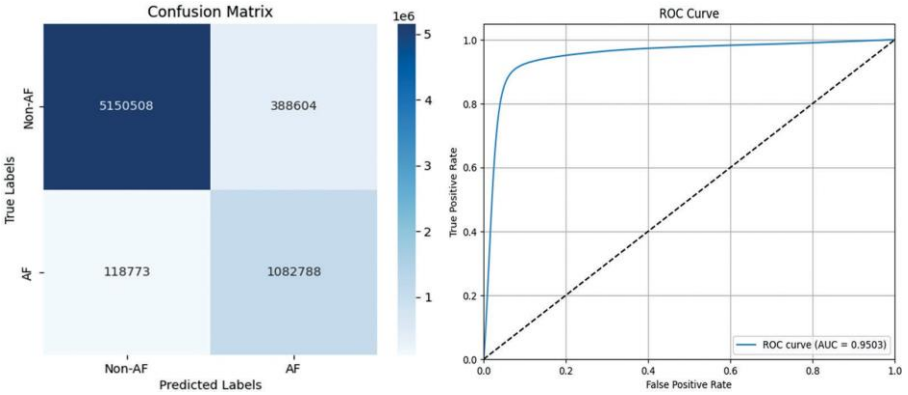

Fig. 3. Confusion matrix and ROC curve for the SHDB-AF.

DISCUSSION

Due to the irregular heart rate in cases of AF, various HRV features are used. Additionally, to assess the presence of atrial waves instead of the typical P-waves, study [20] combines heart rate variability indices (standard deviation of RR intervals, range of RR intervals) with the number of threshold crossings in the atrial wave segment within the QT intervals. Threshold-based parameters are then employed to classify AF and non-AF. In another approach, study [21] proposes using single-parameter wavelet entropy to detect atrial fibrillation by determining the optimal threshold for the wavelet entropy of QT intervals, thereby classifying AF and non-AF. However, this method is sensitive to noise, and variations in QT intervals across ECG signal segments may fluctuate between cardiac cycles, reducing classification accuracy.

Studies that rely on RR interval parameters depend on accurate detection of R-peaks. In many cases, misidentification of R-peaks leads to errors in AF detection. This issue is particularly evident when R-peaks have much lower amplitudes than T-waves. Notable examples include ECG recordings from the MIT-AFDB, specifically in records *04015m*, *04043m*, *04908m*, *04936m*, *06426m*, *06453m*, and *07162m*. In this study, we address these challenges by combining parameters, including RR interval variability, QT interval variability, and the spectral peak distribution in the power spectrum. Calculating QT interval variability based on Eq. (8) helps mitigate the impact of noise on QT interval assessments. Furthermore, computing the spectral peak distribution as a parameter independent of ECG waveform detection enhances the classification accuracy, particularly in cases where R-peak detection is unreliable. This combination of parameters improves the overall specificity, sensitivity, and accuracy of the AF detection algorithm, thereby enhancing its general performance in AF identification.

In recent studies, deep learning models used for AF detection have shown good performance. In study [7], the authors used RR intervals combined with CNN and LSTM networks for feature extraction; our model demonstrates improved performance compared to study [7], with both employing the MIT-AFDB as input. In study [8], the authors utilized raw ECG signals from the MIT-AFDB with CNN and LSTM networks, and our proposed model exhibits higher sensitivity and lower specificity. However, the model in the study [8] has not yet been validated on external unseen data. In study [19], the authors employed signal features and RR intervals from five different databases (CPSC2021, MIT-AFDB, LTAF, MITDB, and NSRDB) and achieved generalization on the training database, but did not extend this generalization to other databases. This study demonstrates that the model performs well across different databases, considering factors such as ethnicity, gender, and lifestyle. The training results obtained using the MIT-AFDB with the LightGBM algorithm and the traditional feature engineering methods compared to recent machine learning models demonstrate that the algorithm achieves performance metrics comparable to those models. Tabl. 3 presents the model performance metrics in comparison with recent studies. Comparative results indicate that the model can classify AF and non-AF with high performance metrics relative to previous studies.

Table 2.

Evaluation metrics of the model on the SHDB-AF

Metrics	SHDB-AF
Se	0.9012
Sp	0.9298
Acc	0.9247
PPV	0.7359
FPR	0.0702

In the algorithm, low-complexity algorithms are used. This allows the algorithm to be applied in embedded systems for real-time AF detection. The embedded system records ECG signals from leads where f-waves may appear when the patient is in an AF episode. The signals are digitized and transmitted to handheld devices, such as phones, through wireless channels like Bluetooth. These signals are stored in buffers with a length equal to the analysis window length. The features are calculated based on algorithms. The machine learning model is stored in the operating system and predicts the output based on the input features through sliding windows. The sliding windows are shifted by approximately one cardiac cycle compared to the previous window. The machine learning model can also be applied and embedded in edge devices in embedded systems, helping to reduce the load on servers.

Based on the method described above, the start and end points of an AF episode can be determined in real-time, allowing for the calculation of its duration. In real-time monitoring of patients with AF, the duration and frequency of HRV associated with AF are critical factors in both diagnosis and the formulation of treatment plans. These factors provide insight into the progression of the disease. Based on charts displaying the duration and frequency of arrhythmia, healthcare providers can make informed recommendations tailored to the patient's condition. In practice, when acquiring ECG signals from patients, for example, when using home monitoring devices such as Holter or real-time monitoring devices, in some cases, the signals are significantly affected by noise, causing signal distortion. This leads to an inability to recognize the signal. Some patients, in addition to AF, may also have other arrhythmias, such as AFL. These two types of signals can be confusing and can be

Table 3.

Comparison of the model's performance with other recent deep learning algorithms developed for AF detection

Study	Methods	Evaluation Metrics		
		Sp, %	Se, %	Acc, %
[7]	RR intervals and CNN - LSTM	96.29	98.17	97.10
[8]	ECG beats and CNN - LSTM	99.29	97.87	-
[19]	ECG and RR intervals with Res-CNN and BiLSTM	-	-	98.63
This study	TFE and LightGBM	96.90	98.38	97.48

misclassified. In future studies, we will continue to develop methods for classifying and recognizing AF with background factors like noise and other arrhythmias.

Limitations

The proposed algorithm faces challenges in accurately detecting AF when the signal quality index of the ECG recording is suboptimal. In such cases, essential ECG waveforms, including the QRS complexes, T waves, and P waves, become indistinct, leading to errors in the detection and classification of AF. The model failed to accurately classify an ECG signal exhibiting junctional rhythm, such as, in record *04013m* of MIT-AFDB. Furthermore, in the case of a patient with AFL and variable F-wave morphology, such as transitions from 2:1 to 3:1 conduction block - the algorithm similarly produced a misclassification. This error is evident in record *07910m* of MIT-AFDB.

CONCLUSIONS

The AF detection algorithm enables the classification and identification of AF as well as NSR. The model employs machine learning techniques that leverage features derived from both the HRV, time-domain and frequency-domain and has been validated using verified databases. Its low computational complexity makes it suitable for integration into real-time AF detection and classification systems. The model is well-suited for implementation in automated ECG signal analysis software for Holter monitors or wearable smart devices designed for home use.

REFERENCE

1. Joglar JA, Chung MK, Armbruster AL et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Journals of the American College of Cardiology*. 2024;83(1): 109-279. https://doi.org/10.1016/j.jacc.2023.08.017.
2. Moody GB, Mark RG. A new method for detecting atrial fibrillation using RR intervals. *Computer in Cardiology*. 1983;10: 227-230.
3. Cerutti S, Mainardi LT, Porta A et al. Analysis of the dynamics of RR interval series for the detection of atrial fibrillation episodes. *Computer in Cardiology*. 1997: 77-80. https://doi.org/10.1109/CIC.1997.647834.
4. Horie T, Burioka N, Amisaki T et al. Sample entropy in electrocardiogram during atrial fibrillation. *Yonago Acta Medica*. 2018;61(1): 049-057. https://doi.org/10.33160/yam.2018.03.007.
5. Slocum J, Sahakian A, Swiryn S. Diagnosis of atrial fibrillation from surface electrocardiograms based-on computer-detected atrial activity. *Journal of Electrocardiology*. 1992;25(1): 1-8. https://doi.org/10.1016/0022-0736(92)90123-H.
6. Hirsch G, Jensen SH, Poulsen ES et al. Atrial fibrillation detection using heart rate variability and atrial activity: A hybrid approach. *Expert Systems with Applications*. 2021;169: 114452. https://doi.org/10.1016/j.eswa.2020.114452.
7. Andersen RS, Peimankar A, Puthusserypady S. A deep learning approach for real-time detection of atrial fibrillation. *Expert Systems with Applications*. 2019;115: 465-473. https://doi.org/10.1016/j.eswa.2018.08.011.
8. Petmezas G, Haris K, Stefanopoulos L et al. Automated atrial fibrillation detection using a hybrid CNN-LSTM network on imbalanced ECG datasets. *Biomedical Signal Processing and Control*. 2021;63: 102194. https://doi.org/10.1016/j.bspc.2020.102194.
9. Jun TJ, Nguyen HM, Kang D et al. ECG arrhythmia classification using a 2-D convolutional neural network. *ArXiv preprint arXiv*. 2018;arXiv1804.06812. https://doi.org/10.48550/arXiv.1804.06812.
10. Xu X, Wei S, Ma C et al. Atrial fibrillation beat identification using the combination of modified frequency slice wavelet transform and convolutional neural networks. *Journal of Healthcare Engineering*. 2018;1: 2102918. https://doi.org/10.1155/2018/2102918.
11. Nankani D, Baruah RD. Effective removal of baseline wander from ECG signals: A comparative study, in: *Arup Bhattacharjee, Samir Kr. Borgohain, Badal Soni, Gyanendra Verma, Xiao-Zhi Gao (Eds). Machine Learning, Image Processing, Network Security and Data Sciences: Second International Conference, MIND 2020, Silchar, India, July30-31, 2020, Proceedings, Part II 2, Springer Singapore*. 2020: 310-324.
12. Hargittai S. Savitzky-Golay least-squares polynomial filters in ECG signal processing. *Computer in Cardiology*. 2005: 763-766. https://doi.org/10.1109/CIC.2005.1588216.
13. Pan J, Tompkins WJ. A real-time QRS detection algorithm. *IEEE Transactions on Biomedical Engineering*. 1985;3: 230-236. https://doi.org/10.1109/TBME.1985.325532.
14. Zhang Q, Manriquez AI, Médigue C et al. An algorithm for robust and efficient location of T-wave ends in electrocardiograms. *IEEE Transactions on Biomedical Engineering*. 2006;53(12): 2544-2552. https://doi.org/10.1109/TBME.2006.884644.
15. Goldberger A, Amaral L, Glass L et al. PhysioBank, PhysioToolkit, and PhysioNet: Components of a new research resource for complex physiologic signals. *Circulation [Online]*. 2000;101(23): e215-e220.
16. Tsutsui K, Brimer SB, Ben-Moshe N et al. SHDB-AF: a Japanese Holter ECG database of atrial fibrillation. *ArXiv preprint arXiv*. 2024 Jun;arXiv: 2406.16974. https://doi.org/10.48550/arXiv.2406.16974.
17. LightGBM. Welcome to LightGBM's documentation, 2025. Accessed 5 March 2025 https://lightgbm.readthedocs.io/en/stable/
18. Frazier PI. A tutorial on Bayesian optimization. *ArXiv preprint arXiv*. 2018; arXiv: 1807.02811. https://doi.org/10.48550/arXiv.1807.02811.
19. Zou Y, Yu X, Li S et al. A generalizable and robust deep learning method for atrial fibrillation detection from long-term electrocardiogram. *Biomedical Signal Processing and Control*. 2024;90: 105797. https://doi.org/10.1016/j.bspc.2023.105797.
20. Du X, Rao N, Qian M et al. A novel method for real time atrial fibrillation detection in electrocardiograms using multiple parameters. *Ann. Noninv. Electrocardiol*. 2014;19(3): 217-225. https://doi.org/10.1111/anec.12111.
21. Rodenas J, Garcia M, Alcaraz R et al. Wavelet-entropy automatically detects episodes of atrial fibrillation from single lead electrocardiograms. *Entropy*. 2015;17(9): 6179-6199. https://doi.org/10.3390/e17096179.

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CARDIOMYOPATHY ASSOCIATED WITH VENTRICULAR PRE-EXCITATION OR DISSYNCHRONOUS CARDIOMYOPATHY IN PATIENTS WITH ASYMPTOMATIC AND SYMPTOMATIC WOLFF-PARKINSON-WHITE SYNDROME: PERSONAL EXPERIENCE IN PATIENT MANAGEMENT

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Aim. To study the causal relationship between the functioning of accessory pathway and changes in intraventricular hemodynamics in patients with dissynchronous cardiomyopathy.

Methods. The study included 83 patients with registered preexitation according to ECG data. Patients were divided into study and control group. The study group included 33 patients with diagnosed echocardiographic signs of dissynchronous cardiomyopathy (reduced ejection fraction (EF), increased chamber volume and/or decreased global longitudinal strain (GLS) of the left ventricle (LV)). The control group included 50 patients with Wolff-Parkinson-White syndrome/ phenomenon without dissynchrony.

Results. After radiofrequency ablation (RFA), patients in the study group showed natural normalization of the QRS complex width and LV GLS. The median QRS width before RFA was 110 ms [100; 120] and after RFA 70 ms [60; 80] ($p<0.0001$). The median LV GLS before RFA was -18.2% [-19.1; -17] and after RFA -21.3% [-23; -19.2] ($p<0.0001$). Despite the absence of statistically significant differences in the QRS width in patients in the study and control groups, statistically significant differences in the size and LV EF were revealed. In the study group, the median of end-diastolic volume (EDV) of LV (as a percentage of the parameter from the individual predicted norm) was 112% [102; 123] and EF was 64% [55; 65], and in patients from the control group 102% [97; 112] and 65% [64; 66], respectively. The level of significance of the differences for EDV was $p=0.0183$, for EF it was $p=0.0003$.

Conclusion. Risk factors of dissynchronous cardiomyopathy (age of patients, right-sided localization of accessory pathway, severity of ventricular preexcitation) are probably of important clinical significance, but are not specific.

Key words: Wolff-Parkinson-White syndrome; dyssynchrony; cardiomyopathy; pediatric population; global longitudinal strain

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In patients with Wolff-Parkinson-White (WPW) syndrome, ventricular preexcitation caused by the presence of right-sided accessory atrioventricular pathways (APs) may lead to interventricular septal (IVS) dyssynchrony [1]. Due to dual ventricular activation via both the heart's normal conduction system (atrioventricular node and His bundle) and the APs, there is an electrical and mechanical eccentric activation of the ventricles, with premature contraction of the basal IVS relative to the rest of the myocardium. This results in disrupted synchrony of left ventricular (LV) myocardial contraction [2]. The IVS becomes thinned, resembling an aneurysmal deformity, with segmental dyskinesia and systolic bulging of the septum into the right ventricle (Figure 1). These changes contribute to the development of LV dyssynchrony, similar to what is observed in patients with left bundle branch block or chronic right ventricular pacing [3-5].

According to the literature, the development of cardiomyopathy (CMP) is more commonly observed in WPW patients without episodes of supraventricular tachycardia (SVT), or with only isolated episodes. This distinguishes dyssynchrony-induced CMP from the well-studied tachycardia-induced CMP. As with tachycardia-induced CMP, the dyssynchrony seen in WPW patients is usually reversible following radiofrequency catheter ablation (RFA) of the APs [6, 7].

It is believed that dyssynchrony-induced CMP occurs more frequently in younger patients, in those with

pronounced preexcitation on ECG, and in cases with right septal or right lateral AP localization [6]. However, CMP may also develop in adult patients [6, 8, 9], and left-sided APs do not preclude the onset of CMP [3].

The first report describing the development of dilated cardiomyopathy (DCMP) in children with WPW syndrome and dyssynchrony appeared in 2004. Nonetheless, many unresolved issues remain - particularly concerning the diagnosis of this condition - as there is still no universally accepted definition. Various terms can be found in the literature, such as “preexcitation-induced cardiomyopathy,” “symptomatic manifesting WPW phenomenon,” “ventricular dysfunction secondary to preexcitation,” and “ventricular preexcitation-associated cardiomyopathy” [6-9]. This inconsistency is largely due to the absence of a specific classification for this type of CMP in the current paediatric cardiomyopathy guidelines [10,11]. For the sake of clarity, this article uses the term dyssynchrony-induced cardiomyopathy.

In most of the available publications, the diagnosis of CMP in patients with Wolff-Parkinson-White (WPW) syndrome was established based on transthoracic echocardiography (TTE) findings - specifically, a left ventricular ejection fraction (LVEF) < 55% and a fractional shortening < 25% - in combination with clinical signs of heart failure (HF) [6]. More recently, speckle-tracking echocardiography (STE) has gained popularity for evaluating left ventricular systolic dysfunction. This method has demonstrated higher sensitivity for detecting contractile dysfunction of the LV, including at a “subclinical” level, compared to the traditional LVEF parameter [12,13]. Moreover, ventricular dyssynchrony itself may lead to inaccuracies in LVEF measurement [14].

Dyssynchrony-induced CMP generally has a favourable prognosis and, in most cases, resolves after RFA of the accessory pathway. Cases of reverse LV remodelling have also been described following spontaneous cessation of accessory pathway conduction, most frequently observed in children under 1 year of age [6,7]. The use of antiarrhythmic drugs - such as flecainide, amiodarone, and propafenone - can result in the suppression of conduction through the accessory pathway. However, literature suggests that pharmacological therapy offers only limited effectiveness, and many of these patients ultimately require RFA [6,15-18]. Given the increased risk of complications during RFA in patients weighing less than 15 kg [19], pharmacotherapy may be considered a temporary alternative in small children until they reach an optimal weight and developmental status suitable for safe ablation.

Study aim: To investigate the causal relationship between the function of an accessory pathway and the onset of intraventricular haemodynamic alterations leading to dyssynchrony-induced cardiomyopathy.

METHODS

Patient Characteristics

The study included 83 patients with documented ventricular pre-excitation based on ECG findings. All patients underwent evaluation and treatment between 2015 and 2025, and were divided into two groups: the main group and the control group.

The main group comprised 33 patients with echocardiographic signs of dyssynchrony-induced CMP, including reduced ejection fraction, chamber dilation, and/or reduced global longitudinal strain (GLS)of the left ventricle. Among these patients, 14 (42%) reported episodes of palpitations; however, only 5 (15%) had paroxysmal SVT documented on ECG. The remaining 19 patients (58%) were asymptomatic.

The control group consisted of 50 patients with WPW syndrome/phenomenon without echocardiographic evidence of ventricular dyssynchrony.

Exclusion criteria were as follows:

- Presence of congenital heart defects (CHDs), primary cardiomyopathies (hypertrophic, dilated, or restrictive), or laboratory-confirmed myocarditis;

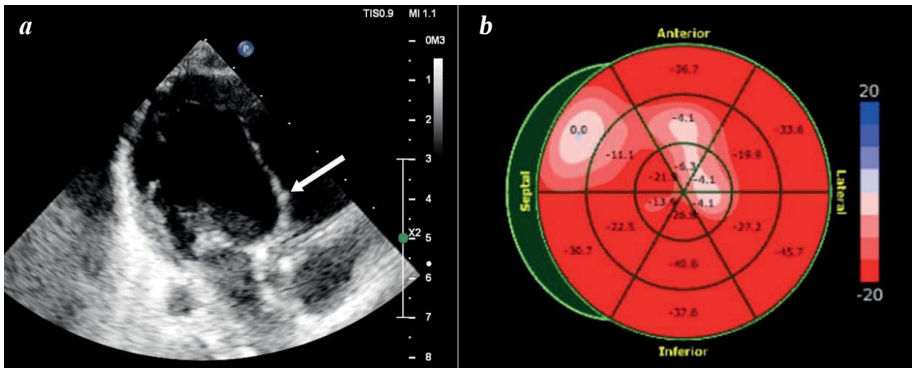

Fig. 1. Echocardiography (a) and speckle-tracking echocardiography (b): aneurysmal bulging of the interventricular septum (indicated by an arrow), accompanied by impaired longitudinal strain in the basal septal segment.

Table 1.

Clinical and Demographic Characteristics of the Patients

	Main group (n=33)	Control group (n=50)	p
Male sex, n (%)	17 (51.5)	28 (56)	0.689
PHA, years (Me [Q1; Q3])	14 [8;16]	11 [8;15]	0.462
PA (RFA), years (Me [Q1; Q3])	13 [8;15]	11 [9;16]	0.462
Manifest preexcitation, n (%)	26 (78.8)	36 (72)	0.487
Intermittent preexcitation, n (%)	7 (21.2)	14 (28)	0.492
Right-sided AP, n (%)	29 (87.8)	31 (62)	0.008
Left-sided AP, n (%)	6 (18.2)	18 (36)	0.074
Nodoventricular tract, n (%)	3 (9.1)	3 (6)	0.595

Note: PHA - primary hospitalisation age; PA - procedure age; RFA - radiofrequency ablation; AP - accessory pathway

• Presence of acute infectious diseases or exacerbations of chronic somatic conditions;
• Presence of arrhythmogenic CMP due to permanent or incessant tachyarrhythmias;
• History of endocrine disorders potentially associated with elevated average heart rate (e.g. hyperthyroidism, Addison's disease, pheochromocytoma, etc.);
• Lack of consent to participate in the study from the patients' parents or from the patients themselves if aged 15 or older.

All patients in both groups underwent RFA of the accessory pathway (AP). The procedure was considered successful if post-procedural ECG showed no signs of pre-excitation and no recurrence of tachycardia was observed during programmed stimulation. No RFA-related complications were reported during the early postoperative period.

Preoperative and postoperative evaluations (conducted 3-5 days after the procedure) included: 12-lead ECG to assess QRS duration; Holter ECG monitoring; TTE to evaluate chamber size, volume, and left ventricular systolic function; Speckle-tracking echocardiography to assess left ventricular GL.

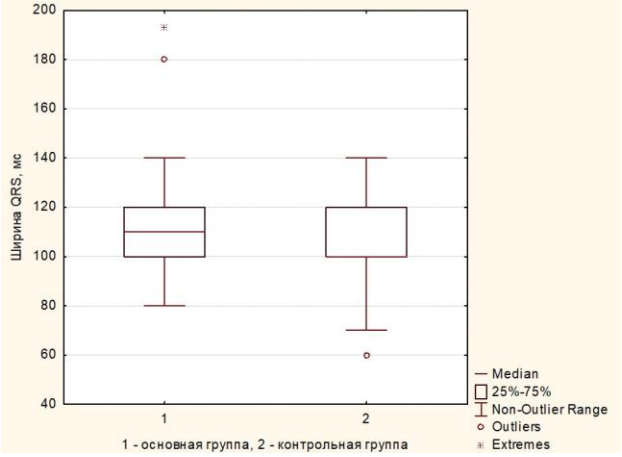

Fig. 2. Box plot of QRS width in the main and control groups before RFA.

Reference ECG parameters were derived from major global population-based paediatric ECG screening studies [20]. Holter ECG results were analysed in accordance with the standardised protocol [21]. Echocardiographic examinations were performed using the Affinity 70cv system (Philips, Netherlands) in line with the recommendations of the American Society of Echocardiography (ASE) [22].

In addition to standard chamber volume measurements, deviations in atrial volumes and left ventricular end-diastolic volume (EDV) from individual anthropometrically predicted normal values were assessed and expressed as percentages. This approach accounted for age and anthropometric heterogeneity among patients and was also suitable for longitudinal assessment of echocardiographic parameters as cardiac dimensions change with age and growth. These calculations were performed automatically using the "Child Heart" software application [23, 24].

LVEFwas measured using the Simpson's method, with values above 62-64%considered normal in children. GLS was analysed using QLAB software in accordance with the guidelines of the European Society of Cardiology (ESC), the European Association of Cardiovascular Imaging (EACVI), and the ASE) [25]. The GLS_Avg values were used in this study. A GLS_Avg threshold of -21% was adopted to indicate impaired systolic function.

Statistical analysis

Statistical analysis was performed using STATISTICA 10 software. Categorical variables are presented as absolute (n) and relative (%) frequencies, n (%). Continuous variables are expressed as medians (Me) and interquartile ranges [Q1; Q3], Me [Q1; Q3]. Differences between two related samples of quantitative variables were assessed using the Wilcoxon signed-rank test. Between-group comparisons of continuous variables were performed using the Mann-Whitney U test. The critical level of statistical significance for hypothesis testing in this study was set at 0.05.

Table 2.

Electrophysiological and Echocardiographic Characteristics of the Patients

	Main group (n=33)		Control group (n=50)	p
	Before RFA	After RFA		
QRS duration, ms (Me [Q1; Q3])	110 [100; 120]	70 [60; 80]	110 [100;120]	p_1<0.0001 p_2=0.6572
LV EDV, ml (Me [Q1; Q3])	78 [58; 88]	78 [54; 86]	72 [50; 90]	p_1=0.1952 p_2=0.5164
LV EDV %, (Me [Q1; Q3])	112 [102; 123]	105 [101; 118]	102 [97; 112]	p_1=0.1153 p_2=0.0183
LV EDI, ml/m² (Me [Q1; Q3])	54.82 [50.5; 60.6]	53.04 [50.5; 57.8]	51.195 [47.76; 55.13]	p_1=0.1624 p_2=0.0081
LV EF (B-mode), % (Me [Q1; Q3])	64 [55; 65]	64 [56; 65]	65 [64; 66]	p_1=0.2636 p_2=0.0003
LV GLS, % (Me [Q1; Q3])	-18.2 [-19.1; -17]	-21.3 [-23; -19.2]	-23.5 [-25.2; -21.9]	p_1<0.0001 p_2<0.0001

Nore: p1 - statistical significance level of the difference in the parameter within the WPW syndrome with dyssynchrony group before and after RFA; p2 - statistical significance level of the difference in the parameter between the main group (before RFA) and the control group; LV EDV - left ventricular end-diastolic volume; LV EDV% - percentage of the parameter relative to the individually predicted norm; LV EDI - left ventricular end-diastolic index; LV EF (B) - left ventricular ejection fraction by Simpson in B-mode; LV GLS - global longitudinal strain of the left ventricle.

RESULTS

The main group included 33 patients, comprising 17 boys (51.5%) and 16 girls (48.5%), aged from 9 months to 17 years. The median age was 14 [8; 16] years. The control group consisted of 50 patients, including 22 boys (44%) and 28 girls (56%), with ages ranging from 4 to 17 years and a median age of 11 [8; 15] years (Table 1). The absence of SVT episodes in some

patients, the rare occurrence of SVT episodes (lasting from several minutes to several hours and occurring from once per month to once per year), as well as normal 24-hour average heart rate values according to Holter ECG monitoring, suggest that preexcitation-related cardiomyopathy differs from tachycardia-induced cardiomyopathy.

In the main group, right-sided AP were significantly more common (p = 0.008). In two patients from the main group (6%) and two from the control group (4%), both right-sided and left-sided APs were identified simultaneously (Table 1).

ECG findings in both the main and control groups showed no significant difference in QRS duration (Figure 2). In the postoperative period, a consistent normalization of QRS duration was observed in patients from the main group. Among these patients, prior to the RFA, left ventricular enlargement was noted in only 5 patients (15.2%), and in 3 of them (9.1%) this was accompanied by atrial enlargement. Reduced LVEF was identified in 9 patients (27.2%).

Echocardiographic data demonstrated that patients with dyssynchrony had larger LV dimensions and lower LVEF compared to the control group (Figure 3). A statistically significant improvement in GLS of the LV was observed in the main group after the procedure. Improvements were also noted in LV contractility parameters (EF in B-mode using Simpson's method) and LV size (end-diastolic volume, EDVi), although these changes did not reach statistical significance (Table 2).

DISCUSSION

Exploring the causal relationship between the functioning of AP and the development of dyssynchrony-related, preexcitation-associated CMPis a relatively new area of research in arrhythmology. Despite an increasing number of recent publications on this topic, many questions remain unanswered.

According to the literature, dyssynchrony-induced CMP is more frequently observed in patients with the WPW phenomenon in the absence of SVT episodes or with only isolated episodes. These findings are consistent with our results, where 79% of patients had no history of tachycardia episodes based on clinical history and Holter ECG data.

Due to the lack of standardised diagnostic criteria and the absence of this condition in current CMP classifications, seven patients in the main group had previously been followed in other institutions under the diagnosis of dilated CMP with a comorbid WPW phenomenon. At the time of admission to our department, the therapy these patients had been receiving (various combinations of ACE inhibitors, beta-blockers, diuretics, mineralocorticoid receptor antagonists, digoxin, and cardiometabolic agents) had no significant clinical effect. In the majority of our patients (n = 24, 72.7%), only subclinical contractile impairment was identified - namely, a reduction in GLS despite preserved EF and normal LV dimensions. This suggests that reliance on the standard echocardiographic protocol alone may lead to underdiagnosis of dyssynchrony and the early manifestations of dyssynchrony-related CMP in children with WPW syndrome.

A.Miyazaki et al. (2022) noted that preexcitation-associated CMP more commonly develops in infants and young children, although cases have also been reported in adults aged 18-59 years [6]. In some infants, rapid progression of ventricular dysfunction occurs shortly after birth [26, 27]. In our study, dyssynchrony and contractile dysfunction were more frequently detected in school-aged children. The current prevalence of dyssynchrony-related CMP among patients with WPW phenomenon/ syndrome remains unknown, partly due to the fact that some patients undergo successful RFA of the APs prior to CMP onset. Others are diagnosed with idiopathic dilated CMP [6, 26], undergo HF therapy, or even end up on the waiting list for heart transplantation or implantation of a ventricular assist device [28, 29].

In line with previous studies [30], right-sided AP localisation was most commonly observed in our cohort. Although left-sided APs can also contribute to CMP development, they appear to do so less frequently.

According to current paediatric guidelines for RFA, in patients with WPW phenomenon and ventricular dysfunction secondary to preexcitation that is refractory to medical therapy, RFA is recommended with a class IIa indication, even for patients weighing less than 15 kg [9]. There are published cases of RFA being performed in infants as young as 2 and 4 months, who presented no episodes of SVT but experienced rapidly progressing LV dysfunction and HFafter birth. In one case, BiVAD implantation was required prior to ablation, but the device was removed 30 days after successful RFA, following the normalisation of echocardiographic parameters [29]. In another case, treatment with amiodarone proved ineffective [31].

In the literature, there are reports on the use of pharmacological therapy (amiodarone, flecainide, propafenone) in WPW syndrome as an alternative management strategy for small children until they reach the physical parameters necessary for performing RFA. In our practice, only one female patient received amiodarone therapy, which had been initiated following an episode of SVT . This patient had previously been observed in other clinics with a primary diagnosis of dilated cardiomyopathy and a concomitant diagnosis of WPW syndrome. Despite the administration of heart failure therapy and amiodarone, a single SVT episode was recorded, and the clinical and instrumental signs

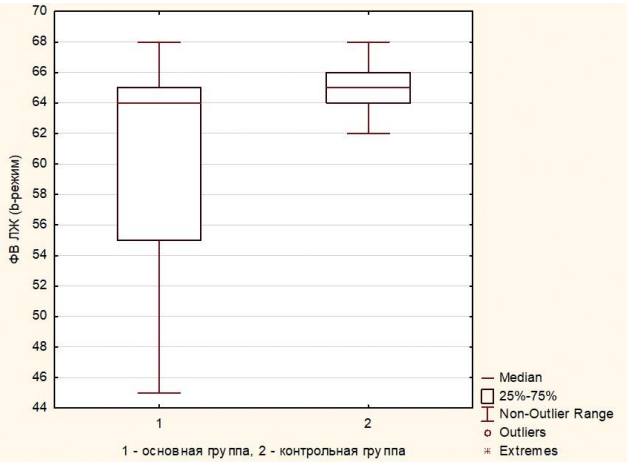

Fig. 3. Box plot of LV ejection fraction (Simpson method, B-mode) in the main and control groups before RFA.

of cardiomyopathy persisted. The patient was first admitted to our department at the age of 9 months, but RFA was only performed at 2 years and 10 months of age, once her body weight reached 16 kg. Complete reverse remodelling of the left ventricle was achieved only two years after RFA [32].

Recovery of cardiac function after RFA of an AP occurs over variable periods, ranging from several days to several years [6]. There are reports of cases in which restoration of LV function required more than three years. The factors that correlate with the duration and degree of functional recovery after RFA include the degree of baseline LV dysfunction and the patient's age (especially over 6 years). Accordingly, children older than 6 years with severe heart failure may experience only partial recovery of LV function following RFA [7, 8].

In our cohort, recovery of LV function was more often observed in the early postoperative period, likely due to the fact that most patients exhibited only subclinical contractile impairment (i.e. abnormal GLS values). Among patients with baseline LV remodelling (LV dilatation and reduced contractility), restoration of function was observed within 6 months to 3 years after RFA (Figure 4). The recovery of LV function after RFA, together with the initial presence of preexcitation on ECG, supports the role of eccentric myocardial activation in the development of dyssynchrony-induced CMP with a dilated phenotype and distinguishes CMP in patients with WPW from idiopathic DCM [6, 7].

The identified risk factors - such as patient age, right-sided AP localisation, and the extent of ventricular preexcitation - are likely to have important clinical implications, although they are not disease-specific. Therefore, identifying new predictors of dyssynchrony-induced CMP in patients with WPW phenomenon is essential for establishing prognosis and guiding treatment strategies.

According to the literature, LV dyssynchrony and abnormal motion of the interventricular septum precede LV remodelling (volume increase, reduced ejection fraction), which may mimic idiopathic DCM [33]. Hence, the prevalence of WPW patients with DCM-like features is lower than that of patients with dyssynchrony alone.

In our study, to assess LV function, we used both the EF and GLS. This approach was chosen because GLS is more reproducible than other strain parameters (such as circumferential or radial strain). Moreover, longitudinal strain analysis via speckle-tracking echocardiography is now widely available and integrated into most modern echocardiographic systems, enabling direct in-device measurement without the need to export images for offline analysis.

The bull's-eye plot (polar map) analysis enables assessment of longitudinal strain in each myocardial segment individually and also provides a global average strain value (GLS_Avg). In patients with WPW syndrome, special attention is paid to the basal and mid-myocardial segments, as APs are typically localised in these regions, and evaluation of apical segments is often limited due to suboptimal tracking.

The colour scale of the polar map ranges from dark red (representing high negative strain or shortening - i.e. normal function) to blue (representing positive strain or stretching - i.e. dysfunction). Affected segments usually show either low negative strain (light pink) or positive strain (blue). G. Abdelmohsen et al. demonstrated that segments adjacent to the AP exhibit an early strain peak, as they receive electrical impulses prematurely, resulting in significant dyssynchrony [3].

The contribution of genetic abnormalities to the development of dyssynchrony-induced CMP remains an open question. The available literature does not provide data on genotype-phenotype correlations in patients with WPW syndrome/phenomenon and dyssynchrony-induced CMP. Only M. Emmel et al. have expressed doubts regarding a genetic aetiology of this condition. The authors based their assumption on the absence of a family history among their patients and the recovery observed following cessation of AP conduction [1].

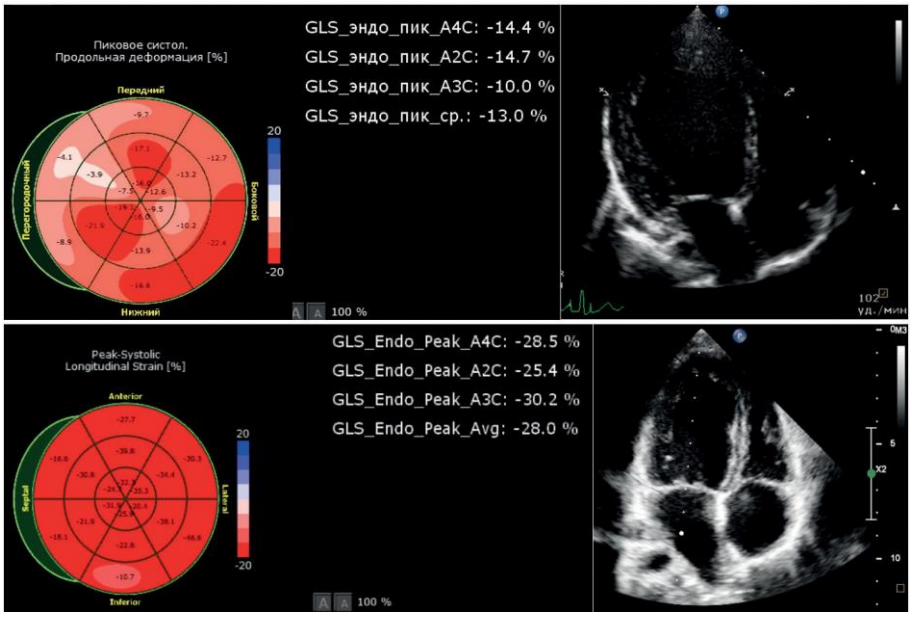

Fig. 4. Examples of echocardiographic measurements: speckle-tracking echocardiography, 18-segment polar map (left), transthoracic echocardiography (right). Dilatation of the left ventricle and reduced longitudinal strain (GLS) in the basal and mid segments of the anteroseptal region in a female patient with a right-sided AP before RFA (aged 9 months) (top). Normalisation of left ventricular size and longitudinal strain 2 years and 9 months after AP RFA (bottom)

However, it is well recognised that the clinical course of diseases may be influenced not only by mutations in specific genes but also by the presence of other genetic factors capable of modifying the effects of such mutations (modifier genes). The influence of genetic modifiers may aggravate disease severity (by increasing susceptibility or worsening progression), or

conversely, they may play a protective role in mitigating clinical manifestations.

CONCLUSION

The presence of pre-excitation and reverse remodelling of the left ventricle following cessation of accessory pathway conduction not only confirms the direct role of eccentric myocardial activation in the development of dyssynchrony-induced cardiomyopathy, but also distinguishes it from dilated CMP. Currently, there is a pressing need to standardise the diagnostic criteria and classification of pre-excitation-induced CMP in patients with the Wolff-Parkinson-White phenomenon.

We believe that in patients with WPW syndrome or phenomenon, echocardiographic assessment should routinely include Speckle-tracking echocardiography, which enables the detection of *subclinical* myocardial contractility impairments that may not be identified using conventional echocardiographic protocols. Early identification of such abnormalities should prompt timely RFA of the AP to prevent the progression of CMP and improve patient prognosis.

REFERENCES

1. Emmel M, Balaji S, Sreeram N. Ventricular preexcitation associated with dilated cardiomyopathy: a causal relationship? *Cardiol Young.* 2004;14(6): 594-599. https://doi:10.1017/S1047951104006031;

2. Mamchur SE, Sizova IN, Shmulevich SA. Evaluation of the intraventricular dyssynchrony in patients with manifesting ventricular preexitation using three-dimensional echocardiography. *Annaly Aritmologii.* 2014;11(1): 31-37 (In Russ.). https://doi.org/10.15275/annaritmol.2014.1.4.

3. Abdelmohsen G, El-Farargy N, Abdelaziz O, et al. Using 2D speckle-tracking echocardiography to localize the accessory pathway and evaluate cardiac function and dyssynchrony in pediatric patients with Wolf-Parkinson-White syndrome. *Eur J Pediatr.* 2023;182(8): 3659-3669. https://doi:10.1007/s00431-023-05040-x;

4. Cheng Z, Liu H, Chen Y, et al. Two-dimensional speckle tracking imaging to assess the hazards of left ventricular function and ventricular wall motion disorders in children with pre-excitation syndrome and the efficacy of radiofrequency ablation treatment. *Eur Rev Med Pharmacol Sci.* 2023;27(17):7882-7890. https://doi:10.26355/eurrev_202309_33545.

5. Mamedova AI, Prihod'ko NA, Lubimceva TA, et al Mechanical dyssynchrony in patients with chronic heart failure and left bundle branch block. *Siberian Journal of Clinical and Experimental Medicine.* 2024;39(3): 72-79 (In Russ.) https://doi.org/10.29001/2073-8552-2024-39-3-72-79.

6. Miyazaki A, Uemura H. Perspective of preexcitation induced cardiomyopathy; early septal contraction, and subsequent rebound stretch. *J Cardiol.* 2022;79(1):30-35. https://doi.10.1016/j.jjcc.2021.08.017.

7. Etheridge SP, Gakenheimer-Smith L, Asaki SY, et al. Asymptomatic Wolff-Parkinson-White Syndrome: An Ounce of Prevention Is Worth the Risk of Cure. *Curr Cardiol Rep.* 2023;25(6): 543-551. https://doi.org/10.1007/s11886-023-01879-6.

8. Savelev AA, Kamenev AV, Berman MV, Medvedev MM. Examination and treatment of a female patient with symptomatic manifesting WPW phenomenon: case report. *Journal of Arrhythmology.* 2022;29(4): e1-e8. (In Russ.). https://doi.org/10.35336/VA-2022-4-11.

9. Philip Saul J, Kanter RJ, et al. PACES/HRS expert consensus statement on the use of catheter ablation in children and patients with congenital heart disease: Developed in partnership with the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American Academy of Pediatrics (AAP), the American Heart Association (AHA), and the Association for European Pediatric and Congenital Cardiology (AEPC). *Heart Rhythm.* 2016;13(6): e251-e289. https://doi.10.1016/j.hrthm.2016.02.009.

10. Pasotti M, The MOGE(S) Classification for a Phenotype-Genotype Nomenclature of Cardiomyopathy: More Questions Than Answers? *J Am Coll Cardiol.* 2014;63(23): 2584. https://doi.org/10.1016/j.jacc.2014.01.078.

11. Lipshultz SE, Law YM, Asante-Korang A, et al. Cardiomyopathy in Children: Classification and Diagnosis: A Scientific Statement From the American Heart Association. *Circulation*. 2019;140(1): e9-e68. https://doi.10.1161/CIR.0000000000000682.

12. Dai C, Guo B, Li WenXiu, et al. The effect of ventricular pre-excitation on ventricular wall motion and left ventricular systolic function. *Europace*. 2018;20(7): 1175-1181. https://doi.10.1093/europace/eux242.

13. Cameli M, Mandoli GE, Sciaccaluga C, Mondillo S. More than 10 years of speckle tracking echocardiography: Still a novel technique or a definite tool for clinical practice? *Echocardiography*. 2019; 36(5): 958-970. https://doi.10.1111/echo.14339.

14. Hayashi T, Ono H, Kaneko Y. Echocardiographic assessment of ventricular contraction and synchrony in children with isolated complete atrioventricular block and epicardial pacing: Implications of interventricular mechanical delay. *Echocardiography*. 2018;35(9):1370-1377. https://doi.10.1111/echo.14035.

15. Suzuki S, Hokosaki T, Iwamoto M. Pharmacologic therapy with flecainide for asymptomatic Wolff-Parkinson-White syndrome in an infant with severe left ventricular dyssynchrony. *Cardiol Young.* 2018;28(7): 970-973. https://doi.10.1017/S1047951118000252.

16. Sekine M, Masutani S, Imamura T, et al. Improvement in Dyssynchrony with Pharmacological Ablation of Right-Sided Accessory Pathway-Induced Cardiomyopathy in Infants. *Int Heart J.* 2019;60(5): 1201-1205. https://doi.org/10.1536/ihj.18-723.

17. Sumitomo NF, Fukushima N, Miura M. Flecainide improves cardiac synchronization in an early infant with Wolff-Parkinson-White syndrome with left ventricular dyssynchrony. *J Cardiol Cases.* 2020;22(1):1-4. https://doi.10.1016/j.jccase.2020.03.004.

18. Chencheng D, Min Z, Wanming S, et al. Case Report: Ventricular preexcitation-induced dilated cardiomyopathy improved by the pharmacologic suppression of ventricular preexcitation in three infants, and literature review. *Front*

Pediatr. 2024; 12. https://doi.10.3389/fped.2024.1302534.
19. Popov SV, Svintsova LI, Kovalev IA, et al. Effectiveness of endocardial radiofrequency ablation of tachyarrhythmias in patients of the first year of life. *Journal of Arrhythmology*. 2012;67(67): 5-10. (In Russ.).
20. Makarov LM, Komolyatov VN, Kiseleva II, et al. Standard ECG parameters in children. Guidelines. PH "Medpractika-M" - Moscow, 2018. (In Russ.).
21. Макаров ЛМ. Холтеровское мониторирование. 2-е изд.- М.: Медпрактика-М, 2003. - 430 с. [Makarov LM. Holter monitoring. 2 nd edition. PH "Medpractika-M" - Moscow. ISBN: 5-901654-55-2. (In Russ.)].
22. Lai WW, Geva T, Shirali GS, et al. Guidelines and standards for performance of a pediatric echocardiogram: a report from the Task Force of the Pediatric Council of the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2006;19(12): 1413-1430. https://doi.org/10.1016/j.echo.2006.09.001.
23. Martsinkevich GI, Sokolov AA. Echocardiography in children: anthropometric and developmental norms. *Rossijskij pediatricheskij zhurnal*. 2012;2: 17-21. (In Russ.).
24. Martsinkevich GI, Sokolov AA. The Child Heart program application for automation of a workplace of the doctor of an echocardiography: the certificate on the state registration of the computer program No. 20096105560, is registered in the Register of the computer programs on January 23, 2009 Moscow 2009; 14.
25. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3): 233-270. https://doi.org/10.1093/ehjci/jev014.
26. Dai CC, Guo BJ, Li WX, et al. Dyssynchronous ventricular contraction in Wolff-Parkinson-White syndrome: a risk factor for the development of dilated cardiomyopathy. *Eur J Pediatr*. 2013;172(11): 1491-1500. https://doi.org/10.1007/s00431-013-2070-z.
27. Fukunaga H, Akimoto K, Furukawa T, et al. Improvement in non-tachycardia-induced cardiac failure after radiofrequency catheter ablation in a child with a right-sided accessory pathway. *Heart Vessels*. 2013;28(6): 802-807. https://doi.org/10.1007/s00380-013-0322-5.
28. Zimmerman FJ, Pahl E, Rocchini AP, et al. High incidence of incessant supraventricular tachycardia in pediatric patients referred for cardiac transplantation. *Pacing clin Electrophysiol*. 1996;19: 663.
29. Kohli U, Pumphrey KL, Ahmed A, Das S. Pre-excitation induced ventricular dysfunction and successful berlin heart explantation after accessory pathway ablation. J *Electrocardiol*. 2018;51(6): 1067-1070. https://doi.10.1016/j.jelectrocard.2018.09.008.
30. Dai C., Guo B., Li WenXiu, et al. The effect of ventricular pre-excitation on ventricular wall motion and left ventricular systolic function. *Europace*. 2018;20(7): 1175-1181.https://doi.org/10.1093/europace/eux242.
31. Kwon EN, Carter KA, Kanter RJ. Radiofrequency catheter ablation for dyssynchrony-induced dilated cardiomyopathy in an infant. *Congenit Heart Dis*. 2014;9(6): E179-E184. https://doi.org/10.1111/chd.12124.
32. Kartofeleva EO, Svintsova LI, Dzhaffarova OYu, Smorgon AV, Krivolapov SN. Effects of accessory pathway catheter ablation on left ventricular function in patients with dyssynchrony-induced cardiomyopathy associated with pre-excitation syndrome. *Journal of Arrhythmology*. 2024;31(2): 5-12. (In Russ.) https://doi.org/10.35336/VA-1314.
33. Plotnikova IV, Svintsova LI, Dzhaffarova OYu, et al. Primary cardiomyopathies in childhood: clinical and diagnostic features (literature review). *Siberian Journal of Clinical and Experimental Medicine*. 2022;37(3): 65-74. (In Russ.) https://doi.org/10.29001/2073-8552-2022-37-3-65-74.

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ARRHYTHMOGENIC CARDIOMYOPATHY IN CHILDREN: GENETIC BASIS AND PHENOTYPIC MANIFESTATIONS. A SINGLE CENTER EXPERIENCE

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Aim. To investigate clinical manifestations, phenotypic variants, genetic features, and outcomes in children with arrhythmogenic cardiomyopathy (ACM).

Methods. The study group consisted of 24 patients (< 18 years of age) with ACM, who were under observation from 2011 to 2024. The median age at ACM diagnosis was 13 years [12-15]. The following data were analyzed: complaints and medical history, laboratory parameters (biochemical markers of inflammation and serum myocardial damage markers, NT-proBNP levels), electrocardiogram, Holter monitoring, echocardiography results, cardiac magnetic resonance imaging, selective coronary angiography, histological and molecular genetic studies. The median follow-up duration for ACM patients was 27 months [16.5-38].

Results. All patients were unrelated probands. All children presented with asymptomatic ventricular arrhythmias (VA) as the initial manifestation of the disease, 23 (95.8%) patients had complaints: palpitations in 21 (87.5%) children, syncope in 14 (58.3%) children, heart failure symptoms in 12 (50.0%), and isolated chest pain in 4 (16.7%) patients. 5 (20.8%) children had a "hot" phase. Analysis of arrhythmic data revealed several features of ACM in childhood: VAs were polymorphic, daily VA density was less than 20% at the time of diagnosis, presence of late ventricular potentials in most patients, and several criteria from the «repolarization abnormalities» group had low informativeness. During follow-up, 9 (37.5%) children had the right-dominant ACM, 7 (29.9%) had ACM with left ventricle involvement, and 8 (33.3%) had biventricular form. Desmosomal mutations were found in 16 children (66.7%), non-desmosomal gene variants in 8 patients (33.3%).

Conclusion. It has been shown that ACM can manifest at an early age and is associated with the development of arrhythmic events and/or severe heart failure. Increasing awareness among physicians about the early onset of ACM is crucial for timely treatment of heart failure, prevention of sudden cardiac death, and family screening.

Key words: arrhythmogenic cardiomyopathy; children; sudden cardiac disease; ventricle arrhythmias; heart failure; genetic cardiomyopathy

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Arrhythmogenic cardiomyopathy (ACM) is a rare hereditary cardiomyopathy characterised by fibro-fatty replacement of the myocardium in both ventricles [1-3]. According to current estimates, the prevalence of ACM among adults ranges from 1 in 1,000 to 1 in 5,000 [4].

Although ACM is relatively uncommon, its clinical significance is extremely high due to the elevated risk of life-threatening complications, including ventricular arrhythmias (VAs), heart failure (HF), and sudden cardiac death (SCD) [1-3]. Published data indicate that ACM accounts for up to 25% of SCD cases among children and adolescents [5].

Despite the severity of the condition, awareness of ACM in paediatric practice remains insufficient, for several reasons.

First, for many years ACM was considered a disease predominantly affecting individuals over the age of 30 to 40 and was thought to be extremely rare in children [1-3,

Table 1.

Data on the age of disease onset in children across different age groups according to the classification of childhood periods by I.M. Vorontsov and A.V. Mazurin (2009)

Age group	Total, n (%)
1-3 y.o.	0
4-6 y.o.	3 (12.5)
7-11 y.o.	6 (25.0)
>12 y.o.	15 (62.5)

6-7]. To date, only a limited number of international studies have described small paediatric cohorts with ACM, and follow-up periods in these studies have generally been short [8-14]. In the Russian literature, we found only isolated case reports of ACM in children [15-17].

Second, prior to 2019, ACM was regarded exclusively as a disorder affecting the right ventricle (RV) [2]. However, subsequent research confirmed that the left ventricle (LV) can also be involved, leading to the recognition of new disease phenotypes, namely the left-dominant and biventricular forms [2, 18-20]. It is important to note that the 2010 Task Force Criteria (TFC 2010) were designed to identify only the classic RV phenotype, which substantially limited the detection of other forms of the disease [18-21]. To address this limitation, the Padua Criteria were introduced in 2020, incorporating diagnostic parameters for evaluating involvement of both ventricles and thereby expanding diagnostic capabilities [18, 22].

Third, existing diagnostic criteria are not adapted for use in children [23-24]. For instance, certain ACM criteria require cardiac magnetic resonance imaging (MRI) with contrast or endomyocardial biopsy, both of which may be difficult to perform in children due to age-related restrictions and the high risk of complications. Additionally, electrocardiographic criteria such as T-wave inversion in the right precordial leads (V1-V3) are considered normal in children younger than 14-16 years, and epsilon waves are rarely seen in paediatric populations, as they tend to appear at later stages of the disease [23-25]. Moreover, the manifestations of ACM, including ventricular arrhythmias and morphofunctional myocardial changes, lack specificity and require careful differential diagnosis with other similar conditions.

Fourth, ACM in children often presents without symptoms or with only minimal clinical signs, making early diagnosis and treatment challenging. In some cases, SCD in children may be the first and only manifestation of the disease [2, 8-9].

Taken together, these factors underscore the need for increased attention to ACM in the paediatric population and the implementation of measures aimed at improving the effectiveness of early diagnosis in order to reduce paediatric mortality. Several key issues remain unresolved, including the natural history of ACM in childhood, the absence of validated paediatric diagnostic criteria, and challenges in differential diagnosis.

The aim of the present study was to describe the clinical features, phenotypic variants, genetic characteristics, and outcomes of ACM in the largest paediatric cohort of patients with this condition in the Russian Federation.

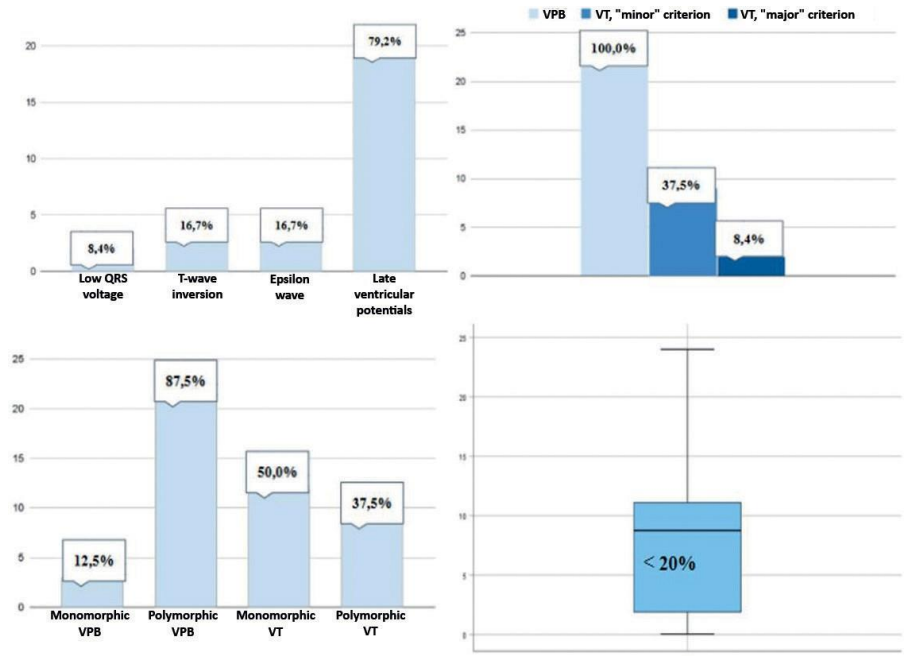

Fig. 1. Electrocardiographic and arrhythmic criteria of arrhythmogenic cardiomyopathy in paediatric patients, where a - repolarisation and depolarisation criteria, b - arrhythmic criteria, c - characteristics of ventricular arrhythmias, d - burden of ventricular arrhythmia at the time of diagnosis., VPB - ventricular premature beats, VT - ventricular tachycardia.

Table 2.

Histological findings in paediatric patients with arrhythmogenic cardiomyopathy

№	Genotype	Conditions	Residual CMCs, %	Fibrosis	Lipomatosis	Inflammation
1	*PKP2/PKP2*	NH	0-30	+	-	+
2	*PKP2*	EMB	37	+	+	-
3	*MYH7*	NH	5-10	+	+	+
4	*FLNC*	EMB	-	+	-	-
5	*SYNE1*	EMB	38	+	-	-
6	*PKP2*	NH	<40	+	+	+

Note: CMCs - cardiomyocytes; NH - native heart; EMB - endomyocardial biopsy.

METHODS

Between 2011 and 2024, 24 patients under the age of 18 were followed as part of the paediatric ACM registry (database registration certificate No. 2022621121, dated 04 May 2022). The diagnosis of ACM was established according to the 2010 Task Force Criteria and the Padua criteria [21-22].

The median age at diagnosis was 13 years (interquartile range, 12 to 15). Among the patients, 15 (62.5%) were boys and 9 (37.5%) were girls. The median follow-up duration was 27 months (interquartile range, 16.5 to 38).

Comprehensive clinical evaluation included history and symptom review, laboratory testing (inflammatory biochemical markers, serum cardiac injury

biomarkers, NT-proBNP), and cardiovascular instrumental assessment. This included electrocardiography (ECG), 24-hour Holter ECG monitoring, transthoracic echocardiography (Echo), contrast-enhanced cardiac MRI, selective coronary angiography (if indicated), histological examination (if indicated), and molecular genetic analysis.

Electrocardiographic and Holter monitoring focused on identifying ACM-specific ECG criteria, including depolarisation and repolarisation abnormalities (age-specific assessment of repolarisation in precordial leads, presence of epsilon wave, QRS voltage in limb leads; low voltage defined as <0.5 mV). In the presence of ventricular rhythm disturbances, their burden, morphology, and origin were assessed.

Echocardiography included measurements of cardiac chamber size, biventricular systolic function, and wall motion abnormalities. Criteria for RV and/or LV dilation or dysfunction were as follows: RV dilation >2 z-score, RV FAC <35%, RVOT PLAX/BSA ≥16 mm/m², RVOT PSAX/BSA ≥18 mm/m²; LV dilation >2 z-score, LVEF <50%, and regional wall motion abnormalities in the LV or RV. RV z-scores were calculated using the Koestenberger calculator, and LV z-scores using the Boston Children's Hospital (BCH) Z-score calculator.

Cardiac MRI with contrast included evaluation of chamber dimensions, biventricular contractility, and myocardial fibrosis. LV dilation and/or dysfunction were defined by end-diastolic volume ≥120 mL/m² and LVEF <50%; RV dysfunction was defined by RVEF <40% and RVEDV ≥120 mL/m² in males or ≥110 mL/m² in females, with associated wall motion abnormalities.

Histological assessment (performed via endomyocardial biopsy of the right heart chambers or native heart tissue after transplantation) included haematoxylin and eosin staining, and Van Gieson staining. Immunohistochemistry using antibodies against CD3, CD68, and HLA-DR was performed to exclude myocarditis. Morphometric analysis of residual cardiomyocyte area and inflammatory infiltrates was conducted using the Image Scope Color M image analyser (Russia).

Genotyping was performed using targeted next-generation sequencing with a panel of 172 genes most commonly associated with cardiomyopathy. Variant pathogenicity was classified according to the 2015 ACMG criteria [26].

Following diagnosis, patients received antiarrhythmic and heart failure therapy, as well as interventional treatments including radiofrequency ablation of arrhythmogenic foci and implantation of implantable cardioverter-defibrillators (ICDs), in accordance with current clinical guidelines at the time of decision-making. In cases of end-stage heart failure, patients were placed on the heart transplant waiting list (HTWL) and subsequently underwent orthotopic heart transplantation using the bicaval technique with cardiopulmonary bypass and pharmacohypothermic cardioplegia.

This study was conducted in accordance with the Declaration of Helsinki (1964) and approved by the Ethics Committee of the Almazov National Medical Research Centre (Protocol No. 01-23, dated 23 January 2023). Written informed consent was obtained from all legal guardians prior to inclusion in the study.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 26 (IBM Corporation, USA). Both parametric and non-parametric methods were applied. Due to the sample size, the Shapiro-Wilk test was used to assess normality of distribution.

Categorical variables were presented as absolute values and percentages. Continuous variables were expressed as mean ± standard deviation for normally distributed data, or as medians with interquartile ranges (50 [25, 75]) for non-normally distributed data. Comparisons between categorical variables were made using Pearson's chi-squared test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant.

Survival analysis without arrhythmic events was performed using the Kaplan-Meier method.

RESULTS

All patients were unrelated probands. A review of the medical records revealed that in all children, the disease onset manifested as asymptomatic ventricular arrhythmias (VAs), with one-third of patients experiencing VA before the age of 12 years (Table 1). In 7 children (29.2%), ventricular rhythm disturbances were detected during routine screening, while in 17 children (70.8%) they were identified by a paediatrician following intercurrent illnesses. The analysis showed that, in most cases, the initial presentation was isolated, infrequent ventricular ectopy (VEs), observed in 22 patients (91.7%). Only 2 patients (8.3%) presented with sustained monomorphic VT as the first manifestation. Clinical symptoms and morphofunctional changes were observed later. The median age at onset of symptoms and morphofunctional abnormalities was 12 years [10.5-15] and 12 years [11-15], respectively. The median age at diagnosis of ACM was 13 years [12-15].

Clinical Picture and Family History

Symptoms were reported in 23 patients (95.8%), while one child (4.2%) remained asymptomatic. Palpitations were reported in 21 children (87.5%), syncope in 14 (58.3%), and HF symptoms, such as dyspnoea

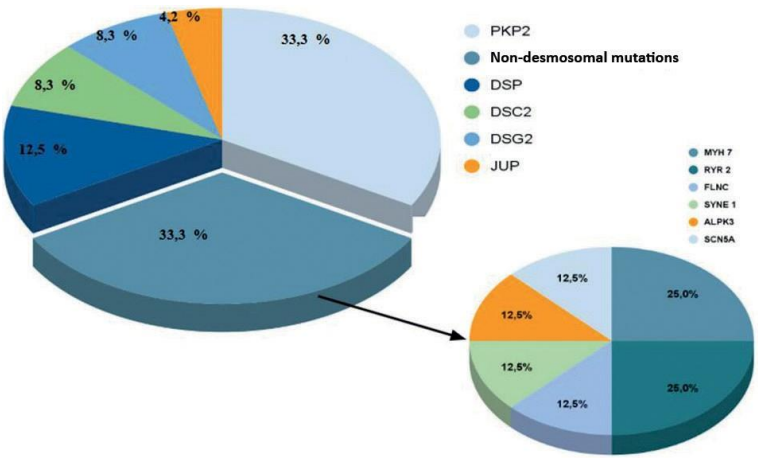

Fig. 2. Genetic spectrum of arrhythmogenic cardiomyopathy in children.

and reduced exercise tolerance, in 12 (50.0%). Chest pain was observed in 4 children (16.7%). Five patients (20.8%) presented with a distinct and rare manifestation - a symptom complex involving chest pain and elevated troponin I, consistent with an "inflammatory phase". This manifestation was independent of ACM phenotype and was more common in patients with desmosomal mutations. Disease progression was noted in all children following this "hot" phase. Myocarditis and acute coronary syndrome were ruled out in all such cases due to similar clinical and laboratory features. None of the patients experienced sudden cardiac arrest. However, 4 patients (16.7%) had a positive family history of SCD, all involving first- or second-degree relatives. No patient had a known family history of ACM.

Table 3.
Outcomes in children with arrhythmogenic cardiomyopathy

Outcomes	Quantity
Syncope, n (%)	14 (58.3)
Sustained VT, n (%)	8 (33.3)
ICD activation, n (%)	5 (20.8)
HTWL / HTx, n (%)	5 (20.8)

Note: VT - ventricular tachycardia; ICD - implantable cardioverter-defibrillator; HTWL - heart transplant waiting list; HTx - heart transplantation.

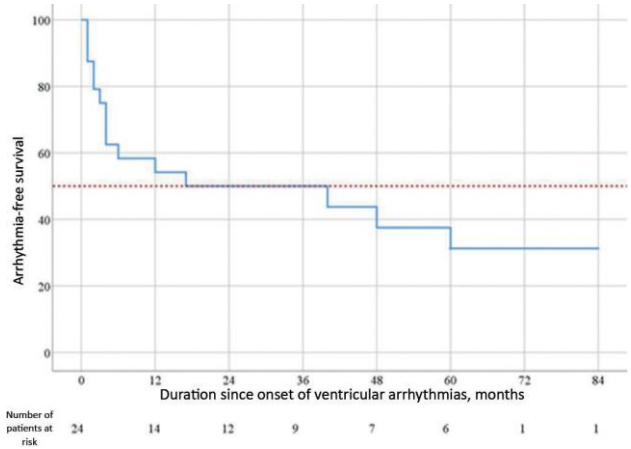

Fig. 3. Kaplan-Meier curve illustrating event-free survival from arrhythmic events.

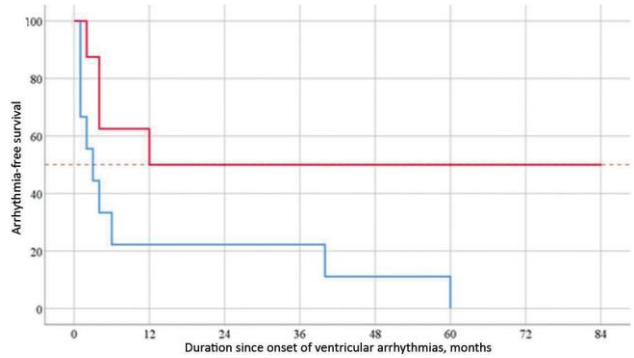

Fig. 4. Kaplan-Meier curves illustrating event-free survival from arrhythmic events: the red line represents patients with a PKP2 mutation, and the blue line represents patients with a non-plakophilin genotype.

Electrocardiographic and Arrhythmic Findings

All paediatric patients had more than 500 VEs per day. Sustained VT was recorded in 16 patients (66.7%). Monomorphic VEs were observed in only 3 patients (12.5%), while the remaining 21 (87.5%) exhibited polymorphic VEs (2 to 4 morphologies). Among those with VT, 12 (50.0%) had monomorphic VT, and 9 (37.5%) had polymorphic VT. Four children (16.7%) presented exclusively with polymorphic VT. Before antiarrhythmic treatment, the median daily burden of ventricular arrhythmias was 8.75% [1.9-11.1], based on 24-hour Holter monitoring.

The "minor" ECG criterion of T-wave inversion in leads V1-V4 with complete right bundle branch block, as defined by the 2010 TFC, was observed in only one patient (4.2%) with RV involvement at age 17. Two children (8.3%) with LV involvement at age 16 had negative T-waves in leads V4-V6, consistent with the "minor" Padua criterion. One patient (4.2%) with biventricular ACM had T-wave inversions in leads V1-V4 at age 17, meeting the "major" Padua criterion. Epsilon waves (a "major" criterion per TFC 2010 and "minor" by Padua) were identified in only 4 patients (16.7%) with biventricular disease, and only in the late stages, after 4 to 5 years of follow-up. Late ventricular potentials were found in 19 cases (79.2%).

In summary, analysis of ECG and arrhythmic data revealed several distinct features of paediatric ACM: polymorphic VAs, VA burden less than 20% at diagnosis, predominance of RV involvement, and low diagnostic value of repolarisation abnormality criteria (Figure 1).

Morphofunctional and Structural Features

At the time of diagnosis, 11 children (45.8%) had a right-dominant form of ACM, 9 (37.5%) had LV involvement, and 4 (16.7%) had biventricular disease. During follow-up, several patients with initial univentricular involvement progressed to a biventricular phenotype. Specifically, 2 patients each (8.3%) with initial LV or RV involvement developed biventricular disease.

Aneurysm formation was documented in 7 children (29.2%) during follow-up: 5 (20.8%) had RV aneurysms, 1 (4.2%) had an LV aneurysm, and 2 (8.3%) developed aneurysms in both ventricles.

Myocardial fibrosis, characteristic of the disease, was detected in all 22 patients (91.7%) who underwent contrast-enhanced cardiac MRI. Two children (8.3%) did not undergo MRI due to severe arrhythmias.

Histological Analysis

Histological evaluation was performed in 6 patients (25.0%, Table 2). Three patients (12.5%) underwent histological analysis of the explanted native heart after heart transplantation (HTx), and three others had endomyocardial biopsy during radiofrequency ablation procedures. In all cases, ACM diagnosis was confirmed by the presence of fibrotic myocardial changes (a "major" Padua criterion), and cardiomyocyte residual area was below 40% (a "major" criterion per TFC 2010). In 3 cases (12.5%), lipomatous changes were also found, consistent with the disease's typical features.

Genetic Analysis and Family Screening

Desmosomal mutations were identified in 16 children (66.7%), including PKP2 variants in 8, DSP in 3, DSC2 and DSG2 in 2 each, and JUP in 1 patient. Three patients

had compound heterozygosity involving two PKP2 variants, and one child had two DSP variants, consistent with Carvajal syndrome. Non-desmosomal gene variants were detected in 8 patients (33.3%), including FLNC, MYH7/FKTN, RYR2, ALPK3, SCN5A, and SYNE1 (Figure 2). Two patients (8.3%) had digenic mutations - MYH7/FKTN and PKP2/CDH2. Homozygous mutations in DSC2 were found in 2 patients (8.3%), while all other variants were heterozygous. Non-desmosomal mutations were significantly more common in LV-dominant forms of ACM ($p<0.05$).

All families were offered cardiovascular and genetic cascade screening. Cardiological screening was completed for all families, and all parents and siblings were asymptomatic at the time. Genetic testing was successful in 3 families with early disease onset, severe phenotype, and compound genotypes. In these three families, one or both parents carried a single PKP2 variant, although they remained asymptomatic at the time of clinical evaluation.

Disease Course and Outcomes

The median follow-up duration was 27 months [16.5-38]. Adverse outcomes included arrhythmic events (syncope, sustained VT, implantable cardioverter-defibrillator [ICD] discharges) and inclusion on the HTx waiting list (Table 3).

Arrhythmic events occurred in 15 children (62.5%). Importantly, there were no cases of SCD or death. ICD shocks were recorded in 5 patients (20.8%), with multiple shocks (3 to 8 discharges) in 4 of these cases.

Kaplan-Meier analysis demonstrated that the median time to the first arrhythmic event was 17 months from VA onset (95% CI: 0.00-63.64). Arrhythmic events were defined as the first occurrence of sustained VT/ventricular fibrillation, syncope, or ICD discharge following VA onset. Hence, by 17 months from disease onset, at least 50% of children with ACM experienced an arrhythmic event (Figure 3). The median time to the arrhythmic event in our cohort was 4 months [2-12].

Since PKP2 mutations were the most frequent in this cohort, survival without arrhythmic events was analysed in patients with PKP2 variants versus other genotypes. The difference in arrhythmia-free survival based on genotype was statistically significant ($p=0.025$). The median time to arrhythmic event was not reached in the PKP2 group, whereas in patients with other mutations, it was 3.0 months (95% CI: 0.078-5.92) (Figure 4).

Five children (20.8%) had severe chronic HF. Their genotypes were characterised as follows: 3 (12.5%) had pathogenic compound heterozygous desmosomal mutations, 2 (8.3%) had digenic mutations involving both desmosomal and non-desmosomal genes, and 1 (4.2%) had a homozygous mutation (Table 4).

Clinical manifestations of NYHA class III-IV HF developed within 12 months [12-26] of follow-up. The median age at inclusion on the HTx waiting list was 12 years [11-14]. At the time of writing, 3 children (12.5%) had undergone heart transplantation.

DISCUSSION

This study presents the clinical and genetic characteristics of a paediatric cohort diagnosed with ACM. Historically, ACM was considered a condition primarily affecting adults, with peak incidence reported in the third and fourth decades of life [1-3, 6-7, 18-20]. However, contemporary evidence indicates that disease onset may occur much earlier, including in infancy [27-28]. In our study, three children (12.5%) presented with initial manifestations in the form of VAs as early as four years of age. One of these patients had Carvajal syndrome, which is known for early phenotypic expression. One-third of the children exhibited disease onset before the age of 12 years.

Recent studies demonstrate that the risk of life-threatening VAs, sudden SCD, and advanced heart failure is higher in paediatric ACM than in adult cases. L. Daliento reported a higher incidence of SCD among young patients compared to adults with ACM [8]. Similarly, A. Te Riele found SCD to be a hallmark complication of paediatric forms of ACM [10]. Literature data also indicate that end-stage HF requiring heart transplantation (HTx) is increasingly observed in ACM, including in paediatric patients. According to K. Chen, the frequency of HTx and HF-related mortality in ACM ranges from 2% to 22% [29].

In our cohort, arrhythmic events were recorded in 50% of patients, with a median time from VA onset to the first event of 4 months. Kaplan-Meier analysis revealed a median time to arrhythmic event of 17 months from VA onset (95% CI: 0.00-63.64). Advanced HF (NYHA class III-IV) was diagnosed in 20% of patients.

These findings underscore the critical importance of early ACM diagnosis in paediatric practice, primarily to prevent SCD and to ensure timely inclusion on the heart transplant waiting list. Nevertheless, diagnosing ACM in children remains particularly challenging. In early stages, the disease may be asymptomatic, making detection during routine evaluations difficult [29, 30]. In our study, 100% of patients presented with infrequent asymptomatic VAs as

Table 4.

Phenotype-genotype characteristics in patients with severe heart failure due to arrhythmogenic cardiomyopathy

№	1	2	3	4	5
Sex	f	f	m	f	m
Age at HTx / inclusion on HTWL, years	11	16	8	12	16
Primary involvement	RV	RV	LV	RV	RV
Phenotype	BiV	BiV	BiV	BiV	BiV
Genotype	PKP2/ CDH2 L/P/VUS	MYH7/ FKTN P| VUS	DSP/ DSP P/LP	PKP2/ PKP2 P/LP	DSC2 L/P
HTx	+	+	HTWL	+	HTWL

Note: BiV - biventricular; LV - left ventricle; HTWL - heart transplant waiting list; RV - right ventricle; HTx - heart transplantation.

the initial manifestation, discovered incidentally. Similar findings were reported by M. Cicenia et al. in an Italian paediatric cohort, describing an asymptomatic disease onset with minor ventricular rhythm disturbances identified by chance [13].

One possible reason for delayed ACM diagnosis may be that VAs go unnoticed due to their rarity and lack of subjective symptoms. Furthermore, clinical manifestations of ACM may resemble other cardiovascular disorders [2], complicating differential diagnosis. This is particularly true for recurrent episodes of substernal chest pain accompanied by elevated troponin I, referred to as the "hot phase" [28, 32]. Unlike in adults, this symptom complex is more frequently observed in children and may constitute the first disease manifestation, requiring careful differentiation from acute coronary syndrome and acute myocarditis [28, 32].

According to published data, paediatric ACM is often diagnosed through cascade family screening of adult relatives with the condition [8-13]. The absence of a positive family history may hinder diagnostic evaluation in children. In our cohort, only 4 patients (16.7%) had a family history of sudden cardiac death (SCD), and none had relatives with a confirmed ACM diagnosis. This is not always attributable to de novo mutations; it may also result from late phenotypic expression among carriers, diagnostic limitations in previous generations, or reduced gene penetrance [33-35].

Electrocardiographic (ECG) markers of repolarisation and depolarisation abnormalities often precede morphological myocardial remodelling and can serve as early indicators of ACM [2]. In our study, T-wave inversions (repolarisation abnormalities) had diagnostic value in only 4 of 24 cases (16.7%) due to age-related limitations. Epsilon waves were detected at a similar frequency (16.7%). These findings are consistent with international studies that demonstrate the low diagnostic yield of repolarisation abnormalities and epsilon waves in paediatric populations [23-25, 36].

Our findings confirm the high prevalence of arrhythmic manifestations in paediatric ACM, with all patients exhibiting VAs However, only 2 patients (8.3%) met the "major" arrhythmic criterion of the 2010 TFC, which includes sustained ventricular tachycardia with left bundle branch block morphology and superior axis. The remainder presented with VTs of different morphologies, including polymorphic forms, at disease onset. These data highlight the potential limitations of applying arrhythmic criteria to paediatric populations and support the hypothesis by R. Shriprasad et al. that any VT in children may serve as a marker of ACM [37].

Another major diagnostic challenge in paediatric ACM lies in identifying lv involvement in left-dominant and biventricular forms. In our cohort, more than half of the patients exhibited non-classical phenotypes (left-dominant or biventricular), which initially led to misdiagnoses such as dilated cardiomyopathy, tachycardia-induced cardiomyopathy, or myocarditis. Cardiac MRI with contrast, genetic testing, and in some cases, histological examination played critical roles in confirming these "non-classical" ACM phenotypes [11].

All patients in our cohort had pathogenic variants. In 66.7% (16/24), desmosomal mutations were identified, most frequently involving PKP2, followed by DSP, DSG2, DSC2, and JUP (associated with Carvajal syndrome) [15]. Among non-desmosomal genes, mutations were found in FLNC, RYR2, MYH7, SCN5A, ALPK3, and SYNE1. Notably, we observed a clear association between non-desmosomal mutations and LV involvement. Additionally, some patients carried pathogenic variants in genes associated with other hereditary cardiac disorders, such as MYH7, SCN5A, FLNC, and RYR2 [2]. This suggests possible differences in the underlying molecular mechanisms and emphasises the importance of long-term follow-up to better understand phenotypic expression.

Rare ACM genotypes were identified in our cohort, including MYH7 and ALPK3 mutations associated with biventricular phenotypes. Only a few such cases have been described in the literature, and they appear to carry a high risk of arrhythmic complications [29, 38-39]. One patient harboured a SYNE1 mutation, which had not previously been reported as causative of ACM. However, the phenotypic profile, including histological findings, met ACM diagnostic criteria.

Genetic testing has both diagnostic and prognostic value. Patients with advanced heart failure (HF) frequently carried either compound heterozygous or homozygous mutations, or digenic mutations. These findings align with existing literature. Furthermore, we observed that patients with PKP2 variants experienced significantly fewer arrhythmic events (syncope, sustained VT/ventricular fibrillation, ICD activation) compared with children with mutations in other genes. These results support international evidence indicating a higher arrhythmogenic risk associated with ALPK3, DSP, and FLNC mutations [2, 38-39].

In summary, increased clinical suspicion of ACM, comprehensive cardiovascular assessment including contrast-enhanced cardiac MRI and genetic screening, and close longitudinal follow-up are essential for early detection of the disease, even in the presence of minimal symptoms. These measures facilitate risk stratification for life-threatening complications and allow for the development of personalised treatment and monitoring strategies.

Study limitations

This study has several limitations. First, the small cohort size reflects the rarity of ACM in the paediatric population. Second, incomplete clinical data may have impacted diagnostic verification; for instance, contrast-enhanced cardiac MRI was performed in 91.7% of patients (22 out of 24), while histological confirmation was available in only 25% (6 out of 24), which could influence the accuracy of diagnosis in certain cases. Another important limitation is the lack of parental genetic testing in most families. This precluded determination of whether the identified mutations were de novo or inherited, thus limiting the assessment of gene penetrance and familial risk.

CONCLUSION

This study presents the first comprehensive description of a paediatric cohort of patients with ACM in Russian clinical practice. Our findings contribute to a broader understanding of the clinical course and outcomes of ACM in

children. It has been demonstrated that ACM may present at an early age and is associated with the development of arrhythmic events and/or severe heart failure. Enhancing clinician awareness of early-onset ACM, as well as implementing modern diagnostic approaches, is essential for the timely management of heart failure, prevention of sudden cardiac death, and initiation of familial screening - measures that may significantly improve clinical outcomes.

REFERENCES

1. Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med.* 2017;376: 61-72. https://doi.org/10.1056/NEJMra1509267.
2. Towbin JA, McKenna WJ, Abrams DJ, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm.* 2019;16(11): e301-e372. https://doi.org/10.1016/j.hrthm.2019.05.007.
3. Marrone D, Zampieri F, Basso C, et al. History of the discovery of Arrhythmogenic Cardiomyopathy. *Eur. Heart J.* 2019;40: 1100-1104. https://doi.org/10.1093/eurheartj/ehz145.
4. McKenna WJ, Maron BJ, Thiene G. Classification, Epidemiology, and Global Burden of Cardiomyopathies. *Circ Res.* 2017;121(7): 722-730. https://doi.org/10.1161/CIRCRESAHA.117.309711.
5. Thiene G, Nava A, Corrado D et al. Right ventricular cardiomyopathy and sudden death in young people. *N Engl J Med.* 1988;318(3): 129-33. https://doi.org/10.1056/NEJM198801213180301.
6. Te Riele AS, James CA, Groeneweg JA, et al. Approach to family screening in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Eur Heart J.* 2016;37(9): 755-63. https://doi.org/10.1093/eurheartj/ehv387.
7. Te Riele AS, James CA, Calkins H, et al. Arrhythmogenic Right Ventricular Cardiomyopathy in Pediatric Patients: An Important but Underrecognized Clinical Entity. *Front Pediatr.* 2021;9: 750916. https://doi.org/10.3389/fped.2021.750916.
8. Daliento L, Turrini P, Nava A, et al. Arrhythmogenic right ventricular cardiomyopathy in young versus adult patients: similarities and differences. *J Am Coll Cardiol.* 1995;25(3): 655-64. https://doi.org/10.1016/0735-1097(94)00433-Q.
9. Bauce B, Rampazzo A, Basso C, et al. Clinical phenotype and diagnosis of arrhythmogenic right ventricular cardiomyopathy in pediatric patients carrying desmosomal gene mutations. *Heart Rhythm.* 2011;8(11): 1686-95. https://doi.org/10.1016/j.hrthm.2011.06.026.
10. Te Riele AS, James CA, Sawant AC, et al. Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy in the Pediatric Population: Clinical Characterization and Comparison With Adult-Onset Disease. *JACC Clin Electrophysiol.* 2015;1(6): 551-560. https://doi.org/10.1016/j.jacep.2015.08.004.
11. Etoom Y, Govindapillai S, Hamilton R, et al. Importance of CMR within the Task Force Criteria for the diagnosis of ARVC in children and adolescents. *J Am Coll Cardiol.* 2015;65(10): 987-95. https://doi.org/10.1016/j.jacc.2014.12.041.
12. DeWitt ES, Chandler SF, Hylind RJ, et al. Phenotypic Manifestations of Arrhythmogenic Cardiomyopathy in Children and Adolescents. *J Am Coll Cardiol.* 2019;74(3): 346-358. https://doi.org/10.1016/j.jacc.2019.05.022.
13. Cicenia M, Cantarutti N, Adorisio R, et al. Arrhythmogenic cardiomyopathy in children according to "Padua criteria": Single pediatric center experience. *Int J Cardiol.* 2022;350: 83-89. https://doi.org/10.1016/j.ijcard.2022.01.008.
14. Surget E, Maltret A, Raimondi F, et al. Clinical Presentation and Heart Failure in Children With Arrhythmogenic Cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2022;15(2): e010346. https://doi.org/10.1161/CIRCEP.121.010346.
15. Fetisova SG, Sivushchina ES, Kofeynikova OA, et al. Rare form of arrhythmogenic cardiomyopathy in a 5-year-old child. *Russian Journal for Personalized Medicine.* 2022;2(2): 104-112. (In Russ.). https://doi.org/10.18705/2782-3806-2022-2-2-104-112.
16. Kofeynikova OA, Alekseeva DYu, Fetisova SG, et al. Clinical characteristics of the "hot phase" of arrhythmogenic cardiomyopathy in a pediatric patient. *Journal of Arrhythmology*. 2023;30(2): e6-e11. (In Russ). https://doi.org/10.35336/VA-2023-2-11.
17. Parfenenko MA, Radzhabova GM, Tsybulskaya DS, et al. Combination of arrythmogenic right ventricular cardiomyopathy with Loeys-Dietz syndrome: case report. *Journal of Arrhythmology*. 2024;31(2):54-61. (In Russ). https://doi.org/10.35336/VA-1206.
18. Comments on the 2023 ESC guidelines for the management of cardiomyopathies. *Revista Española de Cardiología (English Edition).* 2023; https://doi.org/10.1016/j.rec.2023.11.008.
19. Corrado D, Anastasakis A, Basso C, et al. Proposed diagnostic criteria for arrhythmogenic cardiomyopathy: European Task Force consensus report. *Int J Cardiol.* 2024;395: 131447. https://doi.org/10.1016/j.ijcard.2023.131447.
20. Corrado D, Basso C. Arrhythmogenic left ventricular cardiomyopathy. *Heart*. 2021: heartjnl-2020-316944. https://doi.org/10.1136/heartjnl-2020-316944.
21. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation.* 2010;121: 1533-1541.
22. Corrado D, Perazzolo Marra M, Zorzi A, Beffagna G, Cipriani A, Lazzari MD, et al. Diagnosis of arrhythmogenic cardiomyopathy: the Padua criteria. *Int J Cardiol.* 2020;319: 106-114.
23. Alekseeva DYu, Kofeynikova OA, Marapov DI, Vasichkina ES. Electrocardiographic parameters and features of ventricular arrhythmias in various arrhythmogenic cardiomyopathy forms in the pediatric population: a systematic review and meta-analysis. *Russian Journal of Cardiology*. 2022;27(3S): 5147. (In Russ) https://doi.org/10.15829/1560-4071-2022-5147.
24. Deshpande SR, Herman HK, Quigley PC, et al. Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D): Review of 16 Pediatric Cases and a Proposal of Modified Pediatric Criteria. *Pediatr Cardiol.* 2016;37: 646-655.

25. Makarov L.M. Normative parameters of ECG in children. Methodical recommendations. ID MEDPRAKTIKA-M, Moscow, 2018. ISBN: 978-5-98803-384-4 (In Russ).
26. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17: 405-24. https://doi.org/10.1038/gim.2015.30
27. Norgett EE, Hatsell SJ, Carvajal-Huerta L, et al. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. *Hum Mol Genet.* 2020;9: 2761-2766.
28. Martins D, Ovaert C, Khraiche D, et.al. Myocardial Inflammation Detected by Cardiac MRI in Arrhythmogenic Right Ventricular Cardiomyopathy: A Paediatric Case Series. *Int J Cardiol.* 2018;271: 81-86. https://doi.org/10.1016/j.ijcard.2018.05.116.
29. Chen K, Rao M, Guo G, et al. Sarcomere variants in arrhythmogenic cardiomyopathy: Pathogenic factor or bystander? *Gene*. 2019;687: 82-89. https://doi.org/10.1016/j.gene.2018.10.080.
30. Pilmer CM, Kirsh JA, Hildebrandt D, et al. Sudden cardiac death in children and adolescents between 1 and 19 years of age. *Heart Rhythm.* 2014;11(2): 239-45. https://doi.org/10.1016/j.hrthm.2013.11.006.
31. Cicenia M, Drago F. Arrhythmogenic Cardiomyopathy: Diagnosis, Evolution, Risk Stratification and Pediatric Population - Where Are We? *J Cardiovasc Dev Dis.* 2022;9: 98. https://doi.org/10.3390/jcdd9040098.
32. Bariani R, Cipriani A, Rizzo S, et al. 'Hot phase' clinical presentation in arrhythmogenic cardiomyopathy. *Europace*. 2021;23(6): 907-917. https://doi.org/10.1093/EUROPACE/EUAA343.
33. Haggerty CM, James CA, Calkins H, et al. Electronic health record phenotype in subjects with genetic variants associated with arrhythmogenic right ventricular cardiomyopathy: a study of 30,716 subjects with exome sequencing. *Genet Med.* 2017;19(11): 1245-52. 10.1038/gim.2017.40.
34. Headrick AT, Rosenfeld JA, Yang Y, et al. Incidentally identified genetic variants in arrhythmogenic right ventricular cardiomyopathy-associated genes among children undergoing exome sequencing reflect healthy population variation. *Mol Genet Genomic Med*. 2019;7(6): e593. https://doi.org/10.1002/mgg3.
35. Hylind RJ, Pereira AC, Quiat D, et al. Population prevalence of premature truncating variants in plakophilin-2 and association with arrhythmogenic right ventricular cardiomyopathy: a UK biobank analysis. *Circ Genom Precis Med.* 2022;15(3): e003507. https://doi.org/10.1161/CIRCGEN.121.003507.
36. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation.* 2010;121: 1533-1541.
37. Shriprasad R, Deshpande SR, Herman HK, et al. Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D): review of 16 pediatric cases and a proposal of modified pediatric criteria. *Pediatr Cardiol.* 2016;37(4): 646-55. https://doi.org/10.1007/s00246-015-1327-x.
38. Ferradini V, Parca L, Martino A, et. Al. Variants in *MHY7* Gene Cause Arrhythmogenic Cardiomyopathy. *Genes (Basel).* 202;12(6): 793. https://doi.org/10.3390/genes12060793.
39. Herkert JC, Verhagen JMA, Yotti R et al. Expanding the clinical and genetic spectrum of ALPK3 variants: Phenotypes identified in pediatric cardiomyopathy patients and adults with heterozygous variants. *American Heart Journal.* 2020;225: 108-119. https://doi.org/10.1016/j.ahj.2020.03.023.

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CARDIAC RESYNCHRONIZATION THERAPY: TOWARDS PERSONALIZED DEVICE SELECTION. RESULTS OF A TWO-YEAR PROSPECTIVE STUDY

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Aim. To conduct a comparative analysis of clinical, instrumental, and laboratory diagnostic methods and to identify factors determining the likelihood of sustained paroxysmal ventricular tachyarrhythmias (VT) in patients with indications for cardiac resynchronization therapy (CRT).

Methods. The study included 124 patients with chronic heart failure (CHF) and an implanted CRT-D system. The median age was 58 (52-63) years. Patients were followed for 24 months. Clinical and demographic characteristics, electrocardiographic data, speckle-tracking echocardiographic parameters, and blood biomarker levels were assessed. The primary endpoint was the occurrence of sustained VT episodes recorded by the implanted device. A multivariate logistic regression model was developed to predict the two-year probability of VT occurrence.

Results. During the follow-up period, 29 patients (23.3%) experienced episodes of sustained VT. Univariate analysis identified seven candidate predictors with the highest potential for reaching the endpoint. These included: clinical factors (presence of coronary artery disease and atrial fibrillation); ECG parameters (modified QRS index >0.6, presence of left bundle branch block (LBBB) according to Strauss criteria); echocardiographic findings (global longitudinal strain ≥ -6%, mitral regurgitation of grade 2 or higher); and laboratory markers (galectin-3 ≥ 12 ng/mL). Based on these variables, a predictive model was developed using binary logistic regression to estimate the two-year risk of VT in patients with CRT indications. The Strauss LBBB criterion, although statistically significant in univariate analysis, was not included in the final model. At a regression function cut-off value of 0.228, the model demonstrated a diagnostic accuracy of 73.6% (sensitivity - 86.2%, specificity - 69.6%). The area under the ROC curve was 0.779, which, according to expert grading, indicates good model performance.

Conclusion. The study identified several independent predictors of sudden cardiac death risk in patients with implanted CRT-D devices and enabled the construction of a multifactorial prognostic model. The findings suggest the potential for developing a personalized algorithm for device selection.

Key words: chronic heart failure; cardiac resynchronization therapy; ventricular tachyarrhythmias; risk stratification

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Despite significant advances in pharmacological therapy and implantable device technologies, chronic heart failure (CHF) remains one of the leading causes of mortality worldwide [1]. One of the most effective treatment strategies for patients with CHF, reduced left ventricular ejection fraction (LVEF), and signs of electrical dyssynchrony is cardiac resynchronisation therapy (CRT). CRT improves ventricular contraction synchrony, promotes reverse myocardial remodelling, alleviates symptoms, and increases survival rates [2, 3].

Currently, two types of devices are used in clinical practice to deliver CRT: CRT-P (CRT pacemaker without defibrillation function); CRT-D (CRT defibrillator with additional antiarrhythmic capabilities).

CRT-D devices also provide protection against sudden cardiac death (SCD) by delivering high-energy defibrillation or anti-tachycardia pacing (ATP) in the event of life-threatening ventricular tachyarrhythmias (VT) [4].

Although CRT-D appears to offer clear advantages in SCD prevention, the choice between CRT-P and CRT-D remains the subject of ongoing clinical and ethical debate. This is due to concerns regarding: increased risk of infectious complications [5], inappropriate shocks or unneces-

sary electrical therapy, the need for more frequent generator replacements in CRT-D patients [5, 6].

According to the Russian clinical guidelines for the management of CHF, the decision to implant either device type should be based not only on the risk of arrhythmic events and the presence of VT substrate but also on: the individual patient's clinical profile, prognosis and expected survival, quality of life, economic and social factors [7].

However, a specific algorithm for device selection is not provided. In the Russian Federation, CRT-P implantation can be performed at any medical facility operating under the national compulsory health insurance system, making this form of care more accessible to the population.

Large clinical trials such as COMPANION, MADIT-CRT, and others have demonstrated the overall efficacy of CRT. Nevertheless, evidence comparing the relative benefits of CRT-P versus CRT-D in specific patient subgroups remains inconsistent [8, 9]. Moreover, the patient's clinical profile may change over time, underscoring the

Table 1.

Clinical and Demographic Characteristics of Patients

	All patients (n=124)	Patients with VT (n=29)	Patients without VT (n=95)	p
Age, years	58 (52-63)	58 (50.5-63.5)	58 (53-63)	0.820
Male sex, n (%)	94 (76)	23 (79.3)	71 (74.7)	0.615
Body mass index, kg/m^2	29.7 (25.6-32.4)	29.1 (24.1-32.8)	29.8 (26-32.4)	0.508
Coronary artery disease, n (%)	44 (35.4)	14 (48.2)	30 (31.5)	0.1
Post-infarction cardiosclerosis, n (%)	26 (20.9)	9 (31)	17 (17.9)	0.128
Coronary artery lesions, n (%)	67 (54)	15 (51.7)	52 (54.7)	0.776
Arterial hypertension, n (%)	69 (55.6)	18 (62)	51 (53.6)	0.426
Diabetes mellitus, n (%)	27 (21.7)	7 (24.1)	20 (21)	0.725
Obesity, n (%)	55 (44.3)	12(41.3)	43(45.2)	
Stroke history, n (%)	5 (4)	1(3.4)	4(4.2)	0.855
Chronic kidney disease, n (%)	49 (40.8)	13(46.4)	36 (39.1)	0.491
Atrial fibrillation (any form), n (%)	40 (32.2)	15(51.7)	25 (26.3)	0.01
AF (paroxysmal/persistent), n (%)	31 (25)	10 (34.5)	21 (22.1)	0.178
AF (permanent), n (%)	9 (7.3)	5 (17.2)	4 (4.2)	0.018
History of non-sustained VT, n (%)	21 (16.9)	6 (20.7)	15 (15.7)	0.538
NT-proBNP, pg/mL	2268 (1204-4805)	2100 (1064-4177)	2476 (1267-5537)	0.347
sST2, ng/mL	27.1 (17.2-54.8)	39.2 (21.4-64.5)	26.8 (16.4-45.1)	0.154
CKD-EPI, mL/min/1.73 m^2	68 (60.2-77.4)	71.15 (63.8-88.5)	67.2 (59.5-76)	0.247
Cardiac surgery history				
Myocardial revascularisation, n (%)	35 (28.4)	11 (39.2)	24 (25.2)	0.148
Valve repair surgery, n (%)	16 (13)	5 (17.8)	11 (11.5)	0.385
Left ventricular reconstruction, n (%	1 (0.8)	0	1 (1)	0.586
Echocardiographic parameters				
LV EDV, mL	249 (204-304)	240 (211-294)	257 (203-307)	0.913
LV ESV, mL	177 (140-214)	170 (145.5-207)	188 (139-215.5)	0.694
LV EDD, cm	6.9 (6.35-7.5)	6.9 (6.4-7.35)	6.85 (6.3-7.6)	0.974
LV ESD, cm	5.8 (5.35-6.5)	5.6 (5.3-6.3)	5.8 (5.3-6.6)	0.265
LV ejection fraction (Simpson), %	29 (24-33)	30 (26.5-35)	29 (22-33)	0.099
GLS, %	6.9 (8.4-5.2)	5.1 (3.4-6.7)	7.5(5.4-8.5)	0.092
Electrocardiographic predictors				
QRS duration, ms	164 (150-180)	150 (120-175)	170 (152-190)	0.007
LBBB (Strauss criteria), n (%)	77 (63.6)	14 (48.2)	63 (68.4)	0.049
Modified QRS index	0.63 (0.53-0.79)	0.56 (0.49-0.74)	0.65 (0.54-0.79)	0.101

Note here and after: AF - atrial fibrillation; VT - ventricular tachycardia; NT-proBNP - N-terminal pro-brain natriuretic peptide; sST2 - soluble suppression of tumorigenesis-2; CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration formula; LV - left ventricle; EDV - end-diastolic volume; ESV - end-systolic volume; EDD - end-diastolic diameter; ESD - end-systolic diameter; GLS - global longitudinal strain; LBBB - left bundle branch block.

need for a dynamic approach to device selection based on predictors of VT development.

It is evident that the risk of SCD is highest in patients with a verified VT substrate. Cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement is a validated tool for visualising arrhythmogenic substrate with good sensitivity, as confirmed by multiple studies [10], and is also recommended as a decision-making factor in favour of ICD implantation [11]. However, due to its complexity and potential for false negatives, its widespread application is limited.

Thus, the device selection algorithm for CRT should be based on simpler, reproducible clinical, instrumental, and laboratory methods that are accessible in routine practice.

Aim: To conduct a comparative analysis of clinical, instrumental, and laboratory diagnostic methods, and to identify factors associated with the occurrence of sustained ventricular tachycardia (VT) episodes in patients eligible for CRT.

METHODS

The study design complied with international Good Clinical Practice (GCP) standards and the core principles of the Declaration of Helsinki. The study protocol was approved by the local ethics committee. All participants provided written informed consent prior to inclusion.

All patients underwent standard clinical evaluations as part of the diagnostic algorithm for CHF. In addition, speckle-tracking echocardiography was performed, along with the assessment of blood biomarkers, including: serum electrolytes, C-reactive protein, creatinine, soluble suppression of tumorigenicity-2 (sST2), N-terminal pro-brain natriuretic peptide (NT-proBNP), and galectin-3.

A total of 124 patients were included in the postoperative follow-up programme.Summary clinical and demographic characteristics of the patients are presented in Table 1.

Device Implantation and Subsequent Programming

Device implantation was performed in accordance with established clinical standards. A bipolar or quadripolar left ventricular lead was placed in the coronary sinus using a specialised delivery system. The lateral vein branch, anatomically located over the region of latest left ventricular activation in patients with complete left bundle branch block (CLBBB), was considered the preferred site for lead placement.

Device programming was carried out in three stages: intraoperatively, on postoperative days 4-5, and again three months after the procedure. Subsequent follow-up visits were scheduled once per year.

Pacing vector selection was guided by the lowest stimulation threshold and the absence of phrenic nerve capture. The atrioventricular delay was adjusted to achieve the highest possible percentage of biventricular pacing. Optimal interventricular delay was determined based on analysis of the duration of the paced ventricular QRS complex on ECG. Preference was given to the use of manufacturer-provided automatic optimisation algorithms.

To detect ventricular arrhythmias - the study's primary endpoint - a dual-zone detection scheme was employed: the VT zone was programmed to start at 160 bpm, and the ventricular fibrillation (VF) zone at 200 bpm. Supraventricular tachyarrhythmia discrimination algorithms were activated. Programming was aimed at minimising inappropriate therapies and prioritising ATP over high-energy shocks.

All study participants were followed for a period of 24 months. Follow-up visits were scheduled at 3, 12, and 24 months post-implantation. During these visits, recorded device-detected events were reviewed, including detection zone, episode date, accuracy of rhythm discrimination algorithms, and appropriateness of delivered therapy (ATP or shock).

Study Endpoint

The primary endpoint was defined as the first documented episode of sustained VTlasting ≥30 seconds and detected within the programmed VT monitoring zone, or any episode of VT or VFthat triggered delivery of electrical therapy, either ATP or shock.

Statistical Analysis

Statistical analysis was performed using both parametric and non-parametric methods. Initial data processing

Table 2.

Electrocardiographic Predictors of Ventricular Tachycardia (VT)

	All patients (n=124)	Patients with VT (n=29)	Patients without VT (n=95)	P
Sinus rhythm, n (%)	105 (85.4)	23 (79.3)	82 (87.2)	0.291
Atrial fibrillation, n (%)	40 (32.3)	15 (51.7)	25 (26.3)	0.01
LBBB#, n (%)	77 (63.6)	14 (48.2)	63 (68.4)	0.049
LBBB$, n (%)	49 (59)	12 (66.7)	37 (56.9)	0.457
SLI, n (%)	22 (22%)	6 (23.1)	16 (21.6)	0.878
CVI, n (%)	75 (75)	18 (69.2)	57 (77)	0.43
P wave, ms	120 (101-120)	110 (101-122)	120 (101-120)	0.802
P wave >120 ms, n (%)	25 (23.4)	6 (26.1)	19 (22.6)	0.728
QRS complex, ms	164 (150-180)	150 (120-175)	170 (152-190)	0.674
QTc interval, ms	492 (455-507)	482 (447-498)	492 (462-507)	0.216
Tp-Te interval, ms	100 (90-120)	100 (80-120)	100 (100-100)	0.743
Frontal QRS axis, °	156 (120-174)	156 (97-187)	157 (123-173)	0.855
QRSm	0.64 (0.53-0.80)	0.56 (0.49-0.74)	0.65 (0.54-0.80)	0.101
QRSm > 0,6, n (%)	77 (62.3)	13 (44.8)	64 (68.1)	0.024

Note: # - according to Strauss; $ - according to Surawizc; SLI - Sokolow-Lyon Index (Sv1 +Rv5 ≥35 мм, Rv5,v6 >26 мм); CVI - Cornell Voltage Index Sv_3 + RaVL > 28 mm for men, > 20 mm for women; QRSm - Modified QRS Index, ratio of QRS duration to the left ventricular end-diastolic volume (QRS duration / LVEDV)

and cleaning were carried out in Microsoft Excel 2010, while the statistical analyses were conducted using IBM SPSS Statistics version 23.

For continuous variables, the normality of distribution was assessed using the Kolmogorov-Smirnov test. If the data followed a normal distribution, results were presented as mean (M) ± standard deviation (SD), and comparisons between groups were made using Student's t-test. In cases where normality was not confirmed, data were reported as median (Me) and interquartile range (Q1-Q3), and group comparisons were performed using the Mann-Whitney U test.

For categorical variables, the Pearson χ^2 test was used. When analysing relative risks, odds ratios (ORs) were calculated. Statistical significance was considered achieved if the confidence interval excluded the null value (OR = 1). The significance level was set at $p < 0.05$.

To predict the 2-year risk of VT, a multivariate logistic regression model was developed. Missing data were imputed using median substitution from neighbouring points. Independent predictors were selected through stepwise backward elimination based on the Wald criterion. Model significance was evaluated using the χ^2 test, and the proportion of explained variance was assessed using Nagelkerke's R^2.

The model's predictive performance and threshold values were assessed using receiver operating characteristic (ROC) analysis, with calculation of the area under the curve (AUC). To facilitate application of the model in clinical settings, continuous variables included in the final model were transformed into nominal variables by identifying optimal cut-off values based on maximum sensitivity and specificity derived from the ROC curve.

RESULTS

A total of 124 patients with implanted CRT-D systems were included in the study. The mean LVEF was 29% (interquartile range: 24-33%). The mean age of participants was 58 years (IQR: 52-63), and the majority were male - 94 patients (76%). Prior to enrolment, 35 patients (28.4%) had undergone complete myocardial revascularisation, and 16 patients (13%)had received surgical correction of valvular pathology. All patients were receiving optimal guideline-directed medical therapy (GDMT) for chronic heart failure in accordance with the clinical recommendations valid at the time of study inclusion.

Table 3.

Multivariate Analysis of Echocardiographic Parameters

	All patients (n=124)	With VT (n=29)	Without VT (n=95)	P
LVEF (Simpson), %	29 (24-33)	30 (26,5-35)	29 (22-33)	0,095
GLS, %	7,3 (8,95-5,4)	4,6 (5,9-3,4)	7,6 (9,2-5,6)	0,014
LV EDV, mL	249,5 (204,5-304)	240 (212-290)	257 (203-305,5)	0,913
Indexed LV EDV, mL/m^2	126 (104-154)	125 (115-157,1)	127,1 (104-152,1)	0,664
LV ESV, mL	177 (140-214)	170 (147-205)	188 (140-214)	0,694
Indexed LV ESV, mL/m^2	90,1 (73,2-107,3)	82,7 (74-108,6)	90,4 (73,2-106)	0,890
LV EDD, cm	6,9 (6,35-7,5)	6,9 (6,4-7,3)	6,85 (6,3-7,6)	0,974
Indexed LV EDD, cm/m^2	3,5 (3,1-3,9)	3,5 (3,2-3,9)	3,5 (3-3,9)	0,575
LV ESD, cm	5,8 (5,35-6,55)	5,6 (5,5-6,3)	5,8 (5,35-6,6)	0,259
Indexed LV ESD, cm/m^2	2,9 (2,6-3,4)	2,8 (2,6-3)	3 (2,6-3,5)	0,020
IV septal thickness, cm	1 (0,85-1,1)	1 (0,9-1,2)	1 (0,8-1,1)	0,826
Posterior wall thickness, cm	1 (1-1,2)	1,1 (1-1,2)	1 (0,9-1,1)	0,045
Mean posterior wall thickness, cm	1 (0,9-1,1)	1,05 (0,95-1,15)	1 (0,9-1,1)	0,296
LV myocardial mass, g	311,7 (270,9-377,3)	292,9 (246,7-376,8)	311,7 (275,2-386,9)	0,523
sPAP, mmHg	43 (30-50)	30 (26-50)	44 (36-50)	0,014
LA sup-inf diameter, cm	6 (5,4-6,45)	6,1 (5,3-6,3)	6 (5,45-6,5)	0,314
LA medio-lateral diameter, cm	4,7 (4,3-5,1)	4,7 (4,3-5,2)	4,5 (4,2-4,7)	0,037
LA anteroposterior diameter, cm	4,6 (4,28-5)	4,6 (4,1-4,9)	4,6 (4,35-5,1)	0,277
Indexed LA volume, mL/m^2	95 (76,5-118)	98 (78-125)	86 (71,5-99)	0,030
RA sup-inf diameter, cm	5,3 (4,7-6)	4,95 (4,5-5,8)	5,4 (4,7-6)	0,107
RA medio-lateral diameter, cm	4 (3,5-4,6)	4,1 (3,7-4,6)	3,55 (3,3-4,35)	0,017
ARpat, n (%)	53 (47,3)	11 (42,3)	42 (48,8)	0,559
MRpat, n (%)	60 (49,2)	9 (32,1)	51 (54,3)	0,040
TRpat, n (%)	30 (24,4)	5 (17,2)	25 (26,6)	0,305

Note: sPAP - systolic pulmonary artery pressure; ARpat, MRpat, TRpat - aortic, mitral, and tricuspid regurgitation greater than grade 2, respectively.

Throughout the prospective follow-up period, pharmacological treatment was adjusted based on each patient's clinical status and in accordance with the availability of newly approved medications for heart failure management. Particular emphasis was placed on prescribing quadruple therapy, as recommended in contemporary heart failure guidelines.

During the two-year follow-up, 29 patients (23.3%) experienced the primary endpoint - a sustained ventricular tachyarrhythmia episode recorded by the device.

The groups stratified by the occurrence of the primary endpoint were comparable in most clinical and demographic characteristics, as shown in Table 1.

Clinical and Demographic Predictors of VT

The presence of AF of any form increased the likelihood of VT by 3-fold (OR = 3.0; 95% CI: 1.23-7.08; p = 0.01). Moreover, the presence of permanent AF was associated with an even higher risk of life-threatening arrhythmias, increasing the likelihood of VT by more than 4-fold (OR = 4.7; 95% CI: 1.18-19.02; p = 0.018). Clinical data analysis is presented in Table 1. Ischaemic heart disease (IHD) was identified as a potential prognostic factor with borderline statistical significance (OR = 2.95; 95% CI: 0.87-4.72; p = 0.10). Other clinical parameters did not show statistically significant associations with VT development in univariate analysis.

Electrocardiographic Predictors of VT

A total of 15 ECG parameters were analysed (see Table 2). Patients with longer QRS durations were less likely to develop VT (p = 0.007). The presence of complete left bundle branch block (CLBBB) based on Strauss criteria was associated with a ~2-fold reduction in VT risk (OR = 0.43; 95% CI: 0.183-1.00; p = 0.049).

We also analysed the modified QRS duration (QRSm) parameter described by N. Varma et al. [12], calculated as the ratio of QRS duration to left ventricular end-diastolic volume (LVEDV). ROC analysis identified a threshold value of 0.6. QRSm values above 0.6 were significantly associated with a reduced risk of VT (OR = 0.40; 95% CI: 0.167-0.993; p = 0.045), reducing the likelihood of life-threatening arrhythmias by approximately 6-fold.

Echocardiographic Criteria

According to univariate analysis (Table 3), the presence of mitral regurgitation (MR) ≥ grade 2 significantly reduced the likelihood of VT (OR = 0.43; 95% CI: 0.164-0.973; p = 0.04). Larger volumes and dimensions of the left atrium (LA) (p = 0.03), medial-lateral LA diameter (p

Table 4.

Multivariable Analysis of Blood Biomarkers

Biomarker	All patients (n=124)	Patients with VT (n=29)	Patients without VT (n=95)	P
Haemoglobin, g/L	133,5 (109-147)	135 (127-146)	132 (109-147)	0,577
NT-proBNP, pg/mL	2268 (1204-4805)	2100 (1064-4177)	2476 (1267-5537)	0,347
NT-proBNP > 2000, n (%)	32 (57,1)	11 (55)	21 (58,3)	0,809
NT-proBNP > 3000, n (%)	22 (39,3)	8 (40)	14 (38,9)	0,935
sST-2, ng/mL	27,1 (17,2-54,8)	39,2 (21,4-64,5)	26,8 (16,4-45,1)	0,154
sST-2 > 35, n (%)	21 (42)	8 (57,1)	13 (36,1)	0,176
Galectin-3, ng/mL	124,5 (115,1-139,9)	137,1 (126-142,65)	118,8 (114,9-132,2)	0,051
Galectin-3 > 12 ng/mL, n (%)	28 (57,1)	12 (80)	16 (47,1)	0,032
CKD-EPI, mL/min/1.73 m²	68 (60,2-77,4)	71,15 (64-88)	67,2 (60-76)	0,247
C-reactive protein (CRP), mg/L	7 (4-10)	8 (5-9)	6,62 (3,34-10,94)	0,454

Table 5.

Predictor Analysis of Ventricular Tachycardia

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
Predictors						
Presence AF	3	1.23-7.08	0.01	4	1.456-11.1	0.007
Presence IHD	2.95	0.867-4.718	0.1	2.8	1.027-7.626	0.067
Electrocardiographic Criteria						
QRSm ≥0,6	0.4	0.167-0.993	0.045	0.187	0.064-0.55	0.002
LBBB#	0.43	0.183-1.00	0.049	0.82	0.279-2.408	0.718
Echocardiographic Criteria						
GLS ≤6%	13.3	1.364-130.3	0.008	2.38	0.84-6.84	0.228
Mitral regurgitation > 2	0.43	0.164-0.973	0.04	0.285	0.104-0.778	0.014
Laboratory Criteria						
Galectin-3 > 12 ng/mL	4.5	1.073-18.865	0.032	2.37	0.84-6.837	0.102

= 0.037), and right atrium (RA) (p = 0.017) were all associated with an increased risk of VT.

The indexed left ventricular end-systolic dimension (iLVESD) showed a statistically significant protective association, with higher values correlating with lower VT risk (p = 0.02). Likewise, higher systolic pulmonary artery pressure (sPAP) was also associated with reduced VT risk (p = 0.014).

LVEF showed a trend toward statistical significance (p = 0.095), with higher LVEF values observed in patients who experienced VT episodes.

The global longitudinal strain (GLS) parameter was statistically significant (p = 0.014), with lower absolute GLS values observed in patients with VT. ROC analysis validated a GLS cut-off of >-6%; using this threshold in univariate analysis confirmed a statistically significant association (OR = 13.3; 95% CI: 1.364-130.3; p = 0.008).

Biomarkers Associated with VT Risk

Among the laboratory biomarkers analysed (Table 4), galectin-3 showed a near-significant difference in univariate analysis (p = 0.051). Higher values were observed in patients who developed VT. After establishing a threshold value of 12 ng/mL, a statistically significant difference was found (OR = 4.5; 95% CI: 1.073-18.865; p = 0.032). Galectin-3 levels above 12 ng/mL were associated with a 4.5-fold increased risk of VT. This threshold was identified via ROC analysis (sensitivity: 80%, specificity: 53%). Other biomarkers evaluated did not show statistically significant associations with the primary endpoint.

Multivariate Analysis of VT Predictors

During the univariate analysis, seven nominal factors with the highest predictive potential for reaching the primary endpoint were selected (Table 5). These included clinical variables (presence of IHD and AF); electrocardiographic criteria (a modified QRS value greater than 0.6, presence of CLBBB according to the Strauss criteria); echocardiographic criteria (GLS ≥ -6%, presence of mitral regurgitation [MR] of grade 2 or higher); and laboratory indicators (galectin-3 ≥ 12 ng/mL). Based on these variables, a prognostic model was constructed using binary logistic regression to estimate the two-year likelihood of VT in patients with indications for CRT device implantation.

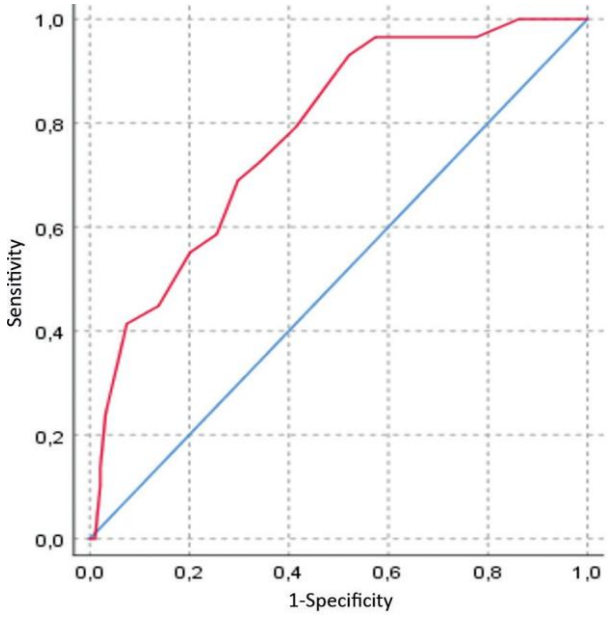

Fig. 1. ROC curve representing the relationship between the 2-year probability of VT and the value of the regression function.

Although the presence of CLBBB according to the Strauss criteria demonstrated statistical significance in the univariate analysis, it was not retained in the final model. The resulting regression equation is as follows: y = -1.337 + 1.029×IHD + 1.438×AF + 0.874×Galectin-3 >12 ng/mL + 0.863×GLS ≤ -6% - 1.676×QRSm ≥ 0.6 - 1.257×MR ≥ 2.

The regression model was statistically significant (p = 0.001). According to the Nagelkerke R^2 coefficient, 28.6% of the variance in the dependent variable (probability of VT occurrence) was explained by the variance in the studied factors. At a cut-off value of 0.228 for the regression function, the model demonstrated a diagnostic accuracy of 73.6%, with a sensitivity of 86.2% and specificity of 69.6%. The area under the ROC curve (AUC), reflecting the relationship between the two-year VT prognosis and the regression function value, was 0.779, which, according to standard expert scales for AUC, indicates good model performance (Figure 1).

DISCUSSION

Over the two-year follow-up period, the primary endpoint was recorded in 29 patients (23.3%), which is comparable with previously published data [13]. The relatively low rate of justified electrical therapy indicates certain limitations in the current criteria used for risk stratification. The relevance of this issue has led to the development of several prognostic models, including the MADIT-ICD Benefit Score, the ESTIMATED Score, and the Seattle Heart Failure Model [14-17]. These tools have demonstrated some effectiveness in prioritising device implantation based on the estimated risk of SCD.

It should be noted that while some of these models include patients with indications for CRT, only the MADIT-CRT study conducted a separate analysis of this subgroup [18]. Patients eligible for CRT represent a specific cohort. If a positive response to CRT is achieved, a significant reduction in the risk of life-threatening ventricular arrhythmias may be observed, as supported by several studies [18, 19]. This suggests that arrhythmic risk reduction may be one of the potential beneficial effects of CRT. Therefore, in the present study, the primary endpoint was defined specifically as the risk of SCD, since this factor determines the choice between CRT-pacemaker (CRT-P) and CRT-defibrillator (CRT-D) implantation. It is evident that predictors of CRT response may also influence the risk of SCD.

The following were identified as independent risk factors for SCD: presence of AF, QRSm >0.6, and MR of grade >2. The prognostic factors included in the multivariate model warrant further discussion.

Among the clinical predictors included in the model were the presence of AF and IHD. The association of AF with increased SCD risk is consistent with published data [20]. AF contributes to increased rate and irregularity of ventricular contractions, thereby reducing myocardial refractoriness and creating conditions conducive to VTde-

velopment [21]. AF is also associated with left ventricular myocardial fibrosis [22], which acts as a substrate for arrhythmias. Additionally, AF has been shown to negatively affect CRT efficacy, potentially amplifying SCD risk [23]. IHD, the second clinical predictor, is a well-established risk factor for SCD [24]. The mechanisms underlying VT in IHD are multifactorial. Acute ischaemic events lead to metabolic and ionic disturbances in the myocardium, resulting in myocyte membrane depolarisation, conduction slowing, and refractoriness prolongation. These changes promote triggered activity and re-entry mechanisms [25]. Subsequently, scar formation in peri-infarct areas provides the anatomical substrate for re-entry, significantly increasing VT risk [26]. Thus, IHD contributes both triggers and substrates for arrhythmogenesis.

The electrocardiographic parameter QRSm >0.6 emerged as a significant predictor in our multivariate model, surpassing the classic Strauss criteria for CLBBB. First described by N. Varma et al. [12], this index has a solid electrophysiological rationale. A 10 ms increase in QRS duration correlates with an 8.3% increase in LV myocardial mass, a 9.2% increase in LV end-diastolic volume, and a 7.8% increase in end-systolic volume [27]. Therefore, QRSm may reflect pronounced LV remodelling with true dyssynchrony, which is relevant when selecting CRT strategy. In our study, higher QRSm values were associated with a lower SCD risk, possibly due to CRT's favourable impact on arrhythmic risk.

Among echocardiographic predictors, mitral regurgitation of grade >2 and GLS below -6% were included in the model. Significant MR may indirectly indicate mechanical dyssynchrony due to asynchronous papillary muscle contraction [28]. This confirms the presence of electromechanical disturbances, which can potentially be corrected by CRT, thereby reducing arrhythmic risk. Although reduced LVEF is widely recognised as a major SCD risk factor [11], it did not demonstrate statistical significance in our study. This may be due to the fact that all patients received CRT-D implantation, making LVEF a potentially modifiable parameter in this context. GLS was found to be a significant predictor, with values below -6% associated with increased SCD risk. Similar findings were reported in a MADIT-CRT subanalysis, where low GLS increased the risk of VT in patients with LVEF <30%, but this correlation was absent in those with LVEF >30% [29]. GLS reduction reflects impaired longitudinal contractility, which may be associated with myocardial fibrosis, ischaemia, and remodelling - known substrates for arrhythmias. Additionally, reduced GLS may signal increased mechanical dispersion, which is also linked to elevated arrhythmic risk [30]. One important limitation of GLS use is the absence of standardised cut-off values, which vary from 6% to 10% across studies [31]. Some publications also examine the role of regional strain in specific LV segments [32]. In our study, only global strain was analysed.

Galectin-3 was the only biomarker significantly associated with the primary endpoint. It plays a key role in fibrosis, inflammation, and myocardial remodelling in CHF. The CARE-HF study demonstrated that elevated galectin-3 levels are linked with adverse outcomes, including death and hospitalisation for CHF decompensation [33]. However, no association between galectin-3 levels and CRT response was found. Conversely, H. Makimoto et al. showed that elevated galectin-3 levels were associated with a higher risk of VT [34]. Nonetheless, galectin-3 use is limited by its lack of myocardial fibrosis specificity, the absence of standardised assays, and inconsistent cut-off values [35]. Despite these limitations, galectin-3 remains a promising biomarker for VT risk stratification and warrants further investigation.

Study limitations

The present study has several limitations. It was a single-centre study with a limited sample size and lacked an external validation cohort. The primary endpoint was based on data from device programming, which may affect arrhythmia detection accuracy. The detection thresholds for VT could have influenced the sensitivity to slower arrhythmic episodes.

CONCLUSION

This study identified several independent predictors of SCD risk in patients implanted with CRT-D devices and enabled the development of a multivariate prognostic model. The findings highlight the potential for creating a personalised device selection algorithm based on routinely available clinical, instrumental, and laboratory data. Novel selection criteria, such as the QRSm index, were proposed and their impact on SCD risk was assessed. Thus, the results contribute to a more individualised approach to SCD risk stratification and device selection in patients with chronic heart failure and reduced left ventricular ejection fraction.

REFERENCES

1. Khan MS, Shahid I, Bennis A, et al. Global epidemiology of heart failure. *Nat Rev Cardio.l* 2024;21: 717-34. https://doi.org/10.1038/s41569-024-01046-6.

2. Postol AS, Neminushchiy NM, Antipov GN, Ivanchenko AV, et al. Factors that Determined a Positive Response to Resynchronization Therapy in Patients With Chronic Heart Failure and Cardiac Dyssynchrony. One Center Experience. *Kardiologiia*. 2024;64(7): 31-39. (In Russ.) https://doi.org/10.18087/cardio.2024.7.n2627.

3. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC) With the special contribution of the European Hear. *Eur Heart J*. 2021;42: 3427-520. https://doi.org/10.1093/eurheartj/ehab364.

4. [Lebedev DS, Mikhailov EN, Neminuschiy NM, et al. Ventricular arrhythmias. Ventricular tachycardias and sudden cardiac death. 2020 Clinical guidelines. *Russian Journal of Cardiology*. 2021;26(7): 4600. (In Russ.). https://doi:10.15829/1560-4071-2021-4600.

5. Barra S, Providência R, Boveda S, et al. Device complications with addition of defibrillation to cardiac resynchronisation therapy for primary prevention. *Heart*. 2018;104: 1529-35. https://doi.org/10.1136/heartjnl-2017-312546.

6. Devesa Neto V, Costa G, Santos LF, et al. Systematic

review and meta-analysis comparing cardiac resynchronization therapy with versus without defibrillation in patients with non-ischemic cardiomyopathy. *EP Eur*. 2024;26: euae102.488. https://doi.org/10.1093/europace/euae102.488.
7. Tereshchenko SN, Galyavich AS, Uskach TM, et al. 2020 Clinical practice guidelines for Chronic heart failure. *Russian Journal of Cardiology*. 2020;25(11): 4083. (In Russ.). https://doi:10.15829/1560-4071-2020-4083.
8. Krueger S, Kass DA, Marco T De, et al. Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure 2004:2140-50.
9. Younis A, Goldberger JJ, Kutyifa V, et al. Predicted benefit of an implantable cardioverter-defibrillator: the MADIT-ICD benefit score. *Eur Heart J*. 2021;42: 1676-84. https://doi.org/10.1093/eurheartj/ehaa1057.
10. Bazylev VV, Ushakov RYu, Durmanov SS, et al. Prognostic value of delayed gadolinium enhancement on cardiac magnetic resonance imaging in patients with ischemic cardiomyopathy and an implanted cardioverter-defibrillator. *Journal of Arrhythmology*. 2024;31(2): 35-43 (in Russ). https://doi.org/https://doi.org/10.35336/VA-1260.
11. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022;43: 3997-4126. https://doi.org/10.1093/eurheartj/ehac262.
12. Varma N, Lappe J, He J, Niebauer M, et al. Sex-Specific Response to Cardiac Resynchronization Therapy: Effect of Left Ventricular Size and QRS Duration in Left Bundle Branch Block. *JACC Clin Electrophysiol*. 2017;3: 844-53. https://doi.org/10.1016/j.jacep.2017.02.021.
13. Frodi DM, Diederichsen SZ, Xing LY, et al. Incidence and risk factors for first and recurrent ICD shock therapy in patients with an implantable cardioverter defibrillator. *J Interv Card Electrophysiol*. 2025;68: 125-39. https://doi.org/10.1007/s10840-024-01873-0.
14. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361: 1329-38. https://doi.org/10.1056/NEJMoa0906431.
15. Li X, Fan X, Li S, et al. A Novel Risk Stratification Score for Sudden Cardiac Death Prediction in Middle-Aged, Nonischemic Dilated Cardiomyopathy Patients: The ESTIMATED Score. *Can J Cardiol*. 2020;36: 1121-9. https://doi.org/10.1016/j.cjca.2019.11.009.
16. Reeder HT, Shen C, Buxton AE, et al. Joint Shock/Death Risk Prediction Model for Patients Considering Implantable Cardioverter-Defibrillators. C*irc Cardiovasc Qual Outcomes*. 2019;12:e005675. https://doi.org/10.1161/CIRCOUTCOMES.119.005675.
17. Mozaffarian D, Anker SD, Anand I, et al. Prediction of mode of death in heart failure: the Seattle Heart Failure Model. *Circulation*. 2007;116: 392-8. https://doi.org/10.1161/CIRCULATIONAHA.106.687103.
18. Ido G, K. AM, Wojciech Z, et al. QRS Morphology and the Risk of Ventricular Tachyarrhythmia in Cardiac Resynchronization Therapy Recipients. *JACC Clin Electrophysiol*. 2024;10: 16-26. https://doi.org/10.1016/j.jacep.2023.09.018.
19. Ilov NN, Stompel DR, Palnikova OV, Nechepurenko AA. Echocardiography parameter for evaluation of various effects of cardiac resynchronization therapy. *Russian Journal of Cardiology and Cardiovascular Surgery*. 2022;15(1): 19-25. (In Russ.) https://doi.org/10.17116/kardio20221501119.
20. Lai Y, Yoshimura H, Zakkak N, et al. Causes of death in patients with atrial fibrillation in the UK: a nationwide electronic health record study. *Eur Hear J Open*. 2024;5: oeae103. https://doi.org/10.1093/ehjopen/oeae103.
21. Fawzy AM, Bisson A, Bodin A, et al. Atrial Fibrillation and the Risk of Ventricular Arrhythmias and Cardiac Arrest: A Nationwide Population-Based Study. *J Clin Med*. 2023;12. https://doi.org/10.3390/jcm12031075.
22. Dzeshka MS, Lip GYH, Snezhitskiy V, Shantsila E. Cardiac Fibrosis in Patients With Atrial Fibrillation: Mechanisms and Clinical Implications. *J Am Coll Cardiol*. 2015;66: 943-59. https://doi.org/10.1016/j.jacc.2015.06.1313.
23. Centurión OA, Scavenius KE, García LB, et al. Atrioventricular nodal catheter ablation in atrial fibrillation complicating congestive heart failure. *J Atr Fibrillation*. 2018;11: 1-8. https://doi.org/10.4022/jafib.2013.
24. Jaiswal V, Taha AM, Joshi A, et al. Implantable cardioverter defibrillators for primary prevention in patients with ischemic and non-ischemic cardiomyopathy: A meta-analysis. *Curr Probl Cardiol*. 2024;49: 102198. https://doi.org/10.1016/j.cpcardiol.2023.102198.
25. Amoni M, Dries E, Ingelaere S, et al. Ventricular Arrhythmias in Ischemic Cardiomyopathy-New Avenues for Mechanism-Guided Treatment. *Cells*. 2021;10. https://doi.org/10.3390/cells10102629.
26. Masarone D, Limongelli G, Ammendola E, et al. Stratification of Sudden Cardiac Death in Patients with Heart Failure: An update. *J Clin Med*. 2018;7. https://doi.org/10.3390/jcm7110436.
27. Stewart RA, Young AA, Anderson C, et al. Relationship between QRS duration and left ventricular mass and volume in patients at high cardiovascular risk. *Heart*. 2011;97: 1766-70. https://doi.org/10.1136/heartjnl-2011-300297.
28. Michalski B, Stankovic I, Pagourelias E, et al. Relationship of Mechanical Dyssynchrony and LV Remodeling With Improvement of Mitral Regurgitation After CRT. J*ACC Cardiovasc Imaging*. 2022;15: 212-20. https://doi.org/10.1016/j.jcmg.2021.08.010.
29. Medvedofsky D, Arany-Lao-Kan G, McNitt S, et al. Predictive value of global longitudinal strain by left ventricular ejection fraction. *ESC Hear Fail*. 2023;10: 1937-47. https://doi.org/https://doi.org/10.1002/ehf2.14193.
30. Jang SY. Application of Global Longitudinal Strain as a Parameter of Left Ventricular Systolic Function in Echocardiography. *Clin Ultrasound*. 2023;8: 53-8. https://doi.org/10.18525/cu.2023.8.2.53.
31. Nikoo MH, Naeemi R, Moaref A, Attar A. Global longitudinal strain for prediction of ventricular arrhythmia in patients with heart failure. *ESC Hear Fail*. 2020;7: 2956-61. https://doi.org/10.1002/ehf2.12910.
32. Biering-Sørensen T, Knappe D, Pouleur A-C, et al. Regional Longitudinal Deformation Improves Prediction of Ventricular Tachyarrhythmias in Patients With Heart

Failure With Reduced Ejection Fraction. *Circ Cardiovasc Imaging*. 2017;10: e005096. https://doi.org/10.1161/CIRCIMAGING.116.005096.
33. Lopez-Andrès N, Rossignol P, Iraqi W, et al. Association of galectin-3 and fibrosis markers with long-term cardiovascular outcomes in patients with heart failure, left ventricular dysfunction, and dyssynchrony: insights from the CARE-HF (Cardiac Resynchronization in Heart Failure) trial. *Eur J Heart Fail*. 2012;14: 74-81. https://doi.org/10.1093/eurjhf/hfr151.
34. Makimoto H, Müller P, Denise K, et al. Clinical Impact of Circulating Galectin-3 on Ventricular Arrhythmias and Heart Failure Hospitalization Independent of Prior Ventricular Arrhythmic Events in Patients with Implantable Cardioverter-defibrillators. *Intern Med* 2022;61: 969-77. https://doi.org/10.2169/internalmedicine.7886-21.
35. Zaborska B, Sikora-Frąc M, Smarż K, et al. The Role of Galectin-3 in Heart Failure-The Diagnostic, Prognostic and Therapeutic Potential-Where Do We Stand? *Int J Mol Sci*. 2023;24. https://doi.org/10.3390/ijms241713111.

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POSSIBILITIES AND DIFFICULTIES OF DIAGNOSTICS OF HEREDITARY ARRHYTHMIC SYNDROMES IN REAL CLINICAL PRACTICE

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The review article discusses current aspects of diagnostics of hereditary arrhythmic syndromes, according to clinical guidelines, and dificulties that have arisen in real clinical practice, as well as possible ways to solve them. A systemic and multidisciplinary approach to solving these problems will contribute to increasing the effectiveness of clinical genetic studies and thereby improving the prevention of malignant arrhythmias and sudden cardiac death.

Key words: sudden cardiac death; channelopathies; hereditary arrhythmias; genetic testing

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Hereditary arrhythmias account for more than half of all initially unexplained cases of sudden cardiac death (SCD) in young individuals [1-3]. Among these, inherited arrhythmias caused solely by abnormalities in cardiac ion channels - known as channelopathies - are identified in approximately 30% of cases, whereas idiopathic structural heart abnormalities, particularly hypertrophic cardiomyopathy (HCM), are detected in around 70% of cases [1, 4]. Inherited arrhythmic syndromes without structural cardiac changes are responsible for approximately 10% of the 1.1 million annual cases of SCD in Europe and the United States [5-7]. Early diagnosis of hereditary arrhythmias may significantly reduce the risk of SCD, as in roughly 30% of cases, SCD is the initial manifestation of these disorders [4, 8].

Monogenic diseases may underlie SCD, and the most frequently encountered entities include the following major nosological forms, which present with unique but often overlapping clinical phenotypes and genetic associations: Long QT syndrome (LQTS), Short QT syndrome (SQTS), Brugada syndrome (BrS), Catecholaminergic polymorphic ventricular tachycardia (CPVT), Early repolarization syndrome (ERS), and idiopathic ventricular fibrillation (VF) [6, 9].

The detection rate of hereditary arrhythmias and the overall effectiveness of SCD prevention depend, in addition to medico-social factors, on the awareness and practical competencies of general practitioners and non-specialised clinicians [10, 11]. This may partly explain the discrepancy between the reported prevalence of hereditary arrhythmias in the general population and actual clinical practice, which typically involves the documentation of isolated case reports. According to a survey conducted by the European Heart Rhythm Association (EHRA) across 23 European countries, more than 50% of clinical centres do not participate in any form of registry - whether national or European - for hereditary arrhythmias, likely due to the low detection rate of such conditions [1, 6, 10].

In clinical practice, hereditary arrhythmias are most often identified in their syndromic forms - such as Brugada syndrome, Jervell and Lange-Nielsen syndrome, Timothy syndrome, and Andersen-Tawil syndrome - which are characterised by both cardiac and extracardiac phenotypes [12-14]. However, hereditary arrhythmias may also present with non-specific symptoms - such as syncope, palpitations, or seizures - and are frequently overlooked by clinicians. This can be attributed to the presence of functionally risky alleles or low-penetrance genetic variants in the general population, whose phenotypic expression requires the presence of additional risk factors, including drug effects, electrolyte imbalances, fever, and others [7, 10].

In recent years, the accessibility of high-tech medical care for patients with cardiovascular diseases, including those with life-threatening arrhythmias, has significantly improved in the Russian Federation. As a result, the number of implantations of cardioverter-defibrillators and pacemakers, as well as the frequency of ablation procedures, has increased substantially [15]. Consequently, this necessitates the optimisation of specialised medical services to improve access to medical genetic testing for patients with hereditary cardiac arrhythmias, along with the development and implementation of educational programmes aimed at raising awareness and enhancing the competencies of healthcare professionals.

Given the above, it is of particular interest to present a systemic approach to the diagnosis of hereditary arrhythmias and to analyse the potential causes of misdiagnosis or delayed diagnosis of these conditions in real-world clinical practice. It is important to note that a detailed analysis of diagnostic challenges - particularly those related to known limitations or misinterpretation of test results - may enhance the effectiveness of medical genetic care for patients with suspected channelopathies.

The literature review was conducted using international databases such as PubMed, Scopus, Web of Science, and the Cochrane Library, as well as Russian-language sources including eLibrary.

PREVALENCE OF HEREDITARY ARRHYTHMIAS IN THE GENERAL POPULATION

It is important to note that current data on the prevalence of individual cardiac channelopathies in the general population are primarily derived from international multicentre studies. These studies have contributed to the development of electronic databases that account for the ethnic, racial, and geographic characteristics of specific hereditary arrhythmic syndromes [3, 5, 10]. For example, the prevalence of Brugada syndrome (BrS) in European and North American populations ranges from 0.012% to 0.26%, whereas in endemic regions of Southeast Asia, it is significantly higher, reaching 0.7% to 1.0% [12]. The global prevalence of Jervell and Lange-Nielsen syndrome is estimated at 1 to 6 cases per 1 million people, with a rate of approximately 1 per 200,000 in Scandinavian countries [3, 16]. Cardiac channelopathies, together with genetic cardiomyopathies, are among the leading causes of morbidity and mortality in the paediatric population, with an annual incidence of 1.1 to 1.5 per 100,000 children under the age of 18 [7, 17].

The variability in the detection rates of cardiac channelopathies may also be explained by the extensive genetic heterogeneity of specific populations and the influence of environmental factors [18, 19]. For instance, the prevalence of SQTS, defined by a corrected QT interval (QTc) ≤300 ms, was highest among African Americans (5.8 per 100,000), followed by Caucasians (3.2), Latin Americans (1.8), and individuals of Asian or Pacific Islander descent (1.6) [3, 15]. The asymptomatic course of latent hereditary diseases further reduces the apparent population frequency of inherited arrhythmias. For example, in 40% of genotyped cases of LQTS, QT intervals fall within the normal range [20, 21]. Thus, the actual prevalence of LQTS is believed to be higher than currently reported figures [13, 16]. Epidemiological studies estimate that the individual prevalence of LQTS, BrS, and CPVT is approximately 1 in 2,000 [5, 22]. The rarest hereditary arrhythmia is SQTS, with a prevalence ranging from 0.1% to 0.003% in the general population [7, 15], whereas ERS is considerably more common, with a reported prevalence ranging from 1% to 13% [23].

The prevalence estimates of LQTS and SQTS are affected by several methodological limitations, including inaccuracies in QT interval measurement on standard electrocardiograms (ECG), as well as the absence of universally accepted diagnostic threshold values for QT intervals, which serve as ECG markers for LQTS and SQTS [13, 24]. Furthermore, the widespread clinical use of ajmaline challenge testing has significantly increased the reported frequency of BrS, leading to what has been termed drug-induced “Brugada phobia” [25]. In this context, it has been reported that in Europe, 70% of asymptomatic patients diagnosed with BrS received this diagnosis following a positive ajmaline test [6].

CLINICAL APPROACH TO THE DIAGNOSIS OF CARDIAC CHANNELOPATHIES

The clinical diagnosis of hereditary arrhythmias is often challenging due to their non-specific symptoms, the occasional absence of ECG patterns, and the predominance of latent (asymptomatic) presentations. The key components for establishing a diagnosis of channelopathy include a thorough evaluation of presenting symptoms, targeted exploration of the patient’s medical and family history, and a rational approach to diagnostic testing [6, 26, 27]. Given that affected individuals may initially present to physicians of various specialities - such as general practitioners, internists, paediatricians, or neurologists - it is crucial that the ability to recognise signs of hereditary arrhythmias is not limited to cardiologists alone.

Symptomatic presentations of hereditary arrhythmias allow for earlier and more frequent detection compared to asymptomatic forms [1, 28]. The most common and life-threatening manifestations include syncope, seizures, and sudden cardiac death, often triggered by specific stimuli. Syncope, in particular, presents a significant diagnostic dilemma, as it may range from a benign vasovagal episode to a potentially fatal event caused by polymorphic VT or VF [2, 13, 29].

In channelopathies, arrhythmogenesis may present as various types of VT, each carrying differential diagnostic significance. For instance, LQTS is most commonly associated with polymorphic VT of the torsades de pointes type; in Brugada syndrome (BrS), polymorphic VT is also characteristic [27, 30]. CPVT typically manifests as bidirectional VT, characterised by alternating polarity of the dominant QRS complexes [31], whereas arrhythmogenic right ventricular cardiomyopathy (ARVC) is marked by monomorphic VT with a left bundle branch block morphology. These arrhythmias may terminate spontaneously, but they also carry the risk of degenerating into VF, requiring electrical defibrillation. During such arrhythmic episodes, patients frequently report palpitations, dizziness, dyspnoea, chest pain, profound fatigue, and sensations of fear or panic.

It should be noted that in syndromic variants of channelopathies, the cardiac phenotype is often accompanied by extracardiac, multisystemic manifestations, which may aid in diagnosis but can also lead to mismanagement. For example, LQTS combined with congenital bilateral sensorineural deafness is characteristic of Jervell and Lange-Nielsen syndrome [13], while facial dysmorphism and syndactyly are features of Andersen-Tawil syndrome [14].

Identifying potential arrhythmic triggers often provides valuable diagnostic clues for channelopathies. For

example, arrhythmic events occurring during physical exertion, particularly swimming, are suggestive of LQT1, while syncope induced by sudden loud auditory stimuli is typical of LQT2 [32]. As both physical and emotional triggers are physiologically associated with increased catecholamine release, syncope in such contexts is a hallmark of CPVT [33]. Arrhythmias that occur during sleep or rest, or in the context of fever, may indicate LQT3 or BrS, which are associated with pathogenic variants in the *SCN5A* gene [12, 22].

It is also important to emphasise that the likelihood of phenotypic expression - and thus the probability of diagnosing a hereditary arrhythmia - is determined by incomplete penetrance and variable expressivity of the disease-causing genes [7, 18]. Nearly all hereditary arrhythmic syndromes exhibit incomplete penetrance (i.e. <100%) [4]. For example, the clinical penetrance of various LQTS genotypes ranges widely from 25% to 100%, with an average of approximately 40% [16]. This implies that a portion of affected individuals will remain asymptomatic. Therefore, a normal corrected QT interval (QTc) on ECG does not exclude LQTS in first-degree relatives of affected individuals. In this regard, the likelihood of a positive genetic test is highest in individuals with the strongest phenotypic expression [18]. Additionally, due to age-related penetrance in several hereditary arrhythmias, repeat evaluation during adolescence or early adulthood is recommended for at-risk children [17, 34].

ALTERNATIVE DIAGNOSES REQUIRING DIFFERENTIAL CONSIDERATION

Given that symptomatic patients with recurrent syncope due to VTor VF may be misdiagnosed and followed for extended periods under the label of “epilepsy,” they may receive ineffective antiepileptic therapy [29]. Therefore, a detailed family history and ECGevaluation are mandatory in all patients with seizure-like episodes that are negative on electroencephalography (EEG), in young children with atypical seizures during febrile episodes, and in families with a history of sudden infant death syndrome (SIDS) [17, 35].

Unlike arrhythmic syncope, epileptic seizures typically have a prodromal phase, including premonitory symptoms (auras). In the case of aborted cardiac arrest, syncope is usually brief and only rarely accompanied by convulsions. In contrast, most epileptic seizures are associated with prolonged, generalised convulsions, followed by profound fatigue, postictal exhaustion, and sometimes tongue biting. Malignant arrhythmias have been shown to occur in a substantial proportion of generalised seizure episodes and are considered a possible pathophysiological link between unexplained sudden death and epilepsy [29]. In one cohort of patients with LQTS, abnormal EEG findings were observed in 71% of cases compared with 13% in the control group ($p < 0.01$) [35]. Detailed evaluation of these patients revealed mutations in the *KCNQ1* gene, which is responsible for LQT1. Notably, *KCNQ1*, which encodes a potassium channel, is expressed not only in the heart but also in the forebrain and brainstem [24, 35]. Thus, some patients with a diagnosis of epilepsy may have coexisting hereditary arrhythmias and face a particularly high risk of fatal arrhythmias [13]. Consequently, any history of sudden death in a family with a member presenting with atypical seizure activity should prompt a thorough cardiological investigation.

Primary periodic paralyses and neuromuscular channelopathies in children also merit attention in the context of cardiac channelopathies. For example, in patients with Andersen-Tawil syndrome (the classic form of LQT7), potassium-sensitive transient periodic paralysis is almost invariably present. These episodes often occur against the background of generalised weakness and typically present without myotonic signs [14]. Such episodes of muscle weakness usually begin before the age of 10 or during adolescence.

ECG PATTERNS OF HEREDITARY ARRHYTHMIAS AND CHALLENGES IN RESTING ECG INTERPRETATION

A common manifestation of the cardiac phenotype in hereditary arrhythmias is ECGabnormalities, including various rhythm and conduction disturbances [4]. ECG patterns specific to individual channelopathies play a critical role in their diagnosis. Therefore, resting 12-lead ECG is an essential component of the initial evaluation in suspected cases of channelopathy. A detailed analysis of all ECG parameters should be conducted, as abnormalities in atrial and ventricular depolarisation and repolarisation may coexist [27, 30].

A corrected QT interval (QTc) ≥500 ms on serial standard ECGs, in the absence of secondary causes of QT prolongation, serves as a strong diagnostic criterion for LQTS according to the LQTS scoring system (Fig. 1) [13, 20]. Conversely, a QTc ≤330 ms is a key criterion for the diagnosis of SQTS [15]. However, these cut-offs represent extreme QTc deviations, potentially resulting in underdiagnosis of LQTS and SQTS in milder cases.

Certain pathological ECG findings at rest, when unexplained by other conditions, may raise suspicion for cardiac channelopathies:

- Prolonged or shortened QT/QTc intervals;
- Ventricular extrasystoles triggered by exercise stress testing;
- Downsloping (coved-type) or saddle-back ST-segment elevation in leads V1-V3 (Fig. 2);
- T-wave alternans (inverted or abnormal T waves);
- Conduction delays (sinoatrial, atrioventricular, or intraventricular blocks);
- Epsilon waves in leads V1-V3;
- Prominent U waves in precordial leads, extending the QT-U interval;
- Prominent J waves, with or without ST-segment elevation, particularly in posterior or posterolateral leads;
- PQ (PR) segment depression in inferior leads.

Despite the diagnostic value of resting ECG, it presents limitations across nearly all types of channelopathies. Accurately determining the QT interval can be difficult, adversely affecting the timely and accurate diagnosis of LQTS and SQTS. This is particularly the case in the presence of ST-T wave morphological abnormalities (e.g. biphasic, low-amplitude, or inverted T waves), which may result from bundle branch block, electrolyte

imbalances, ventricular hypertrophy, digoxin effect, and other causes [8, 24].

The most precise method for determining the end of the T wave is the tangential method, in which a tangent is drawn from the steepest slope of the T wave to intersect the isoelectric line. To correct for heart rate (HR) variability, the QT interval is converted to QTc using mathematical formulae, most commonly Bazett's formula. Even among experts, QT measurement errors in LQTS may range from 10 to 70 ms [16]. A prevalence study of SQTS based on more than 6.3 million ECG recordings from 1.7 million individuals using automated ECG analysis identified 1,086 cases with QTc ≤300 ms; however, only 45 of these were confirmed upon manual QT measurement [5].

It is also known that prominent U waves in precordial leads - commonly seen in Andersen-Tawil syndrome and ankyrin-B syndrome - may mimic QT-U interval prolongation. When U waves are excluded from the QT calculation, the resulting QT intervals are typically normal or borderline (Fig. 3) [8, 18]. Accordingly, ongoing debates persist as to whether ankyrin-B syndrome and Andersen-Tawil syndrome should be classified as "typical" forms of LQTS [13].

EXPANDED EVALUATION OF PATIENTS WITH SUSPECTED HEREDITARY ARRHYTHMIA

When clinical assessment raises a strong suspicion of a specific cardiac channelopathy, additional investigations - including genetic testing - are warranted. Situations such as sudden death in young family members, unexplained syncope, documented VT or VF, or atypical epilepsy in the presence of specific triggers should prompt further diagnostic work-up.

Exercise Stress Testing

In patients presenting with symptoms suggestive of channelopathy and a seemingly normal resting ECG, an exercise stress test may be performed. According to the EHRA, exercise testing was used in 36-82% of patients with syndromic inherited arrhythmias [6]. Given that approximately 40% of LQTS cases show a normal QT interval at rest, assessing the QT/QTc response during exercise is recommended [32]. QTc shortening is expected in LQT2 and LQT3, while paradoxical QTc prolongation during exercise is characteristic of LQT1. The appearance of polymorphic or bidirectional VT during the active phase of the test, which subsides during recovery, is a hallmark of CPVT [22, 33]. However, only 63% of CPVT patients exhibit a positive exercise test, and a negative result does not exclude the diagnosis [31]. When the standard stress test fails to induce arrhythmias despite strong clinical suspicion, a "burst" exercise protocol - designed to provoke a rapid heart rate increase - can improve the likelihood of VT induction [34].

High Precordial Lead ECG Placement

It has been shown that recording leads V1-V3 at one to two intercostal spaces higher than standard positions can unmask a concealed type 1 BrS ECG pattern, particularly in cases with saddle-back ST elevation [12]. Echocardiographically guided lead placement at the anatomical location of the right ventricular outflow tract increases the detection rate of type 1 BrS ECG pattern compared to standard lead positioning: 100% vs. 43% ($p < 0.001$) [25]. Additional diagnostic criteria include the Corrado index for type 1 ECG and β-angle measurement for type 2 [8].

Holter ECG Monitoring

Holter monitoring is used to detect latent rhythm and conduction abnormalities in patients with suspected hereditary arrhythmias. It also helps in identifying the presence of arrhythmic triggers. In Europe, Holter ECG was used in 63-83% of cases involving suspected inherited arrhythmias [6].

The BrS ECG pattern is often intermittent, with a reproducibility rate of only 25% in repeat ECGs [26]. In such cases, Holter monitoring may help reveal a dynamic type 1 BrS pattern, avoiding the need for drug provocation. Holter is also useful for children who cannot perform exercise testing and for patients whose symptoms are emotionally, rather than physically, triggered [32]. When arrhythmic syncope is suspected, implantable cardiac monitors capable of recording ECG continuously for 6 to 24 months may assist in diagnosing arrhythmias [36].

Electrophysiological Study (EPS)

In most channelopathies, EPS to induce VT has limited diagnostic value and is not a standard test [8]. The positive predictive value of EPS in channelopathies ranges from 37-50%, and the negative predictive value from 46-97% [22]. Induction of VT using less aggressive pacing protocols (one or two extrastimuli) improves the test's prognostic accuracy. EPS is primarily recommended for risk stratification, determining indications for implantable cardioverter-defibrillator (ICD) implantation in asymptomatic patients, and assessing the efficacy of drug or ablation therapy [8]. However, failure to induce VT does not necessarily indicate low arrhythmic risk, especially in patients with high-risk clinical features.

According to EHRA, EPS is not routinely used to provoke ventricular arrhythmias in 82-98% of European centres, except in BrS, where 39% report its use [6]. VT or VF, the primary endpoints of EPS, are inducible in 60-70% of cases [22].

Drug Provocation Testing

If no other diagnosis is established and the circumstances of sudden cardiac death suggest BrS, provocation testing with class I antiarrhythmic drugs (e.g. ajmaline, flecainide, procainamide) is recommended in first-degree relatives with structurally normal hearts [30]. After intravenous administration, ECG should be recorded using 12-lead Holter or standard ECG with high precordial lead placement (V1-V3). Ajmaline has demonstrated a higher rate of positive results than procainamide or flecainide [12]. However, despite its high sensitivity, the ajmaline test lacks specificity: a type 1 BrS ECG pattern may be induced in patients with LQT3, ARVC, or r'-ST complexes in V1-V3 [30]. Therefore, a positive ajmaline test does not provide useful prognostic information in asymptomatic individuals with type 2 or 3 BrS ECG patterns [8].

Low-dose adrenaline infusion is an alternative diagnostic method in LQTS patients unable to perform stress testing. The adrenaline test has low sensitivity (28%) but high specificity (98%) compared to exercise testing [13].

EHRA data show that pharmacological provocation is used inconsistently across Europe: 90% of centres used

sodium channel blocker tests to diagnose BrS; 36% used isoproterenol testing for CPVT. However, drug provocation is avoided in 80-92% of centres when diagnosing LQTS, SQTS, or early repolarization syndrome (ERS), and in 67% of centres for idiopathic VF [6, 33].

Cardiac Imaging

In cases where arrhythmia is associated with structural heart disease - such as HCM, dilated cardiomyopathy (DCM), or ARVC - modern imaging techniques, including echocardiography and cardiac magnetic resonance imaging (MRI), may provide additional diagnostic insights [1, 7]. Repeat MRIs are recommended to monitor potential phenotypic evolution. According to EHRA, echocardiography is the most frequently used imaging modality, performed in 72-84% of arrhythmology centres in Europe [6].

MRI is more commonly used in patients with BrS, ERS, and idiopathic VF than in those with LQTS, SQTS, or CPVT (27-54% vs. 11-17%). Some centres also include coronary angiography in the evaluation of suspected idiopathic VF (62%) and CPVT (27%) [33]. Myocardial biopsy and signal-averaged ECG are included in diagnostic protocols for idiopathic VF and BrS, although they are rarely recommended as alternatives.

DIAGNOSTIC SCORING SYSTEMS FOR HEREDITARY ARRHYTHMIAS

In clinical practice, diagnostic scoring systems are widely employed to confirm hereditary arrhythmic syndromes. These systems integrate multiple criteria, including ECG patterns, symptom characteristics, family history, and results of genetic testing [13, 15, 33]. This approach is justified by the absence of absolute QTc interval thresholds for diagnosing LQTS or SQTS, as well as the difficulties in distinguishing BrS ECG patterns from QRS-T configurations seen in J-wave syndromes [6, 23, 31].

For example, the QTc threshold for suspecting or diagnosing SQTS varies broadly - from 220 to 360 ms - creating a “grey zone” between 330 and 370 ms [15]. This uncertainty is addressed in the SQTS diagnostic score, which assigns different point values based on the degree of QTc shortening and the strength of diagnostic suspicion. A QTc <370 ms scores 1 point, <350 ms scores 2 points, and <330 ms scores 3 points.

Moreover, diagnostic scores allow for stratification of the likelihood of a specific hereditary arrhythmic syndrome. In the initial evaluation of patients with suspected LQTS using the scoring system proposed by P. J. Schwartz et al. (2020), a total score of ≤1 indicates a low probability of LQTS, 1.5-3 points suggests an intermediate probability, and ≥3.5 points denotes a high likelihood of LQTS [13]. Despite their structured framework, diagnostic scores may have limited sensitivity when applied to relatives of a proband due to the incomplete penetrance of these syndromes [8, 28].

For Brugada syndrome, the standard diagnostic framework relies on the expert consensus from the Heart Rhythm Society (HRS), EHRA, and Asia Pacific Heart Rhythm Society (APHRS). In cases of drug-induced BrS ECG patterns, the Shanghai scoring system is recommended [12]. In this model, the diagnosis requires not only a type 1 BrS ECG pattern but also the presence of at least one of the following criteria: documented VF or polymorphic VT, unexplained syncope, sudden cardiac death (SCD) in a family member under 45 years of age with negative autopsy, type 1 BrS ECG pattern in a first-degree relative, or nocturnal agonal respiration [8, 25].

To objectively assess the pre-test probability of CPVT, a dedicated diagnostic score was developed that incorporates modern CPVT phenotype features [31]. The score includes factors that increase (age <40 years, genotype-positive status, family history) or decrease (presence of ventricular ectopy, ischaemic heart disease, prolonged QT interval) the likelihood of CPVT. According to this scale, a score of 3.5 to 12 points corresponds to a high pre-test probability, i.e., a definitive or >90% likelihood of CPVT. Notably, stress-induced polymorphic VT occurring at a heart rate >100 bpm is assigned 4 points - equivalent to a positive genetic test for a pathogenic variant [31].

Given the central diagnostic role of stress-induced polymorphic VT in CPVT, a broad spectrum of patients may fall into the “possible CPVT” category. Future guidelines are likely to refine the criteria for a “high probability” diagnosis of CPVT, especially in light of the substantial proportion of patients who remain genetically inconclusive or genotype-negative.

DIAGNOSTIC GENETIC TESTING

According to the EHRA, approximately 40% of patients and their relatives do not undergo genetic testing [6, 19]. Understanding the genetic and molecular basis of cardiac channelopathies can improve the prevention of SCD. Modern next-generation sequencing (NGS) technologies enable comprehensive assessment of arrhythmia gene panels, typically covering up to 40 genes and their mutations associated with channelopathies [19]. A key element of genetic testing is establishing the clinical relevance of identified variants, as the likelihood of a positive test is highest in individuals with high phenotypic penetrance [18].

For all suspected diagnoses involving channelopathies, the indication for genetic testing should be carefully justified. Genetic testing plays a critical role in identifying “presymptomatic” or “mildly symptomatic” individuals with genotypes associated with increased SCD risk, enabling early implementation of preventive strategies [19, 37].

It is important to note that Russian clinical guidelines on Ventricular Arrhythmias, Ventricular Tachycardia and Sudden Cardiac Death are based on European Society of Cardiology (ESC) recommendations, adapted to the national context, including diagnostic, therapeutic, and accessibility considerations [38, 39]. The level of recommendation (LoR) and level of evidence (LoE) supporting diagnostic genetic testing are closely linked to the likelihood of a positive result, depending on the specific hereditary arrhythmic syndrome.

According to these guidelines [38, 39], comprehensive genetic testing for mutations in *KCNQ1*, *KCNH2*, and *SCN5A*(associated with LQT1-LQT3, the most common subtypes) is recommended for all patients with clinical manifestations of LQTS, a positive family history, and QTc prolongation on resting or provoked ECG (ESC

class I, level A; LoR C, LoE 5). It is also recommended for asymptomatic individuals with no clear clinical signs of LQTS but with a QTc >500 ms on ECG, provided secondary causes of QT prolongation have been excluded (ESC class I, level A; LoR C, LoE 5).

When pathogenic mutations are identified in patients with LQTS or Brugada syndrome, cascade screening of first-degree relatives is recommended - even in the absence of clinical symptoms or ECG abnormalities - to aid in individual risk stratification (ESC class IIa, level B; LoR C, LoE 5) [38, 39]. Conversely, genetic testing is not recommended for individuals with type 2 or type 3 BrS ECG patterns in the absence of symptoms or a family history of SCD (ESC class III, level C; LoR C, LoE 5) [38, 39].

Genetic testing for mutations in *RyR2* and *CASQ2* is recommended for all patients with CPVT and for those with clinical features strongly suggestive of the condition, especially when a family history is present, to guide risk stratification (ESC class I, level C; LoR C, LoE 5) [38, 39]. For patients with SQTS, comprehensive molecular screening for mutations in *KCNH2*, *KCNQ1*, and *KCNJ2* is recommended to identify individual risk (ESC class I, level C; LoR C, LoE 5), although the sensitivity of available tests remains low.

Genetic variants are classified based on the strength of evidence as: benign, likely benign, variant of uncertain significance (VUS), likely pathogenic, or pathogenic [18]. A pathogenic variant supports the clinical diagnosis and may inform both prognosis and treatment, as well as serve as the basis for family screening. With few exceptions, a VUS should not guide clinical management or risk assessment in asymptomatic relatives [40].

The EHRA/HRS/APHRS/LAHRS 2022 consensus introduced the concept of “key genes” (as per the ClinGen resource), which should be prioritised in genetic testing panels to improve clinical yield [18]. The average sensitivity of routine genetic testing is ~65% for LQTS, ~60% for CPVT, ~40% for SQTS, and only 25-30% for BrS [18].

Segregation analysis - the co-segregation of genotype with phenotype in multiple family members - remains the most robust support for pathogenicity [8, 28]. A positive genetic result in a proband enables cascade testing of first-degree relatives for the pathogenic variant. In general, cascade screening is recommended when the outcome will impact clinical decision-making. If no pathogenic or likely pathogenic variant is found in relatives, regular clinical monitoring is advised, as phenotypic expression may vary widely within the same family and may emerge later in life [25, 34].

In 30-40% of unexplained sudden deaths, autopsy fails to identify the cause of death despite comprehensive toxicological and histopathological assessment [41]. In such cases, the presumed cause is often sudden arrhythmic death due to a concealed hereditary arrhythmia [8]. Therefore, in accordance with guidelines, post-mortem genetic testing (molecular autopsy) is recommended in all cases of unexplained SCD, and if a pathogenic or likely pathogenic variant is found, cascade screening should be offered to surviving relatives (ESC class I, level C; LoR C, LoE 5) [38, 39].

The advent of high-throughput sequencing technologies has enabled large-scale sequencing using pan-cardiac panels (typically 50-100 heart-related genes), exome sequencing, or even whole-genome sequencing in cohorts with previously unexplained SCD [41]. One major finding has been the high frequency of pathogenic variants in genes associated with hereditary cardiomyopathies, which account for up to 70% of actionable variants in cases of unexplained SCD [41-43].

The combination of molecular autopsy and clinical-genetic evaluation of surviving family members significantly increases the likelihood of identifying a pathogenic or likely pathogenic variant. In fact, molecular autopsy alone yields unique findings in 15-30% of cases [44]. Nevertheless, only about 70% of clinicians report considering molecular autopsy in suspected hereditary cases of sudden death [2, 10].

CHALLENGES IN INTERPRETING GENETIC TEST RESULTS

Genetic and phenotypic heterogeneity continues to expand, and increasing evidence suggests that some hereditary arrhythmias are oligogenic in nature - that is, caused by interactions between multiple genetic variants [18, 45]. This adds substantial complexity to genetic identification and diagnosis. As a result, selecting the appropriate genetic testing panel and interpreting genotyping results requires specialised expertise and a multidisciplinary approach. The identification of a pathogenic variant indicates an increased risk of phenotype expression, but it is not equivalent to a clinical diagnosis. Conversely, a negative genetic test result does not exclude a clinically justified diagnosis. When a variant is identified, its relevance must be critically evaluated, as it may not represent the primary or sole cause of the condition [18].

Due to phenotype overlap and genetic heterogeneity, choosing the appropriate genotyping strategy can be challenging. The same phenotype may be caused by mutations in different genes - a phenomenon known as “genetic overlap” [11, 17]. Conversely, the same mutation can lead to distinct phenotypes even within a single family (variable expressivity). For example, family members with the same *SCN5A* mutation may present with BrS, LQTS, or conduction system disease [19].

Therefore, in the absence of a specific suspected diagnosis, there is little rationale for broad screening of all known genes associated with SCD. Such testing often reveals variants or mutations that are not causally related to the individual’s disease. Even when a working diagnosis is available, interpretation may still be impossible without both genetic and clinical evaluation of family members - especially when the identified variant has not been previously described. Additionally, the detection of numerous low-impact genes associated with a range of potential effects increases the uncertainty surrounding test interpretation [18].

It is important to note that many genetic variants associated with sudden death in young individuals remain classified as VUS for years, which complicates clinical decision-making [38]. These families should be managed as though they carry a negative genotype, and VUS find-

ings should not inform treatment decisions. However, some of these variants may later be reclassified as likely pathogenic following re-evaluation, in which case targeted lifestyle modifications or avoidance of known arrhythmic triggers in asymptomatic individuals may offer clinical benefit.

Genetic research has predominantly focused on mutations in the primary DNA sequence that affect gene transcription and translation [18]. However, a considerable number of cases involving hereditary ventricular arrhythmias with structurally normal hearts do not reveal a causative gene mutation. Among the potential contributors to such genetically elusive cases are epigenetic mechanisms that alter the expression of arrhythmia-susceptibility genes [46]. In BrS, for instance, although approximately 20 pathogenic genes have been identified, monogenic and polygenic mechanisms together still account for only 20-40% of known cases, leaving 60-80% genetically unexplained [12, 45].

Moreover, many primary cardiomyopathies (CMPs) initially present with arrhythmias prior to the development of overt cardiomyopathic changes, and may therefore be misinterpreted as primary electrical diseases [44]. Thus, in patients with suspected cardiomyopathy or hereditary arrhythmia, comprehensive genetic testing holds high diagnostic value and may outweigh the burden of ambiguous findings.

AWARENESS AND COMPETENCIES OF PHYSICIANS REGARDING HEREDITARY ARRHYTHMIAS

Given the rarity of hereditary arrhythmias in the general population, their phenotypic variability, and the predominance of asymptomatic carriers among probands' relatives, physician awareness plays a critical role in identifying affected individuals in clinical practice [5, 28]. Moreover, these patients frequently consult physicians across a range of specialties, which may lead to delayed or incorrect diagnoses and result in missed opportunities for effective intervention - despite a high risk of SCD [2, 6, 35].

In recent years, increasing attention has been directed towards evaluating physicians' awareness of hereditary arrhythmias and their attitudes towards implementing appropriate diagnostic procedures, including referrals to specialised centres [6]. A multicentre study conducted under the auspices of the EHRA assessed current management practices for young patients who had survived an SCD episode [1]. The results of this online survey revealed inconsistencies in the application of exercise stress testing, pharmacological provocation, and genetic testing. Notably, two-thirds of physicians did not consult with a geneticist when interpreting genetic test results. Autopsies were performed in only 43% of cases of sudden death, and post-mortem genetic testing in just 37%.

General practitioners can play a significant role in identifying individuals at risk for hereditary arrhythmias by referring them for genetic counselling. A survey of 106 general practitioners found that only 40% had encountered young patients with a family history of SCD in their practice [28]. Despite the importance of family history in the identification and appropriate management of genetic diseases, only 21% of general practitioners and 46% of cardiologists reported having diagnosed hereditary arrhythmias through family screening. Furthermore, approximately 40% of general practitioners and 30% of cardiologists indicated that they would not pursue further investigations even in the presence of a family history of early-onset SCD.

In another study involving 154 surgeons (including general surgeons, obstetricians, and anaesthesiologists), the majority (80%) lacked sufficient knowledge about SCD or hereditary arrhythmias [47]. When asked about the relevance of such knowledge to their professional practice, 35% considered it "not at all important," 32% rated it as "moderately important," and 28.5% believed it to be "very important." Following the survey, 95% of respondents expressed interest in receiving further education on hereditary arrhythmias via online sessions or in-person seminars.

Patient education on managing arrhythmia-related triggers is also crucial. According to EHRA data, nearly all clinics (86-93%) provided patients diagnosed with hereditary arrhythmias with counselling on the importance of avoiding specific arrhythmic triggers [6]. Furthermore, patients were informed about their condition through dedicated websites (77%) and informational brochures (56%). After initiating therapy, 68% of patients were followed by cardiologists in university hospitals, 14% by electrophysiologists, 13% by hospital-based cardiologists, and only 5% by general practitioners.

Collectively, these findings reflect suboptimal adherence to established guidelines in real-world clinical settings. Eliminating the causes of delayed or missed diagnoses - particularly through the implementation of educational programmes targeting physicians on topics such as SCD and hereditary arrhythmias - can enhance the effectiveness of medical and genetic care for patients with suspected channelopathies and their family members.

CONCLUSION

The analysis of real-world clinical practices in the diagnosis and management of patients with hereditary arrhythmias suggests that, despite the life-threatening consequences of cardiac rhythm and conduction disorders for patients and their families, there remains no optimal, comprehensive solution to the complex challenges posed by cardiac channelopathies. Although clinical guidelines for the identification and management of patients at high risk of sudden arrhythmic death - including those with inherited arrhythmic syndromes - are continuously being developed and refined, their implementation in clinical settings remains fraught with difficulties, which may sometimes result in catastrophic outcomes.

In addition to unresolved issues related to the genetic identification of inherited arrhythmic syndromes, the strict adherence to up-to-date clinical guidelines by healthcare providers is of paramount importance. Equally critical is the adoption of a multidisciplinary approach to patient management and the promotion of educational programmes aimed at improving the competencies of relevant medical specialists. Furthermore, there is an urgent need to consolidate efforts across healthcare institutions to develop a unified patient registry and to establish additional dedicated cardiogenetic centres or departments responsible for

coordinating medical and genetic care for affected individuals and their families.

When determining the diagnostic strategy for patients with suspected hereditary arrhythmias, it should also be taken into account that LQTS and BrS together account for more than two-thirds of all cases. Syncope and sudden cardiac death occur in approximately 40% of individuals with hereditary arrhythmias, while the majority of patients are diagnosed during asymptomatic stages.

In conclusion, addressing these challenges in a systematic and integrated manner may contribute to a more accurate understanding of the epidemiology of hereditary arrhythmias and enhance the effectiveness of preventive strategies aimed at reducing sudden arrhythmic death.

REFERENCES

1. Behr ER, Scrocco C, Wilde AAM, et al. Investigation on sudden unexpected death in the young in Europe: results of the European Heart Rhythm Association Survey. *Europace.* 2022;24(2): 331-339. https://doi.org/10.1093/europace/euab176.
2. Priori SG, Marino M. Sudden cardiac death in the young: are we still missing the opportunity to prevent recurrences in the family? *Heart Rhythm.* 2021;18(10): 1645-1646. https://doi.org/10.1016/j.hrthm.2021.06.1179.
3. Wong CX, Brown A, Lau DH, et al. Epidemiology of sudden cardiac death: global and regional perspectives. *Heart, Lung and Circulation.* 2019;28(1): 6-14. https://doi.org/10.1016/j.hlc.2018.08.026.
4. Schwartz PJ, Ackerman MJ, Antzelevitch C, et al. Inherited cardiac arrhythmias. *Nature Reviews Disease Primers.* 2020;6(1): 58. https://doi.org/10.1038/s41572-020-0188-7.
5. Offerhaus JA, Bezzina CR, Wilde AAM. Epidemiology of inherited arrhythmias. *Nature Reviews Cardiology.* 2020;17(4): 205-215. https://doi.org/10.1038/s41569-019-0266-2.
6. Conte G, Scherr D, Lenarczyk R, et al. Diagnosis, family screening, and treatment of inherited arrhythmogenic diseases in Europe: results of the European Heart Rhythm Association Survey. *Europace.* 2020;22(12): 1904-1910. https://doi.org/10.1093/europace/euaa223.
7. Zeljkovic I, Gauthey A, Manninger M, et al. Genetic testing for inherited arrhythmia syndromes and cardiomyopathies: results of the European Heart Rhythm Association survey. *EP Europace.* 2024;26(9): euae216. https://doi.org/10.1093/europace/euae216.
8. Shlyahto EV, Arutyunov GP, Belenkov YuN, et al. National guidelines on risk stratification an prevention of sudden cardiac death (2-nd edition) M.: MEDPRACTICA-M 2018:247p. (In Russ.). ISBN: 978-5-98803-397-4.
9. Janzen ML, Davies B, Laksman ZWM, et al. Management of inherited arrhythmia syndromes: a HiRO consensus handbook on process of care. *Canadian Journal of Cardiology Open.* 2023;5(4): 268-284. https://doi.org/10.1016/j.cjco.2023.02.006.
10. van den Heuvel LM, Do J, Yeates L, et al. Global approaches to cardiogenetic evaluation after sudden cardiac death in the young: a survey among health care professionals. *Heart Rhythm.* 2021;18(10): 1637-1644. https://doi.org/10.1016/j.hrthm.2021.03.037.
11. Peltenburg PJ, Crotti L, Roston TM, et al. Current gaps in knowledge in inherited arrhythmia syndromes. *Netherlands Heart Journal.* 2023;31(7-8): 272-281. https://doi.org/10.1007/s12471-023-01797-w.
12. Nakano Y, Shimizu W. Brugada syndrome as a major cause of sudden cardiac death in Asians. *Journal of the American College of Cardiology: Asia.* 2022;2(4): 412-421. https://doi.org/10.1016/j.jacasi.2022.03.011.
13. Wilde AAM, Amin AS, Postema PG. Diagnosis, management, and therapeutic strategies for congenital long QT syndrome. *Heart.* 2022;108: 332-338. https://doi.org/10.1136/heartjnl-2020-318259.
14. Pérez-Riera AR, Barbosa-Barros R, Samesina N, et al. Andersen-Tawil syndrome: a comprehensive review. *Cardiology in Review.* 2021;29: 165-177. https://doi.org/10.1097/CRD.0000000000000326.
15. Bockeria LA, Pronicheva IV, Serguladze SYu. Short QT syndrome and sudden cardiac death: recent clinical and genetic advances. *Annaly aritmologii.* 2022;19(3): 196-206. (In Russ.). https://doi.org/10.15275/annaritmol.2022.3.9.
16. Bains S, Neves R, J. Bos M, et al. Phenotypes of overdiagnosed long QT syndrome. *Journal of the American College of Cardiology.* 2023;81(5): 477-486. https://doi.org/10.1016/j.jacc.2022.11.036.
17. Martínez-Barrios E, Cesar S, Cruzalegui J, et al. Clinical genetics of inherited arrhythmogenic disease in the pediatric population. *Biomedicines.* 2022;10(1): 106. https://doi.org/10.3390/biomedicines10010106.
18. Wilde AAM, Semsarian C, Marquez MF, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. *Heart Rhythm.* 2022;19(7): e1-e59. https://doi.org/10.1016/j.hrthm.2022.03.1225.
19. Specterman MJ, Behr E, Cardiogenetics: the role of genetic testing for inherited arrhythmia syndromes and sudden death. *Heart.* 2023;109(6): 434-441. https://doi.org/10.1136/heartjnl-2021-320015.
20. Iskenderov BG, Lokhina TV, Molokova EA, et al. Congenital long QT syndrome: genetic architecture, risk stratification and treatment approaches. *International Journal of Heart and Vascular Diseases.* 2024;12(42): 5-15 (In Russ.. https://doi.org/10.24412/2311-1623-2024-42-5-15.
21. Lahrouchi N, Tadros R, Crotti L, et al. Transethnic genome-wide association study provides insights in the genetic architecture and heritability of long QT syndrome. *Circulation.* 2020;142(4): 324-338. https://doi.org/10.1161/CIRCULATIONAHA.120.045956.
22. Singh M, Morin DP, Link MS. Sudden cardiac death in long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. *Progress in Cardiovascular Diseases.* 2019;62(3): 227-234. https://doi.org/10.1016/j.pcad.2019.05.006.
23. Voskoboinik A, Hsia H, Moss J, et al. The many faces of early repolarization syndrome: a single-center case series. *Heart Rhythm.* 2020;17(2): 273-281. https://doi.org/10.1016/j.hrthm.2019.09.013.

24. Schwartz PJ. 1970-2020: 50 years of research on the long QT syndrome: from almost zero knowledge to precision medicine. *European Heart Journal*. 2021;42(11): 1063-1072. https://doi.org/10.1093/eurheartj/ehaa769.
25. Minier M, Probst V, Berthome P, et al. Age at diagnosis of Brugada syndrome: influence on clinical characteristics and risk of arrhythmia. *Heart Rhythm.* 2020;17(5 Pt A): 743-749. https://doi.org/10.1016/j.hrthm.2019.11.027.
26. Domain G, Steinberg C, Davies B, et al. Long-term monitoring to detect risk of sudden cardiac death in inherited arrhythmia patients. *Canadian Journal of Cardiology Open.* 2024;6(9): 1066-1074. https://doi.org/10.1016/j.cjco.2024.05.007.
27. Guo S, Zha L. Pathogenesis and clinical characteristics of hereditary arrhythmia diseases. *Genes.* 2024;15(11): 1368. https://doi.org/10.3390/genes15111368
28. Piciacchia F, Auricchio A, Behr ER, et al. Family history of sudden cardiac death in the young and inherited arrhythmia syndromes: awareness and attitudes of general practitioners and private practice cardiologists. *Circulation: Genomic and Precision Medicine.* 2023;16: 92-93. https://doi.org/10.1161/CIRCGEN.122.003913
29. Franklin WH, Laubham M. Neurologic complications of genetic channelopathies. *Handbook of Clinical Neurology*. 2021;177: 185-188. https://doi.org/10.1016/B978-0-12-819814-8.00014-7.
30. Badura K, Bufawska D, Dabek B, et al. Primary electrical heart disease - principles of pathophysiology and genetics. *International Journal of Molecular Sciences.* 2024;25(3): 1826. https://doi.org/10.3390/ijms25031826
31. Aggarwal A, Stolear A, Alam MM, et al. Catecholaminergic polymorphic ventricular tachycardia: clinical characteristics, diagnostic evaluation and therapeutic strategies. *Journal of Clinical Medicine*. 2024;13(6): 1781. https://doi.org/10.3390/jcm13061781.
32. Yang Y, Lv TT, Li SY, et al. Utility of provocative testing in the diagnosis and genotyping of congenital long QT syndrome: a systematic review and meta-analysis. *Journal of the American Heart Association.* 2022;11(14): e025246. https://doi.org/10.1161/JAHA.122.025246.
33. Kim CW, Aronow WS, Dutta T, et al. Catecholaminergic polymorphic ventricular tachycardia. *Cardiology in Review.* 2020;28(6): 325-331. https://doi.org/10.1097/CRD.0000000000000302.
34. Kallas D, Roston TM, Franciosi S, et al. Evaluation of age at symptom onset, proband status, and sex as predictors of disease severity in pediatric catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm.* 2021;18(11): 1825-1832. https://doi.org/10.1016/j.hrthm.2021.07.061.
35. Shlobin NA, Thijs RD, Benditt DG, et al. Sudden death in epilepsy: the overlap between cardiac and neurological factors. *Brain Commun.* 2024;6(5): fcae309. https://doi.org/10.1093/braincomms/fcae309.
36. Balfe C, Durand R, Crinion D, et al. The evidence for the implantable loop recorder in patients with inherited arrhythmia syndromes: a review of the literature. *Europace.* 2022;24(5): 706-712. https://doi.org/10.1093/europace/euab256.
37. Loginova EN, Kirkh EA, Nechaeva GI, et al. Role of genetic research in the prevention of life-threatening rhythm and cardiac conduction disorders in young people. *Russian Journal of Cardiology.* 2022;27(10): 4991. (In Russ.). https://doi.org/10.15829/1560-4071-2022-4991.
38. Lebedev D.S., Mikhailov E.N., Neminuschiy N.M. et al. Ventricular arrhythmias. Ventricular tachycardias and sudden cardiac death. 2020 Clinical guidelines. Russian Journal of Cardiology. 2021;26(7):4600. *Russian Journal of Cardiology.* (In Russ.). https://doi.org/10.15829/1560-4071-2021-4600.
39. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. ESC Scientific Document Group. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *European Heart Journal.* 2022;43(40):3997-4126. https://doi.org/10.1093/eurheartj/ehac262.
40. Martin S, Jenewein T, Geisen C, et al. Re-evaluation of variants of uncertain significance in patients with hereditary arrhythmogenic disorders. *BMC Cardiovascular Disorders.* 2024;24(1): 390. https://doi.org/10.1186/s12872-024-04065-w.
41. Martínez-Barrios E, Grassi S, Brión M, et al. Molecular autopsy: twenty years of post-mortem diagnosis in sudden cardiac death. *Frontiers of Medicine.* 2023;10: 1118585. https://doi.org/10.3389/fmed.2023.1118585.
42. Lynge TH, Albert CM, Basso C, et al. Autopsy of all young sudden death cases is important to increase survival in family members left behind. *Europace.* 2024;26(6): euae128. https://doi.org/10.1093/europace/euae128.
43. Isbister JC, Semsarian C. The role of the molecular autopsy in sudden cardiac death in young individuals. *Nature Reviews Cardiology*. 2024;21: 215-216. https://doi.org/10.1038/s41569-024-00989-0.
44. Dellefave-Castillo LM, Cirino AL, Callis TE, et al. Assessment of the diagnostic yield of combined cardiomyopathy and arrhythmia genetic testing. *Journal of the American Medical Association: Cardiology.* 2022;7(9): 966-974. https://doi.org/10.1001/jamacardio.2022.2455
45. Campuzano O, Sarquella-Brugada G, Cesar S, et al. Update on genetic basis of Brugada syndrome: monogenic, polygenic or oligogenic? *International Journal of Molecular Sciences.* 2020;21(19): 7155. https://doi.org/10.3390/ijms21197155.
46. Wang M, Tu X. The genetics and epigenetics of ventricular arrhythmias in patients without structural heart disease. *Frontiers in Cardiovascular Medicine*. Med. 2022;9: 891399. https://doi.org/10.3389/fcvm.2022.891399.
47. McGlinchey L, Barr O, Black P. Healthcare professionals' knowledge of inherited cardiac arrhythmias (ICA) their views towards and confidence in caring for a person with an ICA in a surgical environment. *European Heart Journal.* 2022;43(Suppl.2): ehac544.670. https://doi.org/10.1093/eurheartj/ehac544.670.

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THE POSSIBILITIES OF MONITORING THE EFFECTIVENESS OF ANTICOAGULANT THERAPY USING A THROMBODYNAMICS TEST IN PATIENTS WITH LEFT ATRIAL APPENDAGE THROMBOSIS WITH NON-VALVULAR ATRIAL FIBRILLATION: CLINICAL CASES

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Clinical observations of the possibility of using the thrombodynamics test (TD) in comparison with standard hemostasis tests in patients with non-valvular atrial fibrillation (AF) and detected thrombosis of the left atrial appendage against the background constant oral anticoagulants are presented. It has been shown that the transfer from one direct oral anticoagulant (DOACs) to another (with a different mechanism of action), as well as from DOACs to warfarin, can change the state of the blood plasma coagulation system towards both hyper- and hypocoagulation. Unlike standard hemostasis tests, TD can be used to assess the prothrombotic status of a patient with AF and personalized selection of effective anticoagulant therapy.

Key words: atrial fibrillation; thrombosis of the left atrial appendage; oral anticoagulants; thrombodynamics test

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Atrial fibrillation (AF) is a prognostically unfavourable cardiac arrhythmia, associated with a fivefold increase in the risk of thromboembolic events (TEEs) [1]. In non-valvular AF, left atrial appendage (LAA) thrombosis is the principal source of TEEs [2]. According to both European and national clinical guidelines, direct oral anticoagulants (DOACs) are preferred as first-line therapy over vitamin K antagonists for reducing thromboembolic risk in patients with non-valvular AF [1, 2]. However, even with continuous administration of appropriate anticoagulant therapy - including warfarin under strict international normalised ratio (INR) monitoring - the risk of thrombosis is not completely eliminated. Reported LAA thrombus detection rates range from 0.5% to 8.3% in the literature [3-5].

To explore potential mechanisms of thrombogenesis, it is of particular interest to assess haemostatic function during anticoagulant therapy, as hypercoagulability is one element of Virchow's triad. As is well known, warfarin dosing requires rigorous INR monitoring. In contrast, for DOACs, routine coagulation tests are not used for therapy monitoring or dose adjustment in everyday clinical practice [6, 7]. According to the European Practical Guide on the use of DOACs in patients with non-valvular AF, standard coagulation tests and drug-specific assays to determine DOAC plasma concentrations are recommended only in emergency situations (e.g. stroke, bleeding, surgery) [7].

A review of current literature indicates that changes in core laboratory parameters of plasma haemostasis during anticoagulant therapy remain insufficiently studied. In this context, a personalised approach to anticoagulant selection - based on efficacy monitoring - becomes particularly promising. This can be achieved using a novel global coagulation assay known as the thrombodynamics (TD) test [8]. Only a limited number of studies have explored the use of TD parameters in patients with AF under complex clinical circumstances requiring verification of anticoagulant efficacy - for instance, in cases of documented LAA thrombosis or previous transient ischaemic attack [9, 10].

Principle of the Thrombodynamics Test

The TD test assesses both the qualitative and quantitative characteristics of the coagulation state of plasma, enabling analysis of the spatiotemporal dynamics of fibrin clot formation in vitro [8].

The test is performed using the "Thrombodynamics T-2 Analyser" laboratory system. Prepared platelet-free plasma samples are introduced into two channels of a measuring cuvette, into which a special insert-activator is placed. The edges of this insert are coated with lipids and tissue factor. Upon contact between the plasma and the activator insert, coagulation is initiated, leading to the formation of a fibrin clot. The process is recorded by sequential digital photomicrography using a dark-field method (light scattering registration) over 30 minutes. The resulting series of images reveals the evolution of clot size, shape, and structure over time [11].

Software analysis of the images generates curves

describing clot growth dynamics and spontaneous clot formation area over time. These data yield the following quantitative parameters of fibrin clot propagation: Lag time (Tlag) - delay before clot growth begins; Clot growth velocity (V); Initial clot growth rate (Vi); Steady-state growth rate (Vst); Clot size at 30 minutes (CS); Clot density (D) - based on light scattering intensity.

In addition, the test calculates the time to spontaneous clot formation (Tsp), defined as the time required for spontaneous clots to occupy 5% of the cuvette area away from the main clot front.

To assess anticoagulant efficacy, blood collection for the TD test is recommended at trough DOAC levels (i.e., shortly before the next dose). For warfarin users, the test is performed in the morning, not earlier than on the 7th day of continuous therapy.

The following clinical observations illustrate the potential of thrombodynamics testing - compared to standard haemostasis assays - for guiding anticoagulant therapy selection in patients with non-valvular AF and confirmed LAA thrombosis.

Clinical Case No. 1

Patient Sh., 42 years old, was admitted to the clinic in April 2024 with complaints of palpitations, shortness of breath when walking at a brisk pace, and general weakness. Medical history revealed a diagnosis of arterial hypertension established five years ago; however, the patient had not been taking antihypertensive medication regularly. His condition worsened in February 2024, when, for the first time upon arriving at his remote worksite, he experienced an episode of rapid and irregular heartbeat. ECG revealed atrial fibrillation with a ventricular rate (VR) of 110 bpm. The paroxysm resolved following bisoprolol intake. Subsequently, AF episodes recurred and reportedly transitioned into a persistent form approximately two months prior (AF with VR ranging from 100 to 116 bpm was consistently recorded on serial ECGs).

Transthoracic echocardiography (TTE) revealed hypokinesia of the inferior wall of the left ventricle (LV), with an asynergy zone area of 20%, dilation of both atria, an enlarged LA volume of 107 ml, and a reduced LV ejection fraction (LVEF) of 46%. Before hospital admission for coronary angiography (CAG) and evaluation for catheter ablation (CA), the patient was treated for one month with the following medications: metoprolol succinate 100 mg/day, perindopril 2 mg/day, apixaban 5 mg twice daily, rosuvastatin 20 mg/day, dapagliflozin 10 mg/day, and spironolactone 25 mg/day. CAG revealed no evidence of coronary artery stenosis. TEE showed marked spontaneous echo contrast in the LA and LAA, partial opacification of the LAA on colour Doppler imaging, a reduced LAA flow velocity of 30 cm/sec, and a soft, mobile, unorganised mural thrombus measuring 14 mm at the LAA ostium (Fig. 1a). Laboratory tests (complete blood count, biochemical panel, thyroid-stimulating hormone) showed no significant deviations from reference values.

Final clinical diagnosis: Hypertension, Stage III. Controlled arterial hypertension. Dyslipidaemia. Cardiovascular risk: very high (score 4). Target BP ≤130/70-79 mmHg. Complications: Atrial fibrillation, persistent form. CHA_2DS_2-VASc: 2, HAS-BLED: 1. Secondary atrial dilation. Soft mural thrombus at the LAA ostium. Chronic heart failure (CHF) IIA with moderately reduced ejection fraction (46%), NYHA functional class II.

To assess haemostatic status, the following tests were performed: activated partial thromboplastin time (aPTT),

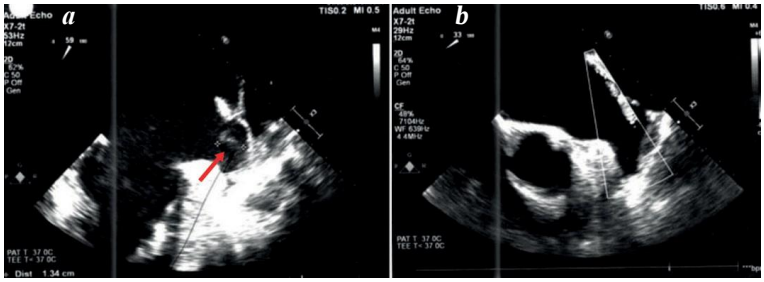

Fig. 1. Transoesophageal echocardiography (TEE) of patient Sh.: a - soft thrombus (indicated by arrow) in the ostium of the left atrial appendage (LAA) during apixaban therapy; b - no evidence of LAA thrombosis during dabigatran therapy.

Table 1.

Haemostasis Test Parameters in Patient Sh. During Apixaban and Dabigatran Therapy

Parameter	Reference Values	Apixaban 10 mg/day	Dabigatran 300 mg/day (3 days)	Dabigatran 300 mg/day (1 month)
Standard Haemostasis Tests				
aPTT, sec	26-36	34,8	49,1	-
PTI, %	80-120	90,6	85,3	-
INR	0,95-1,2	1,17	1,33	-
TT, sec	15-20	16,2	>250	-
Fibrinogen, g/L	2-4	3,76	3,54	-
Thrombodynamics Parameters				
Vi, μm/min	38-56	48,5	42,9	42,8
Vst, μm/min	20-29	27,3	25,1	25
Tlag, min	0,6-1,5	1,1	1,5	1,5
CS, μm	800-1200	1039	955	940
D, a.u.	15000-32000	25765	24163	17698
Tsp, min	none	none	none	none

Note: here and afetr: aPTT - activated partial thromboplastin time; INR - international normalized ratio; PTI - prothrombin index; TT - thrombin time; Vi - initial velocity; Vst - steady-state velocity; Tlag - growth delay; CS - clot size after 30 minutes; D - density; Tsp - time of spontaneous clot appearance.

prothrombin time (PT) expressed as prothrombin index (PI) and international normalized ratio, thrombin time (TT), fibrinogen, and thrombodynamics (TD) assay. Standard coagulation tests and TD analysis (Table 1) showed no abnormalities during apixaban therapy. However, TD parameters revealed no prolongation of clot growth lag time (Tlag), prompting a change in anticoagulant therapy: apixaban was replaced by a direct thrombin inhibitor - dabigatran, 300 mg/day. On day 3 of dabigatran therapy, aPTT and TT were elevated in standard coagulation tests, and TD results showed improvement - slower clot formation, reduced clot density, and prolonged Tlag. After one month of dabigatran therapy, TD parameters (Vst, Vi, Tlag, CS) remained stable, with clot density further reduced from 24,163 to 17,698 units.

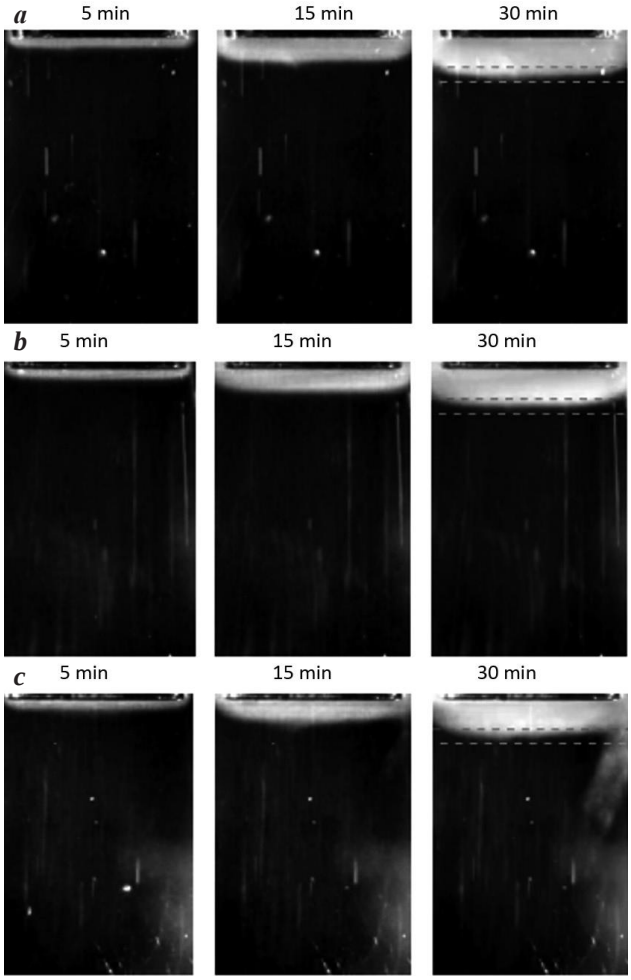

Fig. 2. Fibrin clot images obtained at 5, 15, and 30 minutes of the thrombodynamics (TD) test during apixaban and dabigatran therapy in patient Sh.: a - clot formation after 1 month of apixaban therapy; b - after 3 days of dabigatran therapy; c - after 1 month of dabigatran therapy. Images b and c demonstrate normocoagulation, with no spontaneous clotting, reflecting an optimal anticoagulant effect of the DOAC.

Follow-up TEE after one month showed full opacification of the LAA, mild residual SEC in the LA and LAA, improved LAA flow velocity (increased from 30 to 48 cm/sec), and no signs of thrombosis (Fig. 1b). ECG revealed spontaneous restoration of sinus rhythm. Follow-up TTE showed improvement in LVEF from 46% to 63%, and no residual asynergy zones were observed. Fibrin clot images from TD testing under apixaban and dabigatran therapy are presented in Fig. 2. This clinical case demonstrates the utility of the TD assay in monitoring the dynamics of a prothrombotic state following a change in anticoagulant therapy. The effectiveness of dabigatran was confirmed by the successful resolution of LAA thrombosis.

Clinical Case No. 2

Patient Ts., 64 years old, was admitted to the clinic in June 2022 with complaints of irregular heartbeat, dyspnoea during moderate physical exertion, general weakness, and fatigue. Medical history revealed a diagnosis of arterial hypertension established 15 years prior. The target blood pressure had been achieved through antihypertensive therapy. Approximately five months before admission, the patient experienced his first episode of palpitations, irregular heart rhythm, fatigue, and substernal discomfort not clearly associated with physical activity. AF was recorded on ECG. The patient independently discontinued the prescribed therapy (bisoprolol 10 mg/day, apixaban 10 mg/day, losartan 100 mg/day, atorvastatin 20 mg/day) due to a tendency toward hypotension and bradycardia (heart rate dropping to 50 bpm). He was hospitalised for CAG and further treatment planning.

CAG revealed no haemodynamically significant stenotic lesions of the coronary arteries. TTE showed aortic atherosclerosis, dilation of the left atrium (LA) with a volume of 70 ml (B-mode), dilation of the right atrium (volume 62 ml), and a slight reduction in left ventricular systolic function at rest (LVEF 51%). TEE showed no signs of LAA thrombosis, although moderate spontaneous echo contrast was observed in the LAA and LA cavity. The LAA flow velocity was reduced to 34 cm/sec. Given the absence of regular anticoagulant intake prior to hospitalisation and the presence of spontaneous echo contrast , which increases the risk of thromboembolic complications, the patient was discharged with a recommendation for continuous anticoagulant therapy with dabigatran 300 mg/day, followed by reassessment via TEE and consideration for CA.

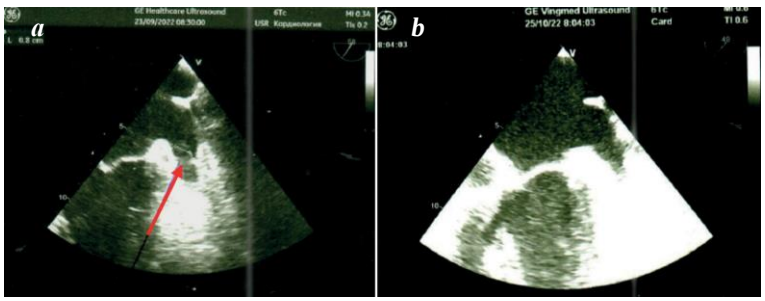

Fig. 3. Transoesophageal echocardiography (TEE) of patient Ts.: a - soft mural thrombus in the LAA (indicated by arrow) during dabigatran therapy; b - no evidence of LAA thrombosis during warfarin therapy.

At repeat hospitalisation in August 2022, the patient was adhering to the prescribed regimen: dabigatran 300 mg/day, losartan 50 mg/day, amlodipine 5 mg/day, and rosuvastatin 20 mg/day. Repeat TEE revealed persistence of moderate SEC in the LAA and LA cavity. The LAA flow velocity had further decreased to 24

cm/sec. A soft, irregularly shaped mural thrombus measuring 8 × 14 mm was visualised on the trabeculae of the LAA (Fig. 3).

The final clinical diagnosis was: Hypertensive heart disease, Stage III. Controlled arterial hypertension. Dyslipidaemia. Cardiovascular risk: very high (score 4). Target BP ≤130/70-79 mmHg. Complications: Atrial fibrillation, persistent form. CHA_2DS_2-VASc: 2, HAS-BLED: 1. Soft mural thrombus in the LAA. CHF IIA, NYHA functional class II.

Standard haemostasis tests revealed significant prolongation of TT to 143 sec, indicating thrombin inhibition by dabigatran. TD testing showed signs of hypercoagulation, specifically an increase in the stationary clot growth velocity to 29.6 sec (Table 2, Fig. 4a). The prolongation of Tlag confirmed inhibition of the clot initiation phase by dabigatran. However, the rate of fibrin clot formation did not decrease and, on the contrary, had increased.

Given the presence of LAA thrombus on TEE and TD indicators of hypercoagulability, the patient was switched to warfarin with close INR monitoring, aiming to maintain values within the therapeutic range of 2.5-3.0. During outpatient follow-up, INR was monitored weekly, and the time in therapeutic range was 70%. TD testing during warfarin therapy revealed hypocoagulation, with reduced initial and stationary clot growth rates and decreased clot density (Table 2, Fig. 4b). Repeat TEE after two months of warfarin therapy (October 2022) showed no evidence of thrombosis or SEC in the LAA (Fig. 3b), which enabled referral of the patient for catheter ablation. This clinical case illustrates a discrepancy between standard coagulation test results (prolonged TT) and thrombodynamics indicators (signs of hypercoagulation) during dabigatran therapy. Warfarin therapy, under tight INR control and guided by TD testing, was associated with hypocoagulation parameters and subsequent thrombus resolution in the LAA as confirmed by TEE.

DISCUSSION

Haemostasis is a complex cascade system comprising the vascular-platelet and coagulation components, as well as the anticoagulant and fibrinolytic systems. Among local haemostasis tests used in clinical practice, the most commonly applied are activated aPTT, PT/INR, TT, which respectively reflect the intrinsic and extrinsic coagulation pathways, and the polymerisation of fibrinogen into fibrin in the presence of fibrinolytic agents and natural anticoagulants.

In recent years, DOACs have increasingly been used in clinical practice for both prevention and treatment of thromboembolic events. Unlike vitamin K antagonists, DOACs have a rapid onset of action, are administered in fixed doses without routine coagulation monitoring, owing to their more predictable pharmacokinetics and pharmacodynamics. Although the absence of regular laboratory monitoring is considered an advantage of DOACs, the assessment of anticoagulant effect or drug concentration can be valuable in certain clinical scenarios, such as thrombosis, bleeding, or surgical interventions [6]. The detection of a thrombus in the LAA during adequate anticoagulant therapy [4] also supports the need for haemostasis monitoring in routine practice.

Standard haemostasis tests, including aPTT, PT/INR, and TT, are readily available and may serve as first-line tools for qualitative evaluation of DOAC effects. TT is particularly used to assess the anticoagulant effect of dabigatran. This test is highly sensitive to dabigatran activity - even low plasma concentrations (≥25 ng/mL) can prolong TT. High-sensitivity tests for dabigatran measurement, such as diluted TT and ecarin clotting time (ECT) using mass spectrometry, exist [6], but they are not accessible in routine clinical settings.

Rivaroxaban prolongs PT in a concentration-dependent manner, but the effect varies significantly depending on the thromboplastin reagent used, due to differing sensitivities to the drug. Rivaroxaban may also increase aPTT, although this test is less sensitive than PT and is not recommended for patients on rivaroxaban [6]. There are even fewer published studies on laboratory monitoring of apixaban compared to rivaroxaban.

In general, standard coagulation tests such as PT and aPTT have limited sensitivity to the effects of apixaban, and thus are not recommended for assessing its anticoagulant activity. Currently, anti-Xa chromogenic assays calibrated specifically for each factor Xa inhibitor are used to quantify their effects. However, the lack of certified calibrators for rivaroxaban and apixaban limits their routine use in clinical settings.

Recent studies have investigated the correlation between DOAC concentrations (apixaban, rivaroxaban) and anti-Xa assay results using low-molecular-weight heparin

Table 2.

Haemostasis Test Parameters in Patient Ts. During Dabigatran and Warfarin Therapy

Parameter	Reference Values	Dabigatran 300 mg/day	Warfarin 6.25 mg/day (2.5 months)
Standard Haemostasis Tests			
aPTT, sec	26-36	32,5	-
PTI, %	80-120	80,1	-
INR	0,95-1,2	1,23	2,3
TT, sec	15-20	143	-
D-dimer, μg/mL	0-0,5	0,3	-
Fibrinogen, g/L	2-4	3,77	-
Antithrombin III, %	75-140	94,6	-
Thrombodynamics Parameters			
Vi, μm/min	38-56	42,7	36,3
Vst, μm/min	20-29	29,6	18,6
Tlag, min	0,6-1,5	2,2	1
CS, μm	800-1200	1041	753
D, a.u.	15000-32000	23855	23412
Tsp, min	none	none	none

(LMWH) calibrators. These studies suggest that anti-Xa assays may detect subtherapeutic DOAC concentrations, but their utility appears restricted to emergency situations, such as bleeding risk assessment before invasive procedures [12, 13].

Our findings demonstrate that TT is a viable test for evaluating dabigatran activity, but in Clinical Case No. 1, local haemostasis tests were not sensitive to apixaban, in line with published literature [6].

Classical local haemostasis tests assess isolated components of the haemostatic system and have limited sensitivity to hypercoagulable states. This highlights the importance of a novel global method for diagnosing plasma coagulation disorders - the TD test - which is designed to identify thrombotic risk in cardiovascular patients and to monitor anticoagulant therapy effectiveness.

The TD test is based on video registration of fibrin clot growth from a simulated damaged vessel wall. Changes in TD parameters correlate closely with the mechanism and concentration of anticoagulants in plasma. Specific diagnostic parameters reflect distinct phases of fibrin clot formation, allowing comprehensive qualitative and quantitative assessment of how different anticoagulants impact the haemostatic system of an individual patient.

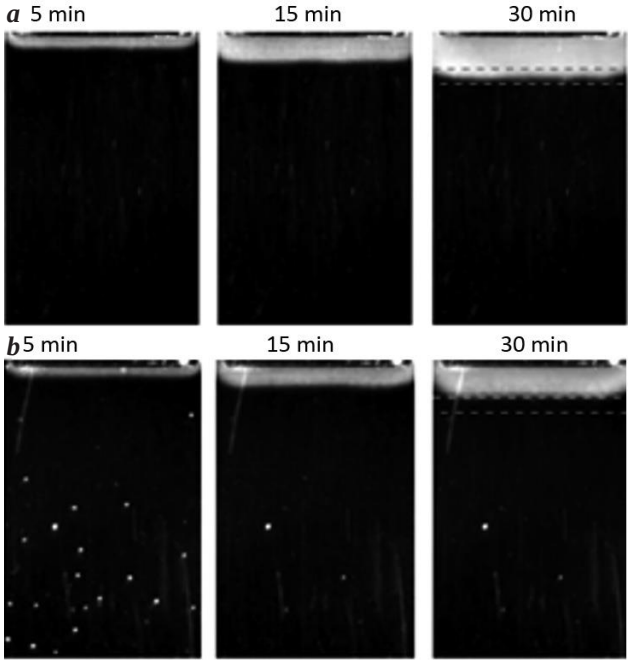

Fig. 4. Fibrin clot images obtained at 5, 15, and 30 minutes of the thrombodynamics (TD) test during dabigatran (a) and warfarin (b) therapy in patient Ts. Dabigatran therapy was associated with hypercoagulation (increased Vst of the fibrin clot), with no spontaneous clotting observed. Warfarin therapy resulted in hypocoagulation, demonstrated by a moderate reduction in the dynamic parameters of clot formation (Vst, Vi, clot size), indicating an adequately selected dose of the anticoagulant.

In limited clinical studies, TD has demonstrated higher sensitivity to anticoagulant therapy (e.g., heparins, warfarin) compared to aPTT and other global coagulation tests such as thrombin generation test and thromboelastography [14, 15]. TD sensitivity was also comparable to that of anti-Xa activity assays [15]. However, similar data for DOACs are not yet available.

Generally, DOACs primarily increase Tlag (indicating inhibition of the clot activation phase) and reduce the clot growth rate V. In 2022, Z.E. Gebekova et al. reported TD parameters in AF patients without prior thrombotic or bleeding events receiving various DOACs [8]. The TD parameters mostly remained within reference ranges, reflecting an optimal anticoagulant effect. These data support the safety and efficacy of DOACs, even with residual drug concentrations.

Our clinical observations showed that in some patients, DOAC use was associated with increased fibrin clot growth rate and density in TD, suggesting a possible reduced sensitivity to certain DOACs. Switching from one DOAC to another (with a different mechanism of action) or from a DOAC to warfarin can markedly alter the coagulation profile - towards either hypercoagulation or hypocoagulation.

Numerous studies have investigated predictors of LAA thrombosis in patients with non-valvular AF [4, 5], but there are still no clear algorithms for anticoagulant management when LAA thrombus is already present. According to national guidelines, a change in anticoagulant is recommended when a thrombus is detected in the LAA prior to cardioversion [2]. However, there remains uncertainty regarding the preferred oral anticoagulant and the optimal timing for follow-up TEE to assess thrombus status.

In this context, the key issue becomes evaluating both the efficacy and safety of the prescribed anticoagulant.

The clinical cases presented suggest that the TD test may be a valuable additional tool for early assessment of the coagulation status and for personalised selection of effective anticoagulant therapy aimed at LAA thrombus resolution - an area warranting further research.

CONCLUSION

The detection of left atrial appendage thrombosis despite adequate anticoagulant therapy highlights the necessity of laboratory monitoring of the coagulation system. The presented clinical cases have demonstrated the advantages of the thrombodynamics test over standard haemostasis assays in assessing the patient's prothrombotic status and in the personalised selection of effective anticoagulant therapy in patients with atrial fibrillation and LAA thrombosis**.**

REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal.* 2021;42(5): 373-498. https://doi.org/10.1093/eurheartj/ehaa612.

2. Arakelyan MG, Bockeria LA, Vasilieva EYu, et al. 2020 Clinical guidelines for Atrial fibrillation and atrial flutter. *Russian Journal of Cardiology.* 2021;26(7): 4594. (In Russ.). https://doi.org/10.15829/1560-4071-2021-4594.

3. Zhan Y, Joza J, Rawahi M, et al. Assessment and management of the Left Atrial Appendage Thrombus in Pa-

tients with Nonvalvular Atrial Fibrillation. *Canadian Journal of Cardiology*. 2018;34(3): 252-261. https://doi.org/10.1016/j.cjca.2017.12.008.
4. Krivosheev YS, Bashta DI, Krasilnikova SY, et al. Left atrial appendage thrombosis in atrial fibrillation - current status of the problem. *Journal of Arrhythmology*. 2019;26(4): 13-20 (In Russ.). https://doi.org/10.35336/VA-2019-4-13-20.
5. Khorkova NYu, Gizatulina TP, Belokurova AV, et al. Additional factors of thrombosis of the left atrial appendage in nonvalvular atrial fibrillation. *Journal of Arrhythmology*. 2020;27(2): 26-32. (In Russ.). https://doi.org/10.35336/VA-2020-2-26-32.
6. Ten Cate H, Henskens YM, Lancé MD. Practical guidance on the use of laboratory testing in the management of bleeding in patients receiving direct oral anticoagulants. *Vasc Health Risk Management*. 2017;13: 457-467. https://doi.org/ 10.2147/VHRM.S126265.
7. Steffel J, Collins R, Matthias Antz M, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. *Europace*. 2021;23: 1612-1676. https://https://doi.org/10.1093/eurheartj/ehy136.
8. Gebekova ZA, Ivanov II., Asambayeva A, et al. Thrombodynamics Test in Assessing the Risk of Thrombus Formation in Patients with Atrial Fibrillation Taking Direct Oral Anticoagulants. *Rational Pharmacotherapy in Cardiology*. 2022;18(5): 544-552 (In Russ.). https://https://doi.org/10.20996/1819-6446-2022-09-07.
9. Gebekova ZA, Ivanov II, Kudrjavtseva AA, et al. New prospects for assessing the hemostasis system in atrial fibrillation and left atrial appendage thrombosis. *Atherothrombosis*. 2022;12(2): 103- 112. (In Russ.). https://doi.org/10.21518/2307-1109-2022-12-2-103-112.
10. Vuimo T, Belikov E, Litinskaya O, Davtyan K. Efficiency of Thrombodynamics for Analysis of Hemostasis in Case of Transitory Ischemic Attack after Radiofrequency Ablation in a Patient with Paroxysmal Atrial Fibrillation. *Am J Med Case Reports*. 2015;3: 333-337. https://https://doi.org/10.12691/ajmcr-3-10-8.
11. Balandina AN, Koltsova EM, Shibeko AM, et al. Thrombodynamics: a new method to the diagnosis of hemostasis system disorders. *Pediatric hematology/oncology and immunopathology*. 2018;17(4): 114–126 (In Russ.). https:// doi.org/10.24287/1726-1708-2018-17-4-114-126.
12. Titaeva EV, Dobrovolsky AB. Chromogenic anti-Xa test: the ratio between heparin activity units and concentration of apixaban and rivaroxaban. *Aterotromboz = Atherothrombosis*. 2020;(2): 96-104. (In Russ.). https://doi.org/10.21518/2307-1109-2020-2-96-104.
13. Billoir P, Barbay V, Joly LM, et al. Anti-Xa Oral Anticoagulant Plasma Concentration Assay in Real Life: Rivaroxaban and Apixaban Quantification in Emergency with LMWH Calibrator. *Ann Pharmacother*. 2019;53(4): 341-347. https:// doi.org/10.1177/1060028018811657.
14. Gracheva MA, Urnova ES, Sinauridze EI, et al. Thromboelastography, thrombin generation test and thrombodynamics reveal hypercoagulability in patients with multiple myeloma. *Leuk. Lymphoma*. 2015;56(12): 3418-25. https://doi.org/10.3109/10428194.2015.1041385.
15. Balandina AN, Serebriyskiy II, Poletaev AV, et al. Thrombodynamics - a new global hemostasis assay for heparin monitoring in patients under the anticoagulant treatment. *PloS One*. 2018;13(6): e0199900. https://doi.org/10.1371/journal.pone.0199900.

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SELECTIVE AND NON-SELECTIVE LEFT BUNDLE BRANCH PACING

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Left bundle branch (LBB) pacing is a novel method of cardiac pacing, which can prevent development of interventricular dyssynchrony, and also could be used as a resynchronization therapy in patients with low ejection fraction and LBB block. Demonstration of the specific electrocardiographic criteria is essential to confirm LBB capture.

Key words: cardiac pacing; left bundle branch; heart failure; conduction system

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Left bundle branch area pacing (LBBAP**)** is a relatively new method of cardiac pacing that allows for the prevention of interventricular dyssynchrony typically associated with conventional right ventricular pacing [1-5]. This technique may also serve as an alternative to cardiac resynchronisation therapy (CRT) in patients with heart failure and left bundle branch block (LBBB). LBBAP involves implantation of a right ventricular lead deep into the interventricular septum (IVS), extending to the subendocardial layers of the left ventricle, with the aim of establishing direct contact between the lead helix and the fibers of the left bundle branch (LBB). Successful capture of the LBB requires a sound understanding of cardiac electrophysiology as well as specific fluoroscopic equipment in the catheterization lab.

Criteria for Left Bundle Branch Area Pacing [1]

1. Transition from Non-selective to Selective LBBAP (sLBBAP) During Pacing Threshold Assessment**:** Selective LBBAP refers to the capture of only the specialised conduction system, while non-selective LBBAP involves simultaneous capture of the left bundle branch (LBB) and adjacent interventricular septal myocardium. Immediately after lead implantation, the myocardial capture threshold is typically higher than that of the conduction system. This difference may diminish within minutes post-implantation, making the transition from non-selective to selective LBBAP difficult to reproduce during subsequent pacemaker checks.

2. Electrocardiographic (ECG) Criteria

• Stimulus-to-R Wave Peak Interval in Lead V6 (St-RV6, Left Ventricular Activation Time): Normally, the time from the onset of the QRS complex to the R-wave peak in lead V6 is ≤50 ms. In the presence of LBBB, this interval typically exceeds 60 ms. Since conduction through the LBB to the distal Purkinje fibres and working myocardium takes approximately 30 ms, this value should be added to the "native" RV6 peak time when evaluating pacing-induced activation. During selective LBB pacing (sLBBP), an isoelectric interval is observed on the ECG during this conduction delay. In non-selective pacing (nsLBBP), a pseudo-delta wave may appear due to depolarisation of the adjacent septal myocardium. Thus, according to established LBB pacing criteria, the St-RV6 interval should be less than 75-80 ms.

• Interval Between R-Wave Peaks in Leads V6 and V1 (RV1-RV6): During LBB pacing, right ventricular activation is delayed relative to the left ventricle. This results in a paced right bundle branch block (RBBB) morphology, with a characteristic late R wave in lead V1. Based on accepted criteria, the RV1-RV6 interval should be at least 33 ms (and ≥44 ms according to more stringent standards).

• Prolongation of the Stimulus-to-RV1 Peak Interval (St-RV1) by >10 ms during transition from nsLBBP to sLBBAP. This criterion reflects the loss of adjacent septal myocardial capture and the subsequent delay in activation of the right ventricular lateral wall. It is essentially a composite of the previous two criteria.

• Prolongation of St-RV6 by >15 ms with Decreased Output Amplitude: This pattern indicates a transition from non-selective LBB capture to isolated septal myocardial pacing, reflecting loss of LBB capture - essentially the reverse of the phenomenon described in section A.

• St-RV6 Should Match the Intrinsic Conduction Time from the LBB Potential to the RV6 Peak: The difference between these two measurements should not exceed 10 ms.

Recording of signals from the implanted lead in the region of the LBB is an essential component of the procedure and determines the success of the implantation. The lead is connected to the electrophysiological recording system and the analyser in a unipolar configuration. To visualise the current of injury (COI), we use the following

bandpass filter settings: high-pass filter - 0.5 Hz; low-pass filter - 500 Hz. The electrogram from the lead tip used to record potentials is typically filtered at 30-500 Hz.

Figure 1 presents surface ECG leads, unfiltered COI signal, and filtered LBB electrogram (LB EGM) from the tip of the implanted lead. Figure 1a shows a native QRS complex with a duration of 94 ms. Intrinsic conduction via the LBB allowed identification of the LBB potential (arrow). The interval from the LBB potential to the R-wave peak in lead V6 was 80 ms. Analysis of the COI endogram revealed an RS morphology, indicating subendocardial positioning of the ventricular lead helix. Figure 1b illustrates non-selective LBB area pacing (nsLBBP). The St-RV6 interval was 84 ms (similar to the intrinsic conduction time from the LBB potential to RV6 peak), St-RV1 was 116 ms, and the RV1-RV6 interval was 32 ms. A pseudo-delta wave is visible in leads I, V5, and V6, suggesting local capture of the adjacent interventricular septal myocardium. Figure 1c shows sLBBP achieved by reducing pacing output from 5 V to 1 V. This is evidenced by a stable St-RV6 interval of 86 ms (matching the previous 84 ms seen during nsLBBP), disappearance of the pseudo-delta wave, prolongation of the St-RV1 interval to 134 ms, an increase in the RV1-RV6 interval to 48 ms (+16 ms compared to nsLBBP).

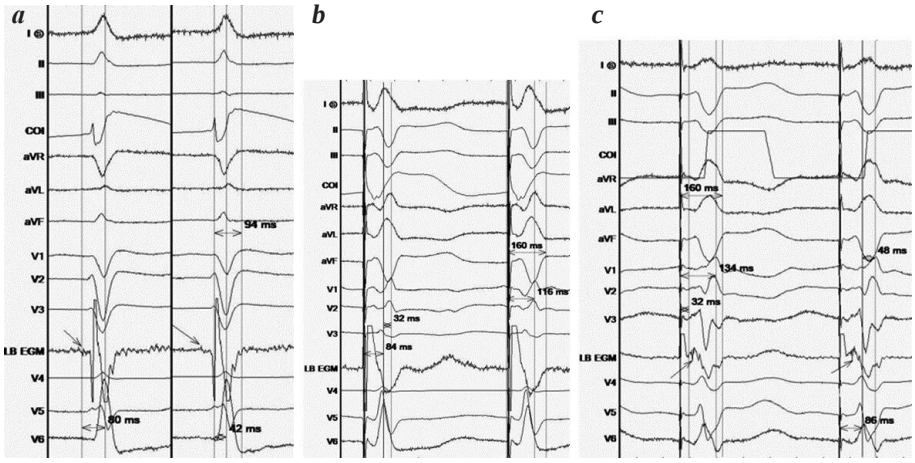

Fig. 1. Selective and Non-selective Left Bundle Branch Area Pacing (a) Native QRS complex with a duration of 94 ms. The LBB potential is indicated by an arrow; the interval from the LBB potential to the R-wave peak in lead V6 was 80 ms. (b) Non-selective LBB pacing: St-RV6 interval was 84 ms (equivalent to intrinsic conduction time from the LBB potential to RV6 peak), St-RV1 was 116 ms, RV1-RV6 interval was 32 ms. A pseudo-delta wave is visible in leads I, V5, and V6. (c) Selective LBB pacing: St-RV6 interval was 86 ms, St-RV1 increased to 134 ms, and RV1-RV6 to 48 ms. The pseudo-delta wave disappeared. A local ventricular myocardial potential is indicated by the arrow.

Additionally, a local ventricular myocardial potential (arrow) becomes apparent, indicating delayed activation of the basal septal segments following conduction through the LBB, Purkinje fibres, and retrograde excitation from the apex back toward the basal regions of the septum.

REFERENCES

1. urri H, Jastrzebski M, Cano O, et al. EHRA clinical consensus statement on conduction system pacing implantation: endorsed by the Asia Pacific Heart Rhythm Society (APHRS), Canadian Heart Rhythm Society (CHRS), and Latin American Heart Rhythm Society (LAHRS). *EP Europace.* 2023;25(4): 1208-36. https://doi.org/10.1093/europace/euad043.

2. Huang W, Chen X, Su L, et al. A beginner's guide to permanent left bundle branch pacing. *Heart Rhythm.* 2019;16(12): 1791-6. https://doi.org/10.1016/j.hrthm.2019.06.016.

3. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC) With the special contribution of the European Heart Rhythm Association (EHRA). *European Heart Journal.* 2021;42(35): 3427-3520. https://doi.org/10.1093/eurheartj/ehab364.

4. Wu S, Su L, Vijayaraman P, et al. Left bundle branch pacing for cardiac resynchronization therapy: non- randomized on-treatment comparison with His bundle pacing and biventricular pacing. *Canadian Journal of Cardiology.* 2020;37: 319-328. https://doi.org/10.1016/j.cjca.2020.04.037.

5. Vijayaraman P, Ponnusamy S, Cano Ó, et al. Left Bundle Branch Area Pacing for Cardiac Resynchronization Therapy: Results From the International LBBAP Collaborative Study Group. J*ACC Clinical Electrophysiology.* 2020;7(2):135-147. https://doi.org/10.1016/j.jacep.2020.08.015.