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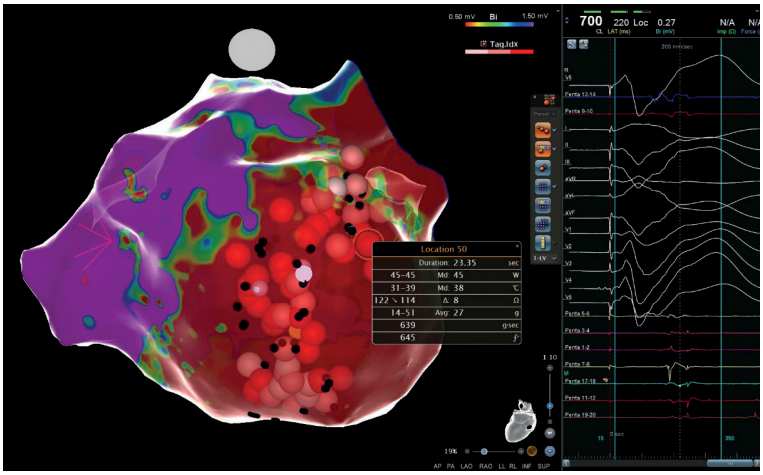

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CONTENT

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LEFT ATRIAL VOLTAGE CHARACTERISTICS IN PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION

V.Yu.Tcivkovskii, A.V.Chapurnykh, V.B.Nizhnichenko

Central Clinical Hospital of the Presidential Administration of the Russian Federation, 15 Marshala Timoshenko str.

Aim. The aim of the study was to assess the impact of comorbidities and duration of arrhythmic anamnesis on the results of left atrium voltage mapping in patients with persistent atrial fibrillation (AF).

Methods. The study enrolled 50 patients who underwent the first radiofrequency ablation of persistent AF. Left atrium endocardial voltage maps were obtained using a 3D electroanatomical mapping system during AF. The voltage maps consisted of at least 2,000 points, with an average of 2,128±104 points. Low-voltage areas (LVA) were defined as <0.5 mV. The percentage of LVA% and very LVA% were calculated.

Results. We found a statistically significant correlation of LVA% with age ($p<0.001$, $r=0.720$), female sex ($p=0.016$), and the duration of arrhythmic history at the time of the start of persistence ($p<0.001$, $r=0.503$). Based on the data obtained, an original scale was developed to predict LVA%. The scale includes age, female sex, and the duration of arrhythmic history at the start of persistence. A score of 1 point was assigned for an age over 65 years, 1 point for female gender, and 1 point for a duration of arrhythmic history over 4 months; otherwise, 0 points were given. The total score ~~on~~ of the scale showed a high correlation with LVA% ($p<0.001$, $r=0.768$). The scale was named AFD-rhythm (Age, Female Sex, Duration of arrhythmic anamnesis at the Start of Persistence).

Conclusions. Age, female sex, and the duration of arrhythmic anamnesis at the start of persistence are predictors of LVA% of the left atrium in patients with persistent atrial fibrillation. The original AFD-rhythm scale can be used to predict the percentage of left atrium low voltage in patients with persistent AF.

Key words: atrial fibrillation; radiofrequency ablation; high-density mapping; left atrial low voltage

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Corresponding author: Tcivkovskii Viktor, E-mail: tsivkov@gmail.com

V.Yu.Tcivkovskii - ORCID ID 0009-0007-5470-4969, A.V.Chapurnykh - ORCID ID 0000-0001-5517-855X, V.B.Nizhnichenko - ORCID ID 0000-0003-2329-8156

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The identification of pulmonary vein (PV) ectopy as a trigger for atrial fibrillation (AF), first reported by M. Haïssaguerre et al. in 1998, led to the development of PV isolation, which today carries a class I indication for radiofrequency ablation (RFA) of AF [1]. However, it soon became evident that ectopic activity may also originate outside the PVs, and that trigger-induced paroxysmal AF can progress to substrate-dependent persistent or long-standing persistent AF. This was confirmed by J. Seitz et al. (2017), who demonstrated that ablation of AF triggers outside the PVs, without PV isolation, resulted in arrhythmia-free survival in 85% of patients during 18 months of follow-up [2].

At the same time, empirical additional linear ablations and substrate modification, performed with the aim of treating substrate-dependent AF, were investigated in the STAR-AF II trial, which did not show a reduction in AF recurrence compared with standard PV antral isolation [3]. The investigators concluded that patient-specific substrate ablation requires a deeper understanding.

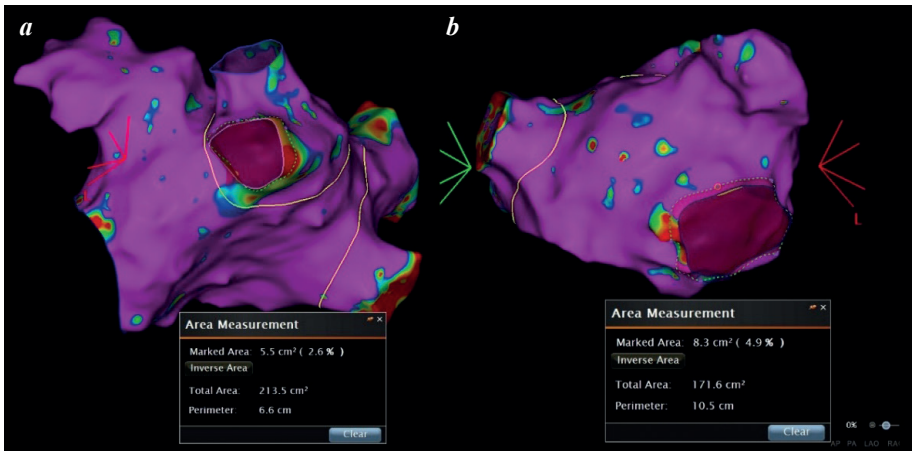

Fig. 1. Left atrial voltage mapping: (a) measurement of the area of the left inferior pulmonary vein ostium; (b) measurement of the mitral valve annulus.

One mechanism of arrhythmia progression is the spread of left atrial (LA) fibrosis and its arrhythmogenic effect. The gold standard for visualising myocardial fibrosis is late gadolinium enhancement magnetic resonance imaging (MRI), which allows indirect assessment of the extent of LA fibrosis [4]. However, this method has several limitations, including cost, contraindications, and poor reproducibility across centres [5]. R. S. Oakes et al. (2009) demonstrated a correlation between the extent of late gadolinium enhancement and low-voltage areas on electroanatomical mapping [6]. Subsequently, it was shown that the extent of low-voltage areas directly correlates with AF recurrence rates [7].

A large number of scoring systems have been proposed to predict the proportion of low-voltage areas in the LA. However, in studies supporting the utility of such scores, electroanatomical mapping was usually performed in sinus rhythm after cardioversion in patients with persistent AF, which may have influenced mapping results. At the same time, little attention has been paid to the assessment of factors influencing atrial signal amplitude during ongoing AF.

Aim: to evaluate the influence of comorbidities and arrhythmia history on LA voltage mapping outcomes in patients with persistent AF.

METHODS

The study included 50 patients with persistent AF referred for first-time RFA. The mean age was 67.10 ± 9.49 years; 36 were men (72%) and 14 women (28%). In all patients, AF was clinically significant, manifesting as persistent or intermittent palpitations and/or reduced exercise tolerance. The presence of AF was documented by both standard electrocardiography and Holter monitoring.

For each patient, the total duration of arrhythmic history, duration of persistent AF, and duration of arrhythmic history prior to the onset of persistence were recorded. The mean duration of arrhythmic history was 50.38 ± 10.00 months, with persistence lasting 17.03 ± 3.76 months, and arrhythmic history prior to persistence amounting to 32.5 ± 8.21 months.

Voltage mapping of the LA was performed using the CARTO 3 navigation system (Biosense Webster, USA). Mapping was carried out with a multielectrode PentaRay catheter (Biosense Webster, USA) using the tissue proximity function, with mapping points located ≤5 mm from the atrial anatomical shell, and the confidense module configured with the following parameters: catheter stability 6 mm, electroanatomical point density 1 mm. All voltage maps comprised a minimum of 2000 points, with a mean of 2128 ± 104. Voltage maps were analysed to identify low-voltage areas and calculate the percentage of low-voltage area.

Regions with a bipolar signal amplitude >0.5 mV were defined as normal voltage, 0.1-0.5 mV as low voltage, and <0.1 mV as very low voltage. These thresholds were chosen based on prior studies, many of which proposed 0.5 mV as the cut-off for low voltage [8-10], a value now widely adopted in the literature. In the study by Y. Lin et al. (2014), voltages <0.1 mV were defined as “dense scar” [11].

For each map, the percentage of low voltage (LVA%) and very low voltage (VLVA%) was calculated. LVA% was computed relative to the total LA surface area. The area measurement tool was used to calculate the total surface area of the LA map, subtracting the area of the mitral annulus and PV ostia. Measurement of the mitral annulus and PV ostia areas is illustrated in Figure 1. The surface area of low-voltage regions was then determined using the same area measurement tool (Fig. 2). Based on the reconstructed anatomical model of the LA, excluding the PVs, LA volume was also calculated, including the LA appendage.

A correlation analysis was performed to assess the relationship of LVA% and VLVA% with sex, age, duration of arrhythmic history, duration of persistence, duration of arrhythmic history at the onset of persistence, comorbidities (coronary artery atherosclerosis, interventricular septal thickness [as a marker of LV hypertrophy], diabetes mellitus, body mass index, estimated glomerular filtration rate [eGFR]), LA anteroposterior diameter (as measured by echocardiography), LA size index, LV ejection fraction,

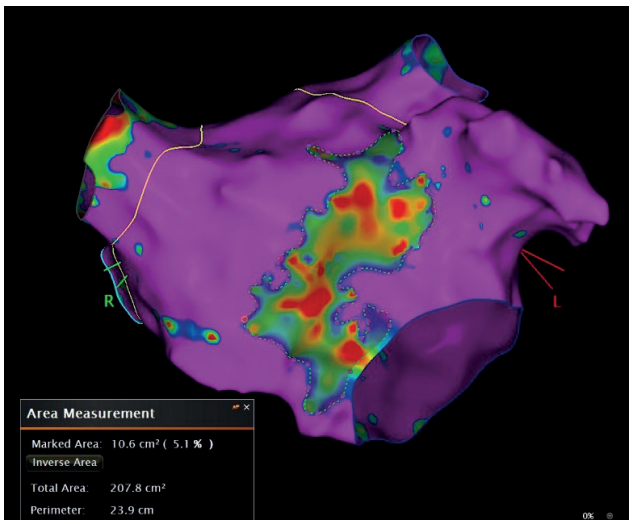

Fig. 2. Measurement of the low-voltage area.

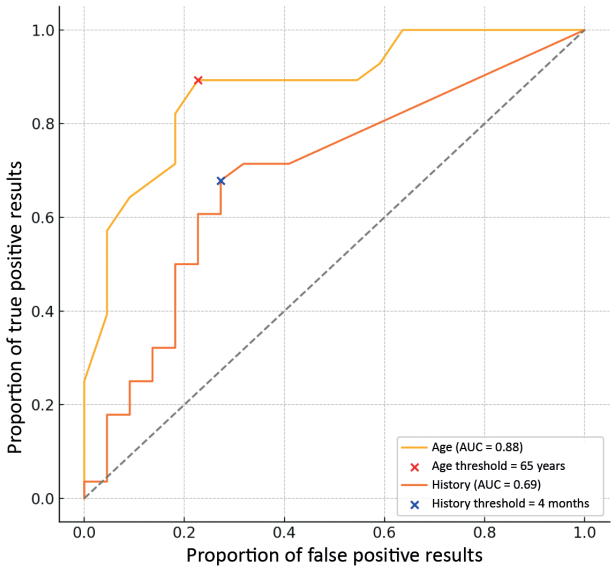

Fig. 3. ROC curves for determining the cut-off points for age and arrhythmic history duration at the onset of persistence in relation to LV% (low-voltage percentage).

left atrial appendage emptying velocity (by preoperative transoesophageal echocardiography), and LA volume as determined from the reconstructed LA model.

Statistical analysis

Statistical analysis was performed using StatTech v.4.6.3 (StatTech LLC, Russia). Quantitative variables were tested for normality using the Shapiro-Wilk test (for sample sizes <50) or the Kolmogorov-Smirnov test (for sample sizes >50). Variables with a normal distribution were described as means (M) with standard deviations (SD) and 95% confidence intervals (95% CI). Non-normally distributed data were described as medians (Me) with interquartile ranges (Q1-Q3).

Comparisons between two groups for non-normally distributed quantitative variables were performed using the Mann-Whitney U test. The strength and direction of correlations between two quantitative variables were assessed using Pearson's correlation coefficient (for normally distributed variables) or Spearman's rank correlation coefficient (for non-normally distributed variables).

A prognostic model describing the dependence of a quantitative variable on selected factors was developed using linear regression analysis. A two-tailed p-value <0.05 was considered statistically significant.

Table 1.

Values at the optimal threshold of sensitivity, specificity, and Youden's index

Parameter	Sensitivity	Specificity	Youden's Index
Age ≥65 years	0.89	0.77	0.67
Anamnesis ≥4 months	0.68	0.73	0.41

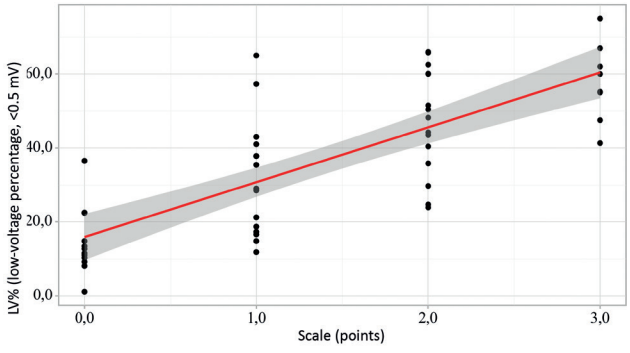

Fig. 4. Regression function graph illustrating the relationship between LV% (low-voltage percentage) and the score on the original scale.

Table 2.

Results of correlation analysis of the relationship between the factors included in the scale, the scale score, and LV% (low-voltage percentage)

Indicator	ρ	p
Age	0.720	<0.001
Female sex		0.016
Duration of arrhythmia history*	0.503	<0.001
Total score on the scale	0.778	<0.001

Note: * - at the onset of persistent atrial fibrillation.

RESULTS

We identified a statistically significant strong correlation between LVA% and age (p<0.001, r=0.720), female sex (p=0.016), and a moderate correlation with the duration of arrhythmic history at the onset of persistence (p<0.001, r=0.503). A statistically significant but weak association was also observed between LVA% and eGFR (p=0.002, r=−0.336), left atrial (LA) volume measured on electroanatomical mapping (p=0.019, r=0.330), LA size index (p<0.001, r=0.432), and LA appendage (LAA) emptying velocity (p=0.023, r=−0.335).

No correlation was found between LVA% and the duration of persistence (p=0.728), interventricular septal thickness (p=0.976), body mass index (p=0.814), presence of coronary atherosclerosis (p=0.058), diabetes mellitus (p=0.192), left ventricular ejection fraction (p=0.125), or anteroposterior LA diameter (p=0.213).

For VLVA%, we observed a statistically significant correlation with age (p<0.001, r=0.656) and female sex (p=0.039), a weak association with eGFR (p=0.013, r=−0.357) and arrhythmic history duration at the onset of persistence (p<0.003, r=0.410), and a very weak correlation with LA size index (p=0.048, r=−0.276). No correlation was found between VLVA% and the duration of persistence (p=0.567), interventricular septal thickness (p=0.876), body mass index (p=0.900), coronary atherosclerosis (p=0.055), diabetes mellitus (p=0.098), left ventricular ejection fraction (p=0.300), anteroposterior LA diameter (p=0.481), LA volume (p=0.618), or LAA emptying velocity (p=0.371).

Thus, the variables showing the strongest correlations with LVA% and VLVA% were age, female sex, arrhythmic history duration at the onset of persistence, and eGFR. Based on these findings, we developed an original predictive score for LVZ%, incorporating age, sex, and arrhythmic history duration at the onset of persistence.

To determine threshold values for age and arrhythmic history duration, ROC analysis was performed for each variable. The area under the ROC curve (AUC) was used to evaluate discriminatory ability, and optimal cut-offs were identified using Youden's index (J = sensitivity + specificity − 1). The point with the maximum Youden index was considered the optimal diagnostic threshold. For dichotomization, LVA%=35% was chosen as the reference threshold, since the median LVA% was 35.57% and the 35% cut-off corresponds to the boundary of advanced fibrosis in the Utah classification. The optimal Youden index for age was achieved at a threshold of 65 years, and for arrhythmic history duration at the onset of persistence at 4 months. ROC curves are shown in Fig. 3, and the sensitivity, specificity, and Youden index values are provided in Table 1.

Patients aged >65 years were assigned 1 point, female sex 1 point, and arrhythmic history duration >4 months at the onset of persistence 1 point; otherwise, 0 points were assigned. The total score demonstrated a strong correlation with LVA% (p<0.001, r=0.778). This scoring system was named the "AGD-rhythm" scale (Age, Gender, Duration of arrhythmic history at persistence onset).

A regression analysis of the relationship between the score and LVA% is shown in Fig. 4, while Table 2 presents

the correlation analysis results for the individual factors included in the score and the overall score in relation to LVA%. The score also showed a moderate correlation with VLVA% ($p<0.001$, $r=0.597$).

DISCUSSION

Various scoring systems have been developed to predict the percentage of low-voltage areas in the left atrium, incorporating different clinical and echocardiographic factors. The DR-FLASH score, which includes diabetes mellitus, renal dysfunction, persistent atrial fibrillation, a left atrial anteroposterior diameter greater than 45 mm, age over 65 years, female sex, and arterial hypertension, has demonstrated high effectiveness in predicting the presence of low-voltage areas [12-14].

To predict AF recurrence after RF ablation in patients undergoing primary and repeat procedures, the APPLE score was developed. This included: age >65 years, persistent AF, reduced eGFR <60 ml/min/1.73m², anteroposterior LA diameter >42 mm, and left ventricular ejection fraction (LVEF) <50%. This score provided a means of predicting the extent of low-voltage areas [12]. Table 3 summarises scoring systems reported in the literature for predicting the distribution of low-voltage areas.

A critical methodological issue is that in most studies validating these scores, electroanatomical mapping was performed during sinus rhythm. Patients with persistent or long-standing persistent AF first underwent cardioversion, followed by voltage mapping during sinus rhythm or atrial pacing. However, A. Lahuerta et al. (2022) demonstrated that voltage mapping results obtained during AF and sinus rhythm in the same patient differ substantially [15]. Similarly, N.A. Qureshi et al. (2019) reported that the correlation between low-voltage areas identified by endocardial mapping and areas of fibrosis detected by late gadolinium enhancement MRI was significantly stronger when mapping was performed during AF compared with sinus rhythm [16]. In addition, J. Chen et al. (2019) showed that most arrhythmogenic regions of the LA (areas of spatiotemporal dispersion and prolonged activity) overlapped with low-voltage zones identified during AF mapping, underscoring the importance of studying low-voltage areas independently of atrial fibrosis [15].

Another methodological concern is that patients with unsuccessful cardioversion or immediate AF recurrence after rhythm restoration were excluded from analysis. In one study, this group comprised 12.9% of patients [17]. Excluding such patients—those with more advanced disease—may bias results. Electrical cardioversion itself, and the fact that mapping is performed immediately afterwards, is an important factor influencing mapping outcomes.

As noted, results of voltage mapping during AF and sinus rhythm in the same patient differ markedly, and it remains unclear which rhythm better reflects the true extent of LA fibrosis. In our view, given these limitations, including mapping immediately after cardioversion and exclusion of patients with unsuccessful cardioversion, voltage mapping during AF in patients with persistent AF appears more rational.

In our study, high-density mapping included >2000 analysed electrograms per LA map, whereas earlier studies typically used ~200 points, which does not meet current definitions of high-density mapping and may have affected their results [18-20]. Moreover, some studies used different

Table 3.

Scales for predicting the extent of low-voltage areas in the left atrium

Scale	Parameters	Number of Mapping Points in LA	Mapping Catheter
DR-FLASH [12, 13]	DM, CKD, PersAF, LA > 45 mm, age > 65 years, female sex, HTN	>1000; 144±76	SmartTouch (Biosense Webster), TactiCath (Abbott), multielectrode circular catheter
APPLE [11, 18]	Age > 65, PersAF, GFR < 60 ml/min/1.73 m², LA > 43 mm, LVEF < 50%	>1000; >200	Age > 65, PersAF, GFR < 60 ml/min/1.73 m², LA > 43 mm, LVEF < 50%
(m)APPLE [19]	Age > 65, PersAF, GFR < 60 ml/min/1.73 m², LAVI ≥ 39 ml/m², LAEF < 31%	>1000	SmartTouch (Biosense Webster), TactiCath (Abbott), multielectrode circular catheter
SPEED [21]	Female sex, PersAF, age > 70 years, proBNP > 400 pg/ml, DM	≥100 (3.5-mm ablation catheter), ≥1000 (multielectrode catheter)	3.5-mm ablation or multielectrode catheter (Biosense Webster/Boston Scientific/Abbott)
ZAQ [20]	Age > 65 years, female sex, LAVI 57 ml/m²	>200	TactiCath (Abbot), ThermoCool SmartTouch (Biosense Webster)
ANP [43]	Age > 65 years, NT-proBNP ≥ 17 ng/ml, PersAF	>1000	Reflexion Spiral (Abbot), Lasso (Biosense Webster)
ATLAS [45]	Age > 60 years, female sex, PersAF, smoking, LAVI (1 point per 10 ml/m²)	2876 ± 1058	PentaRay (Biosense Webster)

Note: LA – left atrium; DM – diabetes mellitus; CKD – chronic kidney disease; PersAF – persistent atrial fibrillation; HTN – arterial hypertension; GFR – glomerular filtration rate; LVEF – left ventricular ejection fraction; LAVI – left atrial volume index.

electrode types (3.5 mm ablation vs. multielectrode catheters) [12, 13, 18, 19, 21]. E. Anter et al. (2015) demonstrated that in areas of preserved voltage, bipolar signal amplitudes were consistent across catheter types, whereas in low-voltage zones, the total area with voltages <0.5 mV measured using multielectrode catheters with 1 mm electrodes was smaller than when measured using a 3.5 mm ablation catheter [9, 22].

One of the most debated issues remains the discrepancy between mapping during sinus rhythm and AF. As highlighted in the aforementioned studies, sequential mapping during both rhythms in the same patient revealed substantial differences when low-voltage thresholds of 0.5 and 0.3 mV were applied [14, 16]. This highlights the need for rhythm-specific voltage thresholds.

Numerous attempts have been made to define a suitable threshold for AF mapping, proposing values from 0.24 to 0.35 mV, which may correspond to the 0.5 mV threshold used during sinus rhythm [16, 23, 24]. However, no consensus has yet been reached. D. Nairn et al. (2023) noted that even with adjusted thresholds, concordance between sinus rhythm and AF maps remains only moderate, with greater detection of low-voltage areas during AF mapping [24].

In our opinion, given the fundamental differences in activation direction and conduction velocity between sinus rhythm and AF, it is unlikely that a single threshold can harmonise voltage maps across both rhythms. Therefore, predictors of low-voltage areas should probably be determined separately for sinus rhythm and AF mapping.

Based on prior studies adopting a 0.5 mV threshold and the findings of N.A. Qureshi et al. (2019) showing higher concordance between AF mapping and late gadolinium enhancement MRI, we applied 0.5 mV and 0.1 mV thresholds to identify predictors of low voltage [16]. Importantly, no significant differences were observed in the results of correlation analysis when comparing the thresholds for low and very low voltage.

Left atrial voltage reduction and age

Atrial fibrillation (AF) is the most common age-associated arrhythmia, and ageing is generally linked to an increased risk of AF [25]. This association has been reported in both animal experiments and small-scale clinical studies, which described age-related alterations in the electrophysiological properties of atrial myocytes and conduction abnormalities [25, 26].

The relationship between LA fibrosis and age has been demonstrated in histological analyses of tissue samples obtained at autopsy and during open-heart surgery. Atrial tissue analysis revealed a correlation between atrial fibrosis and a history of AF. Importantly, the authors reported no significant fibrosis in age-matched control patients without a history of AF [27, 28].

However, findings regarding the correlation between LA fibrosis and age remain inconsistent. In an autopsy-based study, P.G. Platonov et al. (2011) found no association between age and the extent of LA fibrosis [28]. Conversely, in a clinical study by H. Cochet et al. (2015), age was identified as a predictor of fibrosis diagnosed using late gadolinium enhancement MRI [29].

In our study, age demonstrated the strongest correlation with the percentage of low-voltage areas in the LA.

Left atrial voltage reduction and sex

The EORP-AF study demonstrated sex-related differences in the epidemiology, clinical management, and treatment of AF [30]. Women with AF were shown to have a 1.3-2.0-fold higher risk of AF recurrence following RFA [31-33]. The FIRE and ICE trial reported that female sex was associated with an almost 40% increase in atrial arrhythmia recurrences after pulmonary vein isolation [34]. Other studies indicated that although women had higher recurrence rates after RFA, repeat procedures revealed less frequent pulmonary vein reconnections in women compared with men [35, 36]. This finding may be explained by a greater prevalence of non-pulmonary vein AF triggers, which could be related to areas of low voltage.

Previous investigations have identified female sex as an independent predictor of LA fibrosis [37-39]. This observation is believed to be linked to a direct sex-specific effect, driven by differences in the influence of sex hormones on adverse LA remodelling and fibrosis.

In our study, female sex correlated with a higher percentage of low-voltage areas in the LA.

Left atrial voltage reduction and duration of arrhythmic history

An interesting observation was the association between the duration of arrhythmic history at the onset of persistence and the percentage of low voltage (LV%). Patients with a history of paroxysmal AF prior to transition to the persistent form demonstrated a higher LV% compared with those whose first manifestation of AF was persistence. On the one hand, this may indicate distinct mechanisms underlying AF persistence; on the other, it underscores the potential need for earlier intervention to maintain sinus rhythm and to minimise the spread of low-voltage areas, which adversely affect the prognosis and the efficacy of interventional treatment.

Our findings also suggest that the extent of low-voltage areas is primarily driven by preceding paroxysmal AF episodes rather than by the duration of persistence itself. The absence of an association between AF persistence duration and LV% in our cohort is consistent with previous reports [40]. To our knowledge, no prior studies have examined the correlation between the duration of arrhythmic history at the onset of persistence and LV%. The present study is the first to highlight the influence of the duration of preceding paroxysmal AF on the prevalence of low-voltage areas.

Left atrial voltage reduction and associated comorbidities

according to our data, comorbidities did not influence the percentage of very low-voltage areas (VLVA%). This finding is consistent with some studies that failed to demonstrate an association between comorbid conditions and atrial voltage reduction in patients with persistent AF [40]. At the same time, studies evaluating previously proposed scoring systems have shown their utility in predicting the extent of low-voltage areas in the left atrium [12]. Experimental animal models have demonstrated a link between arterial hypertension and atrial fibrosis [41]. Furthermore, obesity has been shown to promote the development of atrial fibrosis in experimental settings, with regression of fibrosis observed following weight reduction [42].

Renal dysfunction merits particular attention, as estimated glomerular filtration rate (eGFR) exhibited a statistically significant moderate correlation with both LVA% and VLVA%. Evidence regarding the association between eGFR and the extent of low-voltage areas is conflicting, with some studies reporting a relationship and others not [43, 44]. It is likely that the lack of a strong correlation in our cohort is related to the fact that only patients with mild-to-moderate renal impairment were included (mean eGFR 61.8 mL/min/1.73m²), while none had stage IV or V chronic kidney disease.

We developed an original scoring system, the AFD-Rhythm score (Age, Female, Duration of arrhythmic history), to predict the extent of low-voltage areas in patients with persistent AF. This score is designed to estimate the percentage of low-voltage burden in patients undergoing mapping during arrhythmia. As noted earlier, previous studies have demonstrated a correlation between the extent of low-voltage areas and AF recurrence following RFA [7]. Based on this, it can be hypothesised that our score may also predict the efficacy of AF ablation. However, this assumption requires validation in future studies.

CONCLUSION

Age, female sex, and the duration of arrhythmic history at the onset of persistence are independent predictors of low-voltage burden in the left atrium among patients with persistent atrial fibrillation. The proposed original AFD-Rhythm score may be employed to predict the extent of low-voltage burden in this patient population.

REFERENCES

1. Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10): 659-66. https://doi.org/10.1056/NEJM199809033391003.
2. Seitz J, Bars C, Théodore G, et al. AF Ablation Guided by Spatiotemporal Electrogram Dispersion Without Pulmonary Vein Isolation: A Wholly Patient-Tailored Approach. J Am Coll Cardiol. 2017;69(3): 303-21. https://doi.org/10.1016/j.jacc.2016.10.065.
3. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015;372(19): 1812-22. https://doi.org/10.1056/NEJMoa1408288.
4. Marrouche NF, Naccarelli GV, Akoum Y, et al. Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation: The DECAAF Study. JAMA. 2014;312(17): 1805-14. https://doi.org/10.1001/jama.2014.3.
5. Sramko M, Peichl P, Wichterle D, et al. Clinical value of assessment of left atrial late gadolinium enhancement in patients undergoing ablation of atrial fibrillation. Int J Cardiol. 2015;179: 351-7. https://doi.org/10.1016/j.ijcard.2014.11.072.
6. Oakes RS, Badger TJ, Kholmovski EG, et al. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. Circulation. 2009;119(13): 1758-67. https://doi.org/10.1161/CIRCULATIONAHA.108.811877.
7. Yamaguchi T, Tsuchiya T, Nagamoto Y, et al. Long-term results of pulmonary vein antrum isolation in patients with atrial fibrillation: an analysis in regard to substrates and pulmonary vein reconnections. Europace. 2014;16(5): 511-20. https://doi.org/10.1093/europace/eut265.
8. Sanders P, Morton JB, Kistler PM, et al. Electrophysiological and electroanatomic characterization of the atria in sinus node disease: Evidence of diffuse atrial remodeling. Circulation. 2004;109(11): 1514-22. https://doi.org/10.1161/01.CIR.0000121734.47409.AA.
9. Anter E, Tschabrunn CM, Josephson ME. High-resolution mapping of scar-related atrial arrhythmias using smaller electrodes with closer interelectrode spacing. Circ Arrhythm Electrophysiol. 2015;8(3): 537-45. https://doi.org/10.1161/CIRCEP.114.002737.
10. Saghy L, Callans DJ, Garcia F, et al. Is there a relationship between complex fractionated atrial electrograms recorded during atrial fibrillation and sinus rhythm fractionation? Heart Rhythm. 2012;9(2): 181-8. https://doi.org/10.1016/j.hrthm.2011.09.062.
11. Lin Y, Yang B, Garcia FC, et al. Comparison of left atrial electrophysiologic abnormalities during sinus rhythm in patients with different type of atrial fibrillation. J Interv Card Electrophysiol. 2014;39(1): 57-67. https://doi.org/10.1007/s10840-013-9838-y.
12. Kornej J, Schumacher K, Dinov B, et al. Prediction of electro-anatomical substrate and arrhythmia recurrences using APPLE, DR-FLASH and MB-LATER scores in patients with atrial fibrillation undergoing catheter ablation. Sci Rep. 2018;8(1): 12686. https://doi.org/10.1038/s41598-018-31133-x.
13. Kosiuk J, Dinov B, Kornej J, et al. Prospective, multicenter validation of a clinical risk score for left atrial arrhythmogenic substrate based on voltage analysis: DR-FLASH score. Heart Rhythm. 2015;12(9): 2207-12. https://doi.org/10.1016/j.hrthm.2015.07.003.
14. Andrés Lahuerta A, Roberto C, Saiz FJ, et al. Atrial low voltage areas: A comparison between atrial fibrillation and sinus rhythm. Cardiol J. 2022;29(2): 252-62. https://doi.org/10.5603/CJ.a2021.0125.
15. Chen J, Arentz T, Cochet H, et al. Extent and spatial distribution of left atrial arrhythmogenic sites, late gadolinium enhancement at magnetic resonance imaging, and low-voltage areas in patients with persistent atrial fibrillation: comparison of imaging vs. electrical parameters of fibrosis and arrhythmogenesis. Europace. 2019;21(10): 1484-93. https://doi.org/10.1093/europace/euz159.
16. Qureshi NA, Kim SJ, Cantwell CD, et al. Voltage during atrial fibrillation is superior to voltage during sinus rhythm in localizing areas of delayed enhancement on magnetic resonance imaging: An assessment of the posterior left atrium in patients with persistent atrial fibrillation. Heart Rhythm. 2019;16(9): 1357-67. https://doi.org/10.1016/j.hrthm.2019.05.032.
17. Kiedrowicz RM, Wielusinski M, Wojtarowicz A, et al. Predictors of the voltage derived left atrial fibrosis in patients with long-standing persistent atrial fibrillation. Cardiol J. 2022;29(4): 660-9. https://doi.org/10.5603/CJ.a2020.0069.

18. Kornej J, Büttner P, Sommer P, et al. Prediction of electro-anatomical substrate using APPLE score and biomarkers. Europace. 2019;21(1): 54-9. https://doi.org/10.1093/europace/euy120.
19. Seewöster T, Kosich F, Sommer P, et al. Prediction of low-voltage areas using modified APPLE score. Europace. 2021;23(4): 575-80. https://doi.org/10.1093/europace/euaa311.
20. D'Ambrosio G, Romano S, Alothman O, et al. Computed tomography-derived left atrial volume index, sex, and age to predict the presence and the extent of left atrial low-voltage zones in patients with atrial fibrillation: The ZAQ score. J Cardiovasc Electrophysiol. 2020;31(4): 895-902. https://doi.org/10.1111/jce.14391.
21. Matsuda Y, Masuda M, Asai M, et al. A new clinical risk score for predicting the prevalence of low-voltage areas in patients undergoing atrial fibrillation ablation. J Cardiovasc Electrophysiol. 2020;31(12): 3150-8. https://doi.org/10.1111/jce.14761.
22. Gasimova NZ, Shabanov VV, Safonov NV, et al. Multipolar mapping in the management of different arrhythmias. Journal of Arrhythmology. 2024;31(1): 110-122. https://doi.org/10.35336/VA-1297.
23. Rodríguez-Mañero M, Valderrábano M, Baluja A, et al. Validating Left Atrial Low Voltage Areas During Atrial Fibrillation and Atrial Flutter Using Multielectrode Automated Electroanatomic Mapping. JACC Clin Electrophysiol. 2018;4(12): 1541-52. https://doi.org/10.1016/j.jacep.2018.08.015.
24. Nairn D, Eichenlaub M, Lehrmann H, et al. Spatial correlation of left atrial low voltage substrate in sinus rhythm versus atrial fibrillation: The rhythm specificity of atrial low voltage substrate. J Cardiovasc Electrophysiol. 2023;34(8): 1613-21. https://doi.org/10.1111/jce.15984.
25. Anyukhovsky EP, Sosunov EA, Plotnikov A, et al. Cellular electrophysiologic properties of old canine atria provide a substrate for arrhythmogenesis. Cardiovasc Res. 2002;54: 462-9. https://doi.org/10.1016/S0008-6363(02)00271-7.
26. Gramley F, Lorenzen J, Knackstedt C, et al. Age-related atrial fibrosis. Age. 2009;31: 27-38. https://doi.org/10.1007/s11357-008-9077-9.
27. Kainuma S, Masai T, Yoshitatsu M, et al. Advanced left-atrial fibrosis is associated with unsuccessful maze operation for valvular atrial fibrillation. Eur J Cardiothorac Surg. 2011;40(1): 61-9. https://doi.org/10.1016/j.ejcts.2010.11.008.
28. Platonov PG, Mitrofanova LB, Orshanskaya V, et al. Structural abnormalities in atrial walls are associated with presence and persistency of atrial fibrillation but not with age. J Am Coll Cardiol. 2011;58(21): 2225-32. https://doi.org/10.1016/j.jacc.2011.05.061.
29. Cochet H, Mouries A, Nivet H, et al. Age, atrial fibrillation, and structural heart disease are the main determinants of left atrial fibrosis detected by delayed-enhanced magnetic resonance imaging in a general cardiology population. J Cardiovasc Electrophysiol. 2015;26: 484-92. https://doi.org/10.1111/jce.12651.
30. Lip GY, Laroche C, Boriani G, et al. Sex-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Observational Research Programme Pilot survey on Atrial Fibrillation. Europace. 2015;17: 24-31. https://doi.org/10.1093/europace/euu155.
31. Xiaocheng C, Qiongwen H, Lei G, et al. Sex-related differences in catheter ablation of atrial fibrillation: a systematic review and meta-analysis. Europace. 2019;21(10): 1509-18. https://doi.org/10.1093/europace/euz179.
32. Wong GR, Nalliah CJ, Lee G, et al. Sex-related differences in atrial remodeling in patients with atrial fibrillation: relationship to ablation outcomes. Circ Arrhythm Electrophysiol. 2022;15(1). https://doi.org/10.1161/CIRCEP.121.009925.
33. Kerr CR, Humphries K. Gender-related differences in atrial fibrillation. J Am Coll Cardiol. 2005;46: 1307-8. https://doi.org/10.1016/j.jacc.2005.07.007.
34. Kuck KH, Brugada J, Schlüter M, et al. The FIRE AND ICE Trial: What We Know, What We Can Still Learn, and What We Need to Address in the Future. J Am Heart Assoc. 2018;7(24). https://doi.org/10.1161/JAHA.118.010777.
35. Tanaka N, Inoue K, Kobori A, et al. Sex differences in atrial fibrillation ablation outcomes: insights from a large-scale multicentre registry. Europace. 2020;22(9): 1345-57. https://doi.org/10.1093/europace/euaa104.
36. Sugumar H, Nanayakkara S, Chieng D, et al. Arrhythmia recurrence is more common in females undergoing multiple catheter ablation procedures for persistent atrial fibrillation: Time to close the gender gap. Heart Rhythm. 2020;17(5 Pt A):692-98. https://doi.org/10.1016/j.hrthm.2019.12.013.
37. Akoum N, Mahnkopf C, Kholmovski EG, et al. Age and sex differences in atrial fibrosis among patients with atrial fibrillation. Europace. 2018;20(7): 1086-92. https://doi.org/10.1093/europace/eux260.
38. Huo Y, Gaspar T, Pohl M, et al. Prevalence and predictors of low voltage zones in the left atrium in patients with atrial fibrillation. Europace. 2018;20(6): 956-62. https://doi.org/10.1093/europace/eux082.
39. Wu N, Liu W, Yang G, et al. Sex difference in atrial scar prevalence: What can we learn from the STABLE-SR-III trial? Heart Rhythm. 2024;21(7): 1001-07. https://doi.org/10.1016/j.hrthm.2024.02.020.
40. Ammar-Busch S, Buiatti A, Tatzber A, et al. Predictors of low voltage areas in persistent atrial fibrillation: is it really a matter of time? J Interv Card Electrophysiol. 2020;57: 345-52. https://doi.org/10.1007/s10840-018-0471-7.
41. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J. 2013;34(35): 2746-51. https://doi.org/10.1093/eurheartj/eht280.
42. Mahajan R, Lau DH, Brooks AG, et al. Electrophysiological, Electroanatomical, and Structural Remodeling of the Atria as Consequences of Sustained Obesity. J Am Coll Cardiol. 2015;66: 1-11. https://doi.org/10.1016/j.jacc.2015.04.058.
43. Matsuda Y, Masuda M, Asai M, et al. Impact of Renal Dysfunction on Left Atrial Low-Voltage Areas in Patients With Atrial Fibrillation. Circ J. 2019;83(5): 985-90. https://doi.org/10.1253/circj.CJ-18-1277.
44. Seewöster T, Büttner P, Zeynalova S, et al. Are the atrial natriuretic peptides a missing link predicting low-voltage areas in atrial fibrillation? Introducing the novel bio-

marker-based atrial fibrillation substrate prediction (ANP) score. Clin Cardiol. 2020;43(7): 762-68. https://doi.org/10.1002/clc.23378.
45. Kiedrowicz RM, Wielusiński M, Wojtarowicz A, et al. Atrial fibrillation risk scores to evaluate left atrial substrate based on voltage analysis in long-standing persistent type of arrhythmia. Kardiol Pol. 2021;79(5): 525-30. https://doi.org/10.33963/kp.15902.

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RISK SCORE FOR DEVELOPING ARRHYTHMIA-INDUCED CARDIOMYOPATHY IN CHILDREN WITH IDIOPATHIC VENTRICULAR ARRHYTHMIAS BASED ON SINGLE CENTER DATA

K.A.Chueva, O.A.Kofeynikova, D.S.Lebedev, R.B.Tatarskiy, E.S.Vasichkina

Almazov National Medical Research Centre of the MH RF, Russia, Saint-Petersburg, 2 Akkuratova str.

Aim. To develop a predictive model and a clinical risk score for developing arrhythmia-induced cardiomyopathy (AIC) in children with idiopathic ventricular arrhythmias (VA).

Methods. The study included 492 children aged 1 to 17 years with idiopathic VA. In 392 patients demographic, clinical and diagnostic-related variables were evaluated as potential prognostic factors using binary logistic regression. The scores for each predictor were set based on the odds ratio. Validation of the model was carried out on a test group (n=100).

Results. It was found that body surface area ≥ 1,7 m^2 increases the ratio of developing AIC by 4,9 times (1 point), the premature ventricular contraction's coupling interval < 434 ms. - by 3,7 times (1 point), the burden of VA 25-29% - by 8,4 times (2 points), the burden of VA 30-34% - 11,3 times (3 points), the burden of VA ≥ 35% - 17,2 times (4 points). The specificity of the risk score was determined by the ROC curve. A low probability of developing AIC was determined with a score of up to 2 (specificity <48.1%), an average probability was determined with a score 3-4 (specificity 67.5-81.8%), a high probability was determined with a score 5-6, (specificity >95.1%). The AUC of the predictive scale was 0.805±0.037 (95% CI: 0.732-0.878), p<0.001.

The AUC of the of the predictive scale in the test group was 0.893±0.034 (95% CI: 0.827-0.96),p<0.001. The difference in the AUC of the scores in training and test groups was 0.088±0.05. The AUCs were comparable (p=0.078).

Conclusion. In this study we identified independent predictors of IAC in children with idiopathic VA. A clinical risk scale of AIC has been developed based on the obtained predictors. Routine use of the AIC risk scale will lead to personalized monitoring and treatment of each child with idiopathic VA.

Key words: idiopathic; ventricular arrhythmia; ventricular tachycardia; arrhythmia-induced cardiomyopathy; tachycardia-induced cardiomyopathy; prognosis; risk scale; children

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Corresponding author: Chueva Ksenia, E-mail: kseniia.chueva@gmail.com

K.A.Chueva - ORCID ID 0000-0002-5027-0565, O.A.Kofeynikova - ORCID ID 0000-0003-4720-9023, D.S.Lebedev - ORCID ID 0000-0001-9948-7303, R.B.Tatarskiy - ORCID ID 0000-0001-6752-3306, E.S.Vasichkina - ORCID ID 0000-0001-7336-4102

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Ventricular arrhythmias (VA) are highly prevalent in childhood. According to screening studies, isolated premature ventricular contractions (PVCs) are recorded in approximately half of adolescents [1]. In the vast majority of cases, VA in children are idiopathic and follow a benign course [2-5]. However, long-standing VA may lead to the development of arrhythmia-induced cardiomyopathy (AIC). The incidence of cardiomyopathy associated with idiopathic VA in children does not exceed 20% [6-11].

Despite considerable interest in this issue, only a limited number of studies have been published investigating predictors of AIC in the paediatric population [6, 9, 11]. The main limitations of these studies are small patient cohorts, which result in contradictory findings and preclude their application in clinical practice. Identification of independent predictors and the development of a risk scoring system for AIC would optimise strategies for monitoring and treatment in children with idiopathic VA.

Aim: to develop a prognostic model and a scoring system for assessing the probability of arrhythmia-induced cardiomyopathy in children with idiopathic VA.

METHODS

To achieve this objective, we analysed data from 492 children aged 1 to 17 years with idiopathic VA who underwent evaluation and treatment at the Centre between 2011 and 2025. Exclusion criteria were the presence of structural heart disease, active myocardial inflammation or a history of myocarditis, confirmed channelopathies, and extracardiac causes of VA. The diagnosis of idiopathic VA was made by exclusion following careful history taking and comprehensive cardiological assessment.

All patients underwent clinical and biochemical blood tests including measurement of cardiac-specific enzymes and acute-phase proteins, electrolytes, and thyroid function, as well as standard 12-lead surface electrocardiography (ECG), 24-hour Holter ECG monitoring, and echocardiography. A treadmill exercise test was performed in 403 patients, and cardiac magnetic resonance imaging (MRI) was carried out in 116 patients.

Arrhythmia-induced cardiomyopathy was defined as reduced left ventricular (LV) ejection fraction (EF) and/or LV dilatation after the onset of VA. Cardiac chamber size and myocardial contractility were assessed using standard methodology [12]. Echocardiographic parameters were indexed using the Boston Children's Hospital z-score calculator. LV dilatation was defined as an LV end-diastolic dimension z-score > +2.0. LV ejection fraction was measured using the Teichholz and Simpson methods.

In the overall cohort, 12% (59/492) of children met the criteria for AIC. Of these, 15% (n=9/59) had both LV dilatation and reduced EF, 14% (n=8/59) had dilatation without reduced EF, and 71% (n=42/59) had isolated LV systolic dysfunction.

At the first stage, we searched for predictors of AIC in the training cohort (n=392). To this end, we analysed and compared clinical parameters, medical history, and findings from instrumental examinations in relation to the presence of AIC. The results of this first stage of the study have been published previously [13].

The second stage consisted of constructing a prognostic model and a probability scoring system for AIC using variables identified in the training cohort. The developed scoring system was then validated in a test cohort that included 100 children with idiopathic VA. The size of the test cohort was determined based on an 80% to 20% split between the training and test groups. Patients in the training and test cohorts were comparable in terms of age, anthropometric parameters, and sex. The clinical characteristics of the patients are presented in Table 1.

Statistical analysis

The analysis was performed using IBM SPSS Statistics v.26. At the initial stage, in the training cohort, potential predictors of AIC were identified using univariate logistic regression. To address potential multicollinearity among predictors, a

Table 1.

Clinical characteristics of patients in the training and test cohorts

Variable	Training cohort (n=392)	Test cohort (n=100)	p
Age, years, Me [IQR]	13.0 [9.0; 15.0]	12.0 [9.0; 15.0]	0.069
BSA, m², Me [IQR]	1.48 [1.12; 1.72]	1.55 [1.37; 1.68]	0.053
Male sex, n (%)	222 (56.6)	64 (58.1)	0.183
Presence of VT, n (%)	214 (54.6)	64 (64)	0.090
VA burden, %, Me [IQR]	25.2 [16.2; 36.4]	24.0 [15.0; 36.5]	0.548
AIC, n (%)	35 (8.9)	24 (24.0)	-
Reduced EF and LV dilatation, n (%)	6 (17.1)	3 (12.5)	0.917
LV dilatation only, n (%)	5 (14.3)	3 (12.5)	
Reduced EF only, n (%)	24 (68.6)	18 (75)	

Note: throughout the text, p denotes the level of statistical significance; BSA - body surface area; VT - ventricular tachycardia; VA - ventricular arrhythmia; AIC - arrhythmia-induced cardiomyopathy; LV - left ventricle; EF - ejection fraction.

Table 2.

Characteristics of the association between model predictors and the probability of arrhythmia-induced cardiomyopathy in children

Predictors	Unadjusted		Adjusted	
	OR; 95% CI	p	OR; 95% CI	p
BSA	4.531; 1.774-11.576	0.002	5.742; 2.161-15.254	<0.001
Age	1.124; 1.015-1.245	0.025		
POS	2.455; 1.118-5.388	0.025		
Presence of VT	3.677; 1.566-8.637	0.003		
VA burden	1.049; 1.026-1.072	<0.001	1.04; 1.014-1.067	0.003
Paired PVCs	3.698; 1.309-10.445	0.014		
Mean PEI	0.956; 0.909-0.990	0.021	0.997; 0.996-0.999	0.006

Note: throughout the text, OR - odds ratio; CI - confidence interval; BSA - body surface area; POS - presence of symptoms; PVC - premature ventricular contraction; PEI - pre-ectopic interval.

Table 3.

Scoring system for the probability of arrhythmia-induced cardiomyopathy in children

Predictors	Change in Probability in the Presence of the Predictor		p	Points
	AOR	95% CI		
VA burden 25-29%	8.434	1.291-55.106	0.026	2
VA burden 30-34%	11.276	1.686-75.416	0.012	3
VA burden ≥35%	17.15	3.603-81.639	<0.001	4
Mean PEI ≤434 ms	3.742	1.304-10.738	0.014	1
BSA ≥1.7 m²	4.945	1.766-13.461	0.002	1

Note: AOR - adjusted odds ratio. Probability of arrhythmia-induced cardiomyopathy was classified as low (0-2 points), intermediate (3-4 points), and high (5-6 points).

correlation matrix was constructed. Spearman's correlation coefficient was used as the criterion for evaluating associations. The prognostic model was constructed using binary logistic regression. Independent predictors were selected by stepwise Wald statistics. The statistical significance of the model and its predictors was determined using the χ^2 test. The threshold probability (P) for AIC occurrence with optimal sensitivity and specificity was determined by receiver operating characteristic (ROC) curve analysis.

For the development of the risk scoring system for AIC, quantitative variables in the model were converted into categorical variables. For each predictor, odds ratios (OR) were determined by binary logistic regression. The minimum OR value obtained in the model was assigned a weight of 1 point. The score for each predictor was then calculated by dividing its OR value by the minimum OR in the model. The sum of points was calculated for each patient in the training cohort. Cut-off values of the total score, which stratified patients into groups of high, intermediate, and low probability of developing AIC, were determined using ROC curve analysis.

Risk probability was assessed according to the specificity of the total score: <50% was classified as low probability, 50-90% as intermediate probability, and >90% as high probability of AIC. For validation of the scoring system, the total score was calculated for patients in the test cohort, followed by assessment of sensitivity and specificity of the score using ROC curve analysis.

RESULTS

For the development of a multivariable model, factors with the highest prognostic potential ($p<0.05$) were included in the analysis (Table 2). In constructing the correlation matrix, significant correlations were observed between age and body surface area (BSA) ($\rho=0.849$; $p<0.001$). Predictors with significant correlations were not included simultaneously in the prognostic model. To describe the probability of arrhythmia-induced cardiomyopathy (AIC) in children with idiopathic VA as a function of the studied factors, the model with the highest sensitivity and specificity was selected. The observed relationship is described by Equation (1):

$$P = 1 / (1 + e^{-z})$$

$$z = -5{,}217 + 0{,}039*X_{PVCburden} - 0{,}003*X_{PEI} + 1{,}748*X_{BSA} \quad (1)$$

where P is the probability of developing AIC, $X_{pvc\ burden}$ = PVC burden (%), X_{pEI} = mean pre-ectopic interval (PEI) of PVCs (ms), and X^BS^A = body surface area (m²).

The regression model was statistically significant ($p<0.001$). Based on Nagelkerke's coefficient of determination, 35.3% of the variance in AIC probability was explained by the factors included in Model (1). According to the regression coefficients, BSA and PVC burden were positively associated with AIC risk, while mean PEI was inversely associated. Characteristics of each predictor are presented in Table 3.

In particular, an increase in BSA by 1 m² was associated with a 5.742-fold higher risk of AIC ($p<0.001$). An increase in PVC burden by 1% increased the risk of AIC 1.04-fold ($p=0.003$). A decrease in mean PEI by 1 ms increased the risk of AIC 1.003-fold ($p=0.006$).

Figure 1 shows adjusted odds ratios (ORs) with 95% confidence intervals (CI) for the predictors included in Model (1). The threshold value of the logistic function P was determined using ROC curve analysis. The resulting curve is shown in Figure 2a. The area under the ROC curve (AUC) was 0.833±0.042 (95% CI: 0.751-0.915). The threshold probability for AIC was 0.0655. At $P \geq 0.0655$, patients were classified as high risk for AIC; at $P < 0.0655$, patients were classified as low risk. At this cut-off, the sensitivity and specificity of Model (1) were 75.0% and 77.1%, respectively.

For clinical application of the model, a scoring system was developed to estimate the probability of AIC. All quantitative variables were transformed into categorical variables based on medians and percentiles. The resulting scoring system is shown in Table 3.

Cut-off values for the total score separating patients into low-, intermediate-, and high-risk groups for AIC were determined using ROC curve analysis (Figure 2b). The AUC of the prognostic score was 0.805±0.037 (95% CI: 0.732-0.878). This model was statistically significant ($p<0.001$). The sensitivity and specificity of the scoring system in predicting spontaneous resolution of VA are presented in Table 4.

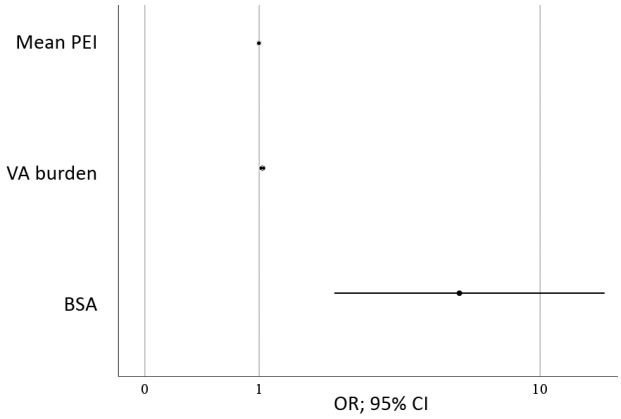

Figure 1. Odds ratio estimates with 95% confidence intervals for predictors of arrhythmia-induced cardiomyopathy in children: mean PEI (pre-ectopic interval), VA burden (ventricular arrhythmia burden), BSA (body surface area).

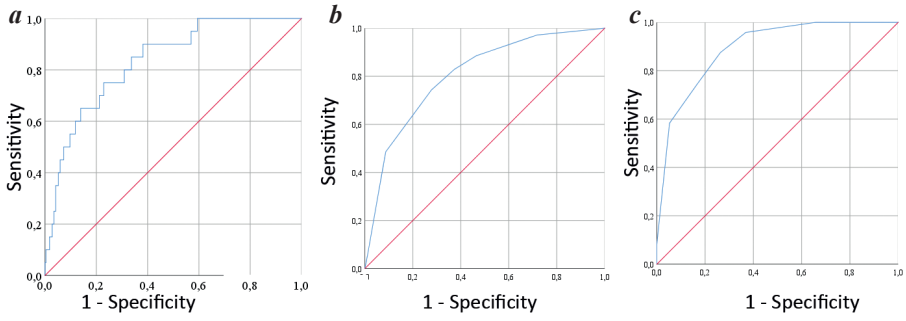

Fig. 2. ROC curves characterising the probability of arrhythmia-induced cardiomyopathy according to logistic function values (a), in the training cohort (b), and in the test cohort (c).

Accordingly, three risk groups were identified: Group 1 (low probability): total score 0-2; Group 2 (intermediate probability): total score 3-4; Group 3 (high probability): total score 5-6 (Table 3). In the training cohort, among patients with AIC, 6 children (17.1%) were classified as low probability, 12 (34.3%) as intermediate probability, and 17 (48.6%) as high probability.

For validation of the risk score, the total score was calculated for 100 children in the test cohort. A ROC curve was constructed to evaluate the sensitivity and specificity of the scoring system (Figure 2c). The AUC of the score in the test cohort was 0.893±0.034 (95% CI: 0.827-0.960), and the model was statistically significant (p<0.001). In the test cohort, among children with AIC, 1 child (4.2%) was classified as low probability, 7 (29.2%) as intermediate probability, and 16 (66.6%) as high probability. A score of 3-4 demonstrated specificity >50%, while a score ≥5 had specificity approaching 100%. The difference in AUC between the training and test cohorts was 0.088±0.05. AUCs were comparable (p=0.078).

DISCUSSION

Current clinical guidelines recommend treatment of children with idiopathic VA in the presence of symptoms, or when LV dilatation and/or reduced EF are present [14]. At the same time, identifying patients at high risk of AIC may allow modification of follow-up strategies or initiation of preventive therapy before the onset of heart failure symptoms.

The problem of AIC has been extensively studied in adults with VA and structurally normal hearts. It has been demonstrated that arrhythmia burden plays a key role in the development of AIC in adult patients with VA. According to numerous studies, a PVC burden of 20-26% is strongly associated with AIC formation in adults [15-18]. In domestic guidelines, LV dysfunction is reported in patients with a PVC burden exceeding 15% [14]. Observational studies in children indicate that a VA burden of 15-20% rarely leads to AIC, whereas LV dysfunction usually develops at a PVC burden >26-30% [7, 8, 10, 19]. In our study, we also demonstrated that the number of premature ventricular complexes (PVCs) per day is one of the main factors influencing AIC development. With increasing VA burden, the risk of AIC rises: at 25-29% the risk increased 8-fold, at 30-34% 11-fold, and at >35% 17-fold.

Another important electrocardiographic parameter is the mean pre-ectopic interval of PVCs, which also contributes significantly to AIC development. Several studies have shown a direct relationship between PEI duration and haemodynamic indices. Shorter PEI has been associated with reduced systolic blood pressure [20] and lower LV EF [6, 11]. S. Abadir et al. reported that a mean PEI <365 ms was associated with AIC, with a sensitivity of 85.7% and specificity of 86.5% [6]. In our study, we similarly found that a shorter mean PEI increased the likelihood of AIC. Specifically, a mean PEI <434 ms increased the risk of AIC 4-fold.

It should also be noted that AIC risk depends on age and anthropometric characteristics. Both in our study and in others, LV dysfunction was more frequently observed in adolescents compared with other age groups [9, 13]. However, in constructing our prognostic model we established that anthropometric indices, particularly body surface area (BSA), had greater prognostic significance than chronological age. An increase in BSA was associated with a higher probability of AIC, and BSA >1.7 m² increased the risk 5-fold.

Table 4.

Sensitivity and specificity of the scoring system for predicting spontaneous resolution of ventricular arrhythmia in the training and test cohorts

Score	Sensitivity	Specificity	Total patients, n (%)	Patients with AIC, n (%)
Training cohort				
0	100.0%	0.0%	102 (26.0)	1 (2.9)
1	92.8%	40.9%	93 (23.7)	3 (8.6)
2	85.8%	48.1%	35 (8.9)	2 (5.7)
3	78.6%	67.5%	37 (9.4)	3 (8.6)
4	61.5%	81.8%	77 (19.6)	9 (25.7)
5	51.5%	95.1%	42 (10.7)	15 (42.9)
6	3.0%	99.5%	6 (1.5)	2 (5.7)
Test cohort				
0	100.0%	0.0%	26 (26.0)	0 (0.0)
1	97.9%	50.7%	23 (23.0)	1 (4.2)
2	95.8%	68.5%	10 (10.0)	2 (8.3)
3	89.6%	78.3%	10 (10.0)	3 (12.5)
4	72.9%	88.8%	13 (13.0)	4 (16.7)
5	35.4%	97.4%	16 (10.0)	12 (50.0)
6	4.2%	100.0%	2 (2.0)	2 (8.3)

In our multivariable analysis, three independent predictors of AIC development in children with idiopathic VA were identified: VA burden, mean PVC PEI, and BSA. Based on this model, a scoring system was developed to stratify patients into low-, intermediate-, and high-risk groups. These factors accounted for 35.3% of the variance in AIC probability. Nevertheless, the search for additional predictors of AIC remains an important task.

For validation, a test cohort was recruited with an optimal total number of patients and sufficient outcome events. Validation data confirmed the strong predictive performance of the model (AUC = 0.893±0.034; 95% CI: 0.827-0.960). Thus, the risk scoring system for AIC in children with idiopathic VA, developed in the present study, has demonstrated its effectiveness and may be applied in clinical practice. Use of this model will allow the identification of children at high risk of AIC and enable timely treatment before the development of complications.

CONCLUSION

In this study, three independent predictors of arrhythmia-induced cardiomyopathy were identified in children with idiopathic VA: VA burden >25%, mean PEI <434 ms, and BSA >1.7 m². Based on these predictors, a prognostic scoring system for AIC was developed for this patient group. The proposed score is based on data from standard clinical and instrumental examinations and does not require complex calculations. Its simplicity enables routine assessment of AIC risk and supports the development of a personalised approach to the monitoring and management of each child with idiopathic ventricular rhythm disturbances.

REFERENCES

1. Makarov LM. Holter monitoring. 4-th edition. Moscow «MEDPRACTICE-M»; 2017:504 (In Russ.) ISBN 978-5-98803-362-2.
2. Alexander ME, Berul CI. Ventricular arrhythmias: When to worry. *Pediatr Cardiol*. 2000;21(6): 532-41.
3. Davis AM, Gow RM, McCrindle BW, et al. Clinical spectrum, therapeutic management, and follow-up of ventricular tachycardia in infants and young children. *Am Heart J*. 1996;131(1): 186-91.
4. Şengül FS, Kafali HC, Güzeltaş A, et al. Clinical spectrum and long-term course of sustained ventricular tachycardia in pediatric patients: 10 years of experience. *Anatol J Cardiol*. 2021;25(5): 313-22.
5. Song MK, Baek JS, Kwon BS, et al. Clinical spectrum and prognostic factors of pediatric ventricular tachycardia. *Circ J*. 2010;74(9): 1951-8.
6. Abadir S, Blanchet C, Fournier A, et al. Characteristics of premature ventricular contractions in healthy children and their impact on left ventricular function. *Hear Rhythm*. 2016;13(11): 2144-8.
7. Kakavand B, Ballard HO, Disessa TG. Frequent ventricular premature beats in children with a structurally normal heart: A cause for reversible left ventricular dysfunction? *Pediatr Cardiol*. 2010;31(7): 986-90.
8. Bertels RA, Harteveld LM, Filippini LH, et al. Left ventricular dysfunction is associated with frequent premature ventricular complexes and asymptomatic ventricular tachycardia in children. *Europace*. 2017;19(4): 617-21.
9. Przybylski R, Meziab O, Gauvreau K, et al. Premature ventricular contractions in children and young adults: natural history and clinical implications. *Europace*. 2024;26(3).
10. Spector ZZ, Seslar SP. Premature ventricular contraction-induced cardiomyopathy in children. *Cardiol Young*. 2016;26(4): 711-7.
11. Sun Y, Blom NA, Yu Y, et al. The influence of premature ventricular contractions on left ventricular function in asymptomatic children without structural heart disease: An echocardiographic evaluation. *Int J Cardiovasc Imaging*. 2003;19(4): 295-9.
12. Lopez L, Saurers DL, Barker PCA, et al. Guidelines for Performing a Comprehensive Pediatric Transthoracic Echocardiogram: Recommendations From the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2024;37(2): 119-70.
13. Chueva KA, Kofeynikova OA, Tatarskiy RB, et al. Risk factors for the development of tachycardia-induced cardiomyopathy in children with idiopatic ventricular arrhythmia. *Children's Heart and Vascular Diseases*. 2024; 21 (4): 297-304 (in Russ.). https://doi.org/10.24022/1810-0686-2024-21-4-297-304.
14. 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.org/10.15829/1560-4071-2021-4600.
15. Baman TS, Lange DC, Ilg KJ, et al. Relationship between burden of premature ventricular complexes and left ventricular function. *Hear Rhythm*. 2010;7(7): 865-869.
16. Remme CA, Leclercq C, Behr ER. The European Cardiac Arrhythmia Genetics (ECGen) Focus Group. *European heart journal*. 2022;43(20): 1891-1894. https://doi.org/10.1093/eurheartj/ehab698.
17. Cha YM, Lee GK, Klarich KW, Grogan M. Premature ventricular contraction-induced cardiomyopathy: a treatable condition. *Circ Arrhythm Electrophysiol*. 2012;5(1): 229-236. https://doi.org/10.1161/CIRCEP.111.963348.
18. Ban JE, Park HC, Park JS., et al. Electrocardiographic and electrophysiological characteristics of premature ventricular complexes associated with left ventricular dysfunction in patients without structural heart disease. *Europace*. 2013;15(5): 735-741. https://doi.org/10.1093/europace/eus371.
19. Alekseeva K, Kruchina T, Maliarova M, et al. Hemodynamic effects of premature ventricular contractions in children. *REJR*. 2021;11(2): 143-152 (in Russ.). https://doi.org/10.21569/2222-7415-2021-11-2-143-152.
20. Shubik YuV, Korneev AB, Morozov AN. Hemodynamic significance of ventricular ectopic beats: the im- pact of coupling intervals. Journal of Arrhythmology. 2025;32(1): 64-70 (in Russ.). https://doi.org/:10.35336/VA-1390.

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LOCAL CAPTURES OF THE PULMONARY VEIN MYOCARDIUM ARE A PREDICTOR OF IMPROVED LONG-TERM RESULTS OF RADIOFREQUENCY ABLATION OF NONPAROXYSMAL ATRIAL FIBRILLATION

V.V.Bazylev, A.V.Kozlov, S.S.Durmanov

"Federal Center for Cardiovascular Surgery" the MH RF, Russia, Penza, 6 Stasova str.

Aim. To evaluate the prognostic value of local captures after pulmonary vein isolation in patients with nonparoxysmal atrial fibrillation (AF) for the long-term results of radiofrequency ablation (RFA).

Methods. A single-center observational prospective study. The total number of patients 110. All patients underwent primary catheter ablation for nonparoxysmal AF. During the operation, the activity of pulmonary veins and the presence of local captures were assessed. Patients with local captures in at least one pulmonary vein were included in the first group. Patients who had no local captures were included in the second group. The number of patients in the first group is 54 patients, the number of patients in the second group is 56 patients. The groups had no statistically significant differences in the main indicators -gender, weight, age, duration of medical history, volume of the left atrium and left ventricular ejection fraction, as well as in concomitant pathology. The time of RFA and fluoroscopy, and the duration of operations between the groups also had no statistically significant differences.

Results. The follow-up period was 800 [286.5;800] days. The overall effectiveness of the treatment was 68.2% (75 patients out of 110), considering repeated operations. In the group with local captures, sinus rhythm was maintained at the end of the follow-up period in 42 out of 54 patients (77,7%), in the group without local captures in 33 out of 56 patients (58,9%). The difference is statistically significant (odds ratio 2,439 (95% confidence interval 1,060 -5,615 p=0,034). The presence of local captures in the construction of a multifactorial logistic regression model is a predictor of the effectiveness of RFA (χ^2=14,710; p=0,012).

Conclusion. In this study, local captures in the pulmonary veins in patients with nonparoxysmal atrial fibrillation were a predictor of improved long-term results of radiofrequency ablation.

Key words: nonparoxysmal form of atrial fibrillation; radiofrequency ablation; local captures; predictors of effectiveness; pulmonary veins

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Corresponding Author: Kozlov Aleksandr, E-mail: kozlov3619@yandex.ru

V.V.Bazylev - ORCID ID 0000-0001-6089-9722, A.V.Kozlov - ORCID ID 0000-0002-0529-0081, S.S.Durmanov - ORCID ID 0000-0002-4973-510X

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Atrial fibrillation (AF) is the most common arrhythmia in the human population, increasing the risks of stroke and adverse cardiovascular outcomes [1]. The effectiveness of AF treatment remains far from optimal, particularly in patients with non-paroxysmal forms [2]. Randomised clinical trials have demonstrated that catheter ablation is more effective than pharmacological therapy, reducing the risk of AF recurrence and improving patients' quality of life. Moreover, it may positively influence survival in patients with congestive heart failure [3-5].

AF is typically initiated by triggers and subsequently sustained by various mechanisms over time. Ectopic activity, especially originating from the pulmonary veins (PVs), plays a central role in AF initiation [6]. Myocardial in the PVs are extensions of the left atrial (LA) myocardium containing cells with the capacity for spontaneous depolarisation [7]. These cover the distal segments of the PVs. Compared with LA myocardium, PV myocardial exhibit slower conduction, a shorter effective refractory period, and greater susceptibility to AF induction during programmed electrical stimulation [8]. These electrophysiological properties make PVs an arrhythmogenic substrate responsible for the initiation and maintenance of AF.

PV respond to electrical stimulation, and the resulting electrical activity can be recorded and quantified. During pacing, local electrical signals occurring after the pacing artefact can be detected by a circular catheter positioned at the PV ostium. These signals, termed local captures (LCs), reflect electrical activity arising in close proximity to the catheter. Since PV are relatively small in volume, the electrical activity induced by pacing may not always be detectable [9]. The prognostic role of LCs in

interventional AF treatment has not been extensively studied.

We hypothesised that the presence of LCs in isolated PVs indicates a larger myocardial mass and, consequently, a greater role in AF initiation and maintenance. Thus, in patients with non-paroxysmal AF, the detection of LCs after PV isolation may signify a higher probability of eliminating both triggering and sustaining mechanisms of AF. Conversely, the absence of LCs may serve as a surrogate marker of advanced fibrotic remodelling of the LA, reducing the likelihood of long-term sinus rhythm maintenance after catheter ablation. Therefore, the presence of LCs may act as a predictor of AF ablation outcomes.

Aim: to assess the prognostic significance of local captures after PV isolation in patients with non-paroxysmal AF in relation to the long-term outcomes of radiofrequency catheter ablation (RFCA).

METHODS

This was a single-centre, prospective, observational study conducted between April 2021 and April 2022.

Inclusion criteria:

- Non-paroxysmal AF (persistent or long-standing persistent, as defined by the expert consensus [1]);
- Symptomatic AF refractory to antiarrhythmic therapy (AAT) (at least one class IC or class III drug) or intolerance to AAT;
- First RFCA procedure;
- Adequate anticoagulation (target INR 2.0-3.0 in patients on warfarin or direct oral anticoagulant therapy);
- Absence of significant valvular heart disease;
- Age 40-75 years.

Exclusion criteria:

- Coexistence of AF with typical or atypical atrial flutter;
- LA diameter >60 mm on echocardiography (Echo);
- History of cardiac surgery for mitral valve disease;
- Reversible causes of AF;
- LA appendage thrombus.

Table 1.

Baseline characteristics of patients

	All patients (n=110)	First group LA(+) (n=54)	Second group LA(-) (n=56)	P
Age (years)	60.8±9.1	59.8±9.5	61.8±8.6	0.256
Male sex, n (%)	70 (63.6%)	38 (70.4%)	32 (57.1%)	0.152
BMI, kg/m²	30.4±4.6	30.0±4.5	30.8±4.6	0.349
LVEF, %	56.1±9.3	55.2±9.8	57.1±8.7	0.293
LA volume, mL	101.8±30.7	97.8±26.7	105.8±33.8	0.169
LA diameter, mm	43.4±5.6	42.9±5.4	43.8±5.8	0.404
AA, months	36 (12;72)	42 (12;75)	36 (10;69)	0.472
PD, months	6.0 (3.0;10.25)	6.0 (2.0;9.5)	6.0 (2.5;10.0)	0.642
DM, n (%)	14 (12.7)	10 (18.5)	4 (7.1)	0.075
AH, n (%)	97 (88.2)	51 (94.4)	48 (85.7)	0.082
IHD, n (%)	16 (14.5)	8 (14.8)	8 (14.3)	0.938

Note: BMI - body mass index; LVEF - left ventricular ejection fraction; LA - left atrium; ADA - arrhythmic anamnesis; PD - persistence duration; DM - diabetes mellitus; AH - arterial hypertension; IHD - ischaemic heart disease.

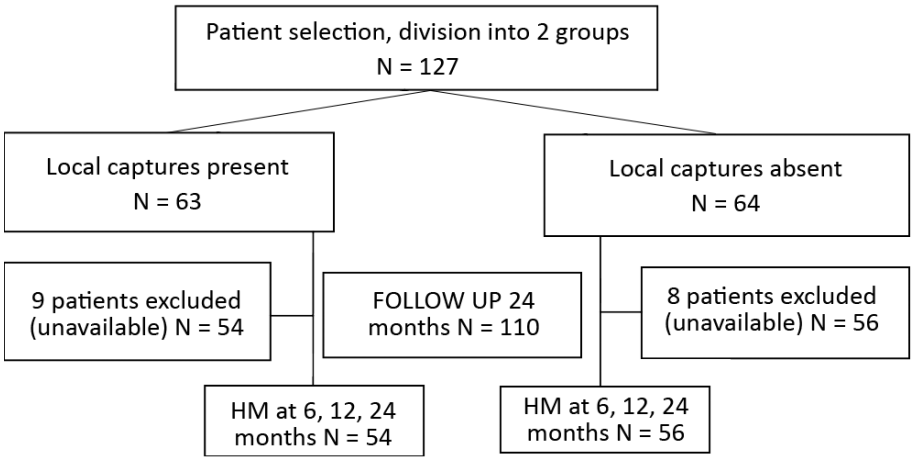

Fig. 1. Study design, where HM - Holter monitoring.

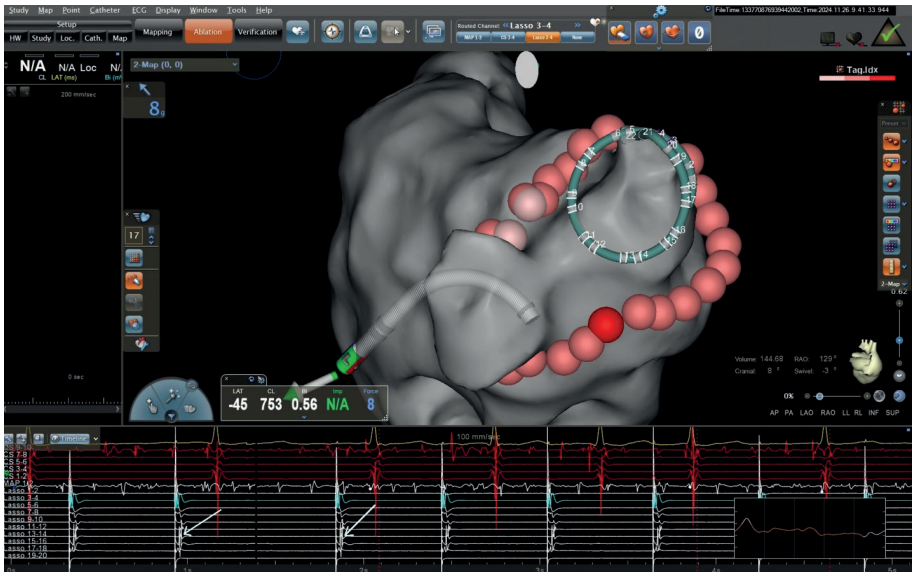

Fig. 2. Local captures in the right superior pulmonary vein. White arrows indicate local captures recorded on the Lasso catheter. The "Tissue Proximity Indication" module (white markers identifying the electrodes on the Lasso catheter) shows tight electrode contact with the pulmonary vein tissue.

A total of 127 patients undergoing first RFCA for persistent or long-standing persistent AF were enrolled. The patients were divided into two groups: Group 1 included those with LCs after PV isolation (63 patients), and Group 2 consisted of patients without LCs (64 patients). Seventeen patients were excluded due to inability to complete follow-up (9 from Group 1, 8 from Group 2). Thus, the final analysis included 110 patients: 54 in Group 1 and 56 in Group 2 (Fig. 1). The groups showed no statistically significant differences in baseline characteristics, including age, sex, body weight, AF history, comorbidities, LA volume, or left ventricular ejection fraction (Table 1).

Prior to the procedure, all patients underwent either transoesophageal echocardiography (TEE) or contrast-enhanced cardiac computed tomograph to exclude LA appendage thrombus. Procedures were performed under intravenous sedation. Patients remained responsive throughout the intervention. Dexmedetomidine was used for sedation, and fentanyl for analgesia.

Catheterisation of the coronary sinus with a multipolar catheter was performed via femoral or subclavian venous access, depending on operator preference. Double transseptal puncture was performed under fluoroscopic guidance without TEE. Two non-steerable introducers were advanced into the LA. To achieve target activated clotting time (ACT >300 seconds), an intravenous bolus of heparin was administered. Heparin dosing depended on anticoagulant therapy: patients on direct oral anticoagulants received a higher heparin dose compared with those on warfarin (17.9±4.4 thousand IU vs. 14.8±5.1 thousand IU, respectively) [10]. Target ACT values were subsequently maintained with continuous heparin infusion.

Table 2.

Main characteristics of the procedures performed

	First group N=54	Second group N=56	P
Procedure time, min	108±27,2	101,9±26,9	0,194
Fluoroscopy time, s	164,1±77,7	170,7±96,5	0,695
RFA time, min	32,2±10,3	29,8±9,9	0,213

Note: RFA - radiofrequency ablation

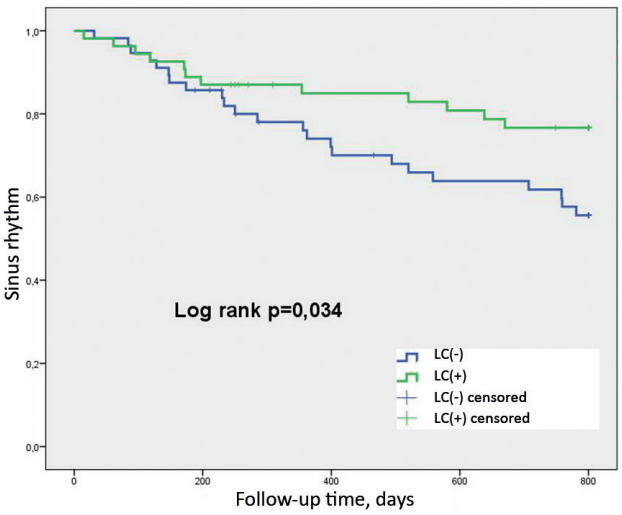

Fig. 3. Maintenance of sinus rhythm in the first and second patient groups.

Oesophageal position was visualised with contrast oesophagography using Omnipaque (GE Healthcare Ireland). A 20-pole Lasso® catheter (Biosense Webster, Johnson & Johnson, USA) was used to construct LA anatomical maps with the CARTO 3 system (Biosense Webster, Johnson & Johnson, USA). PV activity was assessed with the Lasso catheter. The catheter depth was confirmed fluoroscopically, with positioning at the cardiac contour in LAO 30° projection for the left PVs and RAO 30° for the right PVs. If no spike activity was recorded inside a vein, the vein was considered electrically inactive.

Following the CLOSE protocol [11], PV ostial isolation was performed with EZ Steer Nav SmartTouch catheters (Biosense Webster, Johnson & Johnson, USA). RF applications were delivered using a Stockert RF generator (Biosense Webster, Johnson & Johnson, USA) in power-control mode. Maximum RF power was 40 W. Irrigation with saline was performed using the CoolFlow pump (Biosense Webster, Johnson & Johnson, USA) at 30 ml/min.

On the posterior LA wall adjacent to the oesophagus, RF power was limited to 30 W with a maximum duration of 10 seconds. RF application points were annotated using CARTO 3 Visitag settings: contact force >4 g for at least 35% of the application time and catheter tip displacement ≤2.5 mm. The distance between neighbouring ablation points was ≤6 mm. The ablation index (AI) targets were 450 for the anterior wall and 300 for the posterior wall. These thresholds were established by Biosense Webster specialists for our centre after reviewing 10 blinded PV isolation procedures [12].

After isolation of the right and left PVs, the Lasso catheter was placed sequentially in each PV. The Carto 3 "Tissue Proximity Indication" module was used to assess electrode-tissue contact. Stimulation was delivered from all electrode pairs with a current of 10 mA and pulse duration of 1 ms. Endograms were analysed for the presence of LCs by two physicians. If their opinions coincided, the LC was considered present (Fig. 2). Any disagreement or doubt by at least one of the experts was interpreted as absence of LCs. Statistics on inter-observer disagreement were not collected.

If the patient was in sinus rhythm at the time of the procedure, the intervention was limited to PV isolation alone. In cases where AF was ongoing during the procedure, some patients—at the operator's discretion—in addition to PV isolation underwent AF substrate modification, which involved identifying and ablating atrial myocardium regions with spatiotemporal dispersion of activation [13]. There was no standardised lesion set in the LA; additional ablations were tailored individually to each patient depending on the localisation of dispersion zones. If sinus rhythm was not restored, external cardioversion was performed. Entrance and exit block of all PVs was then reassessed.

One case of haemopericardium occurred in a patient from Group 2, which resolved after pericardial drainage. No other complications were observed. All patients continued antiarrhythmic therapy for 4 weeks after RFCA. Discontinuation of antiarrhythmic drugs was at the discretion of the attending physician depending on the clinical situation. Anticoagulant therapy was not discontinued regardless of procedural efficacy.

Postoperative follow-up was performed both in person and remotely. Some patients were seen on schedule at the outpatient clinic, where clinical status was assessed and Holter monitoring (HM) performed. Patients from remote regions submitted medical documentation including symptom reports and HM data at 6, 12, and 24 months after RFCA. Recurrence of arrhythmia was defined as any documented AF or atrial tachycardia lasting longer than 30 seconds. In such cases, patients were referred for repeat ablation. The primary endpoint was the absence of atrial arrhythmias at the end of follow-up, accounting for repeat interventions.

Statistical Analysis

Statistical analysis was performed using IBM® SPSS® Statistics (Version 20, 2011). Normality of distribution was assessed using the Kolmogorov-Smirnov test. For normally distributed data, results are presented as arithmetic mean ± standard deviation (M ± SD) with 95% confidence interval (95% CI). For non-normally distributed data, results are expressed as median and interquartile range. For comparisons of means, the Student's t-test was used for normally distributed data, and the Mann-Whitney test for non-normally distributed data. Treatment efficacy was evaluated using the Kaplan-Meier method, with differences compared using the two-sided log-rank test.

Multivariate regression modelling was performed using the binary logistic regression module. Parameters whose predictive role for RFCA efficacy was demonstrated in univariate analysis at a significance level of $p < 0.1$ were included in the regression analysis. The decision to retain a predictor in the model was based on the Wald statistic. The enter method was applied to include variables simultaneously into the equation. Model performance was evaluated using ROC analysis. A critical level of statistical significance of $p < 0.05$ was assumed when testing hypotheses.

RESULTS

In the first group (LC+), AF was recorded intraoperatively in 90.7% of patients (49), while 9.3% (5 patients) were operated in sinus rhythm. In the second group (LC-), 85.7% (48 patients) underwent the procedure during AF, and 14.3% (8 patients) in sinus rhythm. The difference between groups was not statistically significant ($p = 0.652$). In the first group, PV isolation without additional LA interventions was performed in 51.9% (28 patients), compared with 46.4% (26 patients) in the second group ($p = 0.574$). Isolation of PV ostia was achieved in 100% of patients.

In the LC+ group, the majority of PVs were active (213 of 216, 98.6%), whereas in the LC- group the proportion of active PVs was lower (174 of 224, 77.7%). This difference was statistically significant ($p < 0.05$). No significant differences were observed in the main procedural characteristics between the two groups (Table 2). Spontaneous ectopic activity in isolated PVs was observed only in the LC+ group, recorded in 25 PVs of 19 patients; in the LC- group no ectopic PV activity was noted ($p < 0.05$). The distribution of PVs with ectopic activity was as follows: right superior PV - 15 cases, left superior PV - 7 cases, left inferior PV - 2 cases, right inferior PV - 1 case. In all cases with ectopic activity in a PV, LCs were simultaneously detected in the same PV (100%).

The frequency of LCs coincided with the frequency of ectopic PV activity. LCs were recorded in the right superior PV in 44 cases, left superior PV in 36, left inferior PV in 15, and right inferior PV in 12. LCs were detected in all four PVs in 1 patient (1.9%), in three PVs in 14 patients (25.9%), in two PVs in 22 patients (40.7%), and in one PV in 17 patients (31.5%). Among patients with LCs in one PV, RFCA efficacy was 75%. Patients with LCs in two or three PVs demonstrated similar efficacy - 64.3% and 65.2%, respectively. The single patient with LCs in all four PVs experienced AF recurrence after 580 days of follow-up. No statistically significant difference in treatment efficacy was observed according to the number of PVs with LCs ($p = 0.317$). PVs with LCs were completely isolated in 100% of cases, both during sinus rhythm and AF.

Of the total cohort, 46 patients (41.8%) were followed up in person and 64 patients (58.2%) remotely. Maintenance of sinus rhythm after RFCA was achieved in 31 patients (67.4%) with in-person follow-up and in 44 patients (68.8%) with remote follow-up; this difference was not statistically significant ($p = 0.621$).

The median follow-up period was 800 [286.5; 800] days. Overall treatment efficacy in the entire cohort was 68.2% (75 of 110 patients). Repeat procedures were performed in 12 patients (22.2%) in the LC+ group and in 19 patients (33.9%) in the LC- group, with no significant difference between groups ($p = 0.122$). During repeat procedures, reconduction in at least one PV was observed in all LC+ patients, while in the LC- group PV isolation persist-

Table 3.

Data from univariate and multivariate regression analysis

	Univariate regression			Multivariate regression		
	OR	95%CI	P	OR	95% CI	P
Age (years)	1.162	0.223-6.145	0.859			
Male sex, n (%)	1.500	0.689-3.478	0.344			
BMI, kg/m²	1.086	0.898-1.875	0.086	1.112	1.005-1.230	0.039
LVEF, %	1.083	0.992-1.095	0.105			
LA volume, mL	1.002	0.984-1.014	0.787			
LA diameter, mm	0.982	0.952-1.067	0.837			
AA, months	0.994	0.984-1.014	0.121			
DP, months	1.173	0.490-2.793	0.719			
DM, n (%)	3.364	0.664-14.03	0.136			
AH, n (%)	1.408	0.989-1.344	0.099	1.779	0.424-7.467	0.431
CAD, n (%)	1.009	0.940-4.707	0.719			
Local captures	0.424	0.178-0.944	0.036	0.293	0.115-0.747	0.010

Note: OR - Odds Ratio; CI - Confidence Interval

ed in 10 patients (52.6%). This difference was statistically significant ($p < 0.05$).

At the end of follow-up, sinus rhythm was maintained in 42 of 54 patients (77.7%) in the LC+ group compared with 33 of 56 patients (58.9%) in the LC- group. This difference was statistically significant, with an odds ratio (OR) of 2.439 (95% CI 1.060-5.615, $p = 0.034$) (Fig. 3).

Univariate regression analysis identified several factors with the strongest predictive potential: body mass index (BMI), arterial hypertension, and the presence of LC (Table 3). Based on these findings, a multivariate regression analysis was performed. Variables (BMI, LC) that demonstrated a statistically significant association with the endpoint were included in the prognostic model. The constructed model was statistically significant ($\chi^2 = 14.710$; $p = 0.012$). The Nagelkerke R^2 was 0.175, and the Hosmer-Lemeshow test result was 0.247. Both univariate and multivariate regression analyses identified the presence of LC as a predictor of long-term sinus rhythm maintenance after RFCA.

The quality of the resulting model was assessed using ROC analysis. The area under the ROC curve (AUC) was 0.70 ± 0.057 (95% CI 0.588-0.813) (Fig. 4). The cut-off value of the function was 0.6058 (sensitivity 73.3%, specificity 63%). The AUC for the new dichotomized variable was 0.718 (95% CI 0.611-0.814). After adjusting the classification threshold according to ROC analysis, the diagnostic performance of the multivariate model reached 70% (sensitivity 78.3%, specificity 65%).

DISCUSSION

The results of interventional treatment in patients with persistent AF remain suboptimal. Numerous attempts to improve efficacy by adding additional lesions to PV isolation initially yielded promising outcomes in pilot studies [14]. However, large randomized multicentre trials failed to demonstrate any advantage of additional LA lesions compared with PV isolation alone [15]. Thus, the optimal ablation set for patients with persistent AF has not yet been established. Persistent AF is likely to involve multiple underlying electrophysiological mechanisms, and identifying the dominant mechanism in each individual patient is critical for designing a tailored ablation strategy [16]. Unlike paroxysmal AF, which is predominantly trigger-driven, persistent AF is largely substrate-dependent. One limitation of substrate modification is the difficulty of identifying patients who may benefit from this approach. This makes it challenging to propose a standardized and, more importantly, reproducible ablation strategy for persistent AF [17].

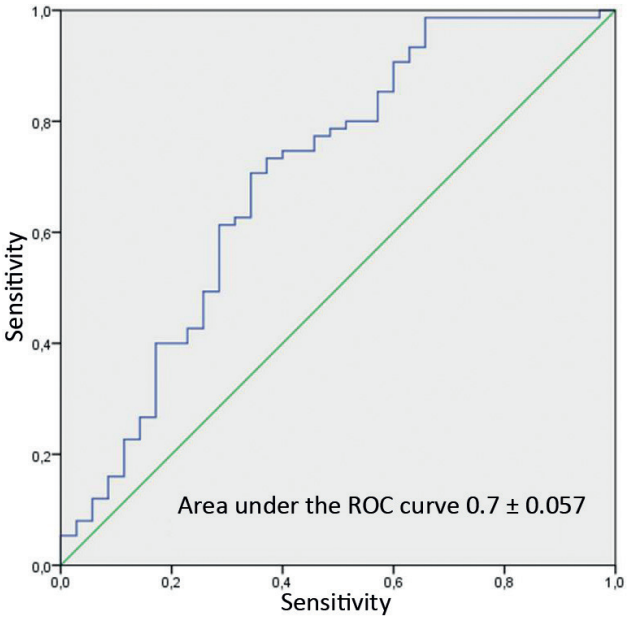

Fig. 4. ROC curve of the multivariable logistic regression model.

One potential option for individualising interventional treatment in non-paroxysmal AF is to determine the extent of ablation based on the presence or absence of LCs in isolated PVs. It is well established that the more advanced the degree of fibrosis in the LA, the higher the likelihood of AF recurrence after catheter ablation [18, 19]. The absence of LCs may therefore serve as a surrogate marker of fibrotic remodelling not only in the LA myocardium but also in the PV myocardial. In such cases, the role of PVs in initiating and maintaining persistent AF may be minimal, and achieving clinical success may require more extensive ablation within the LA. Conversely, the presence of LCs may indicate a greater involvement of PVs in sustaining AF, and their isolation alone might be sufficient to maintain sinus rhythm. Unfortunately, in this study, no direct assessment of LA fibrosis or its relationship with LC presence/absence was performed, and this issue requires further investigation.

The relationship between LC presence and the effectiveness of interventional treatment across different AF types remains poorly understood. The literature contains limited data on the prognostic role of LCs in catheter procedures, with most publications describing their use as a convenient marker of achieved PV isolation [20]. The authors identified only one published study, by A. Babak et al. (2024) [21], which investigated the electrophysiological properties of PVs after cryoballoon ablation in 390 patients with different AF types, and their impact on long-term outcomes. In patients with persistent AF, LCs were observed in 17.1% of cases, compared with 49.1% in our study. The use of the Carto 3 system's Tissue proximity indication module may have allowed us to ensure denser electrode-tissue contact, thereby optimising conditions for sleeve stimulation and LC detection. Patients with persistent AF who demonstrated LCs after PV isolation achieved higher rates of sinus rhythm maintenance than those without LCs. The authors therefore also proposed the use of LCs as a factor guiding ablation strategy in patients with persistent AF. Our findings were consistent with these results, despite differences in the type of ablation energy used.

The assumption that LCs reflect greater PV arrhythmogenicity has been supported in patients with paroxysmal AF [9]. Patients with LCs showed greater RFCA efficacy than those without. Although LCs are not generally considered a mandatory criterion for successful PV isolation, their presence has been described as a favourable prognostic sign [22]. Of particular interest is the study by F. Marshlinski et al. [23], which considered the disappearance of LCs after PV isolation as a marker of durable isolation. That study involved 30 patients undergoing

primary or repeat PV isolation. Before ablation, 99.8% of PVs exhibited LCs, while after ablation LCs persisted in only 60.9% of PVs. The absence of LCs correlated with a lower likelihood of reconduction during adenosine testing (4% in PVs without LCs versus 23% in PVs with LCs). Although the article did not provide a clear electrophysiological explanation for LC disappearance after PV antral isolation, the authors hypothesised that PVs losing LC had thinner myocardial . Antral ablation lines might also have damaged ganglionated plexuses or fibres projecting to PVs, thereby reducing sleeve excitability and abolishing LCs. They proposed LC disappearance as a marker of reliable PV isolation.

In our study of patients with persistent AF, the presence of LCs after PV isolation was a predictor of RFCA efficacy. In all LC+ patients undergoing repeat RFCA procedures, reconduction was observed in at least one PV. By contrast, in more than 50% of LC- patients PV isolation was preserved, yet RFCA efficacy was lower compared with the LC+ group. This may be explained as follows: in LC+ PVs, the greater myocardial sleeve mass likely contributes more to AF initiation and maintenance, making reconduction in these veins more arrhythmogenic. In contrast, LC- PVs contain fewer myocardial fibres, reducing arrhythmogenic potential and increasing the likelihood of durable isolation. Thus, reconduction in LC+ PVs may confer a higher risk of AF recurrence than reconduction in LC- PVs. These findings suggest that, when LCs are present, more stringent verification of PV isolation may be warranted, including the use of concealed conduction testing.

Study Limitations

The limitations of this study include its single-centre design and the relatively small sample size. In addition, the assessment of LC requires specific technical expertise, which may complicate the interpretation of the findings. Furthermore, the absence of data on interobserver variability in evaluating the presence of LC may have introduced bias, potentially leading to an overestimation of their frequency.

CONCLUSION

In this study, local captures (LCs) in the pulmonary veins (PVs) of patients with non-paroxysmal atrial fibrillation (AF) were predictors of improved long-term outcomes after radiofrequency ablation (RFA).

REFERENCES

1. Stylianos T, Edward P, Jonathan K, et al. 2024 European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on catheter and surgical ablation of atrial fibrillation. *EP Europace* 2024;26(4). https://doi.org/10.1093/europace/euae043.

2. Chander S, Kumari R, Luhana S, et al. Antiarrhythmic drug therapy and catheter ablation in patients with paroxysmal or persistent atrial fibrillation: a systematic review and meta-analysis. *BMC Cardiovasc Disord.* 2024;24(1): 32. https://doi.org/10.1186/s12872-024-03983-z.

3. Packer D, Mark D, Robb R, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA*. 2019;321(13): 1261-1274. https://doi.org/10.1001/jama.2019.0693.

4. Sohns C, Fox H, Marrouche N, et al. Catheter Ablation in End-Stage Heart Failure with Atrial Fibrillation. *N Engl J Med.* 2023;389(15): 1380-1389. https://doi.org/10.1056/NEJMoa2306037.

5. Bazylev VV, Kozlov AV, Durmanov SS, et al. Quality of life after staged interventional or simultaneous surgical treatment of paroxysmal atrial fibrillation and coronary heart disease. *Annaly aritmologii.* 2021;18(1): 53-61. (In Russ.) https://doi.org/10.15275/annaritmol.2021.1.

6. Haissaguerre M, Jais P, Shah D, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med.* 1998;339(10): 659–66. https://doi.org/10.1056/NEJM199809033391003.

7. Bredeloux P, Pasqualin C, Bordy R, et al. Automatic Activity Arising in Cardiac Muscle Sleeves of the Pulmonary Vein. *Biomolecules*. 2021;12(1): 23. https://doi.org/10.3390/biom12010023.

8. Teh A, Kistler P, Lee G, et al. Electroanatomic properties of the pulmonary veins: slowed conduction, low voltage and altered refractoriness in AF patients. *J Cardiovasc Electrophysiol.* 2011;22(10): 1083-91. https://doi.org/10.1111/j.1540-8167.2011.02089.x.

9. Bazylev VV, Kozlov AV, Durmanov SS. The presence of local captures of the myocardium of the pulmonary veins after radiofrequency isolation improves the outcome of treatment in patients with paroxysmal atrial fibrillation. *Journal of Arrhythmology.* 2023;30(4): 5-12. (In Russ.) https://doi.org/10.35336/VA-1186.

10. Popylkova OV, Durmanov SS, Bazylev VV, et al. Warfarin versus direct oral anticoagulants: how the degree of coagulation differs during catheter ablation of atrial fibrillation. *Journal of Arrhythmology.* 2022;29(3): 13-20. (In Russ.) https://doi.org/10.35336/VA-2022-3-02.

11. Phlips T, El Haddad M, Duytschaever M, et al. Improving procedural and one-year outcome after contact force-guided pulmonary vein isolation: the role of interlesion distance, ablation index, and contact force variability in the 'CLOSE'-protocol, *EP Europace.* 2018;20(3): 419-427. https://doi.org/10.1093/europace/eux376.

12. Mikhaylov EN, Gasimova NZ, Ayvazyan SA, et al. Factors associated with the efficacy of atrial fibrillation radiofrequency catheter ablation: opinion of the specialists who use the "ablation index" module. *Journal of Arrhythmology.* 2020;27(3): 9-24. (In Russ.) https://doi.org/10.35336/VA-2020-3-9-24.

13. Seitz J, Bars C, Théodore G, et al. AF Ablation Guided by Spatiotemporal Electrogram Dispersion Without Pulmonary Vein Isolation: A Wholly Patient-Tailored Approach. *J Am Coll Cardiol.* 2017;69(3): 303-321. https://doi.org/10.1016/j.jacc.2016.10.065.

14. Griffin M, Calvert P, Gupta D. Persistent Atrial Fibrillation Ablation: Ongoing Challenges Defining the Target Population and Substrate. *Curr Treat Options Cardio Med.* 2023;25(10): 461–475. https://doi.org/10.1007/s11936-023-01011-5.

15. Cheng-ming M, Ye-jian H, Wen-wen L, et al. Optimal

Catheter Ablation Strategy for Patients with Persistent Atrial Fibrillation and Heart Failure: A Retrospective Study. *Cardiology Research and Practice.* 2022;1: 1-7. https://doi.org/10.1155/2022/3002391.
16. Dhillon GS, Honarbakhsh S, Graham A, et al. Driver characteristics associated with structurally and electrically remodeled atria in persistent atrial fibrillation. *Heart Rhythm O2*. 2022;3(6Part A): 631–638. https://doi.org/10.1016/j.hroo.2022.09.016.
17. Palamà Z, Nesti M, Robles AG, et al. Tailoring the Ablative Strategy for Atrial Fibrillation: A State-of-the-Art Review. *Cardiol Res Pract.* 2022;2022: 9295326. https://doi.org/10.1155/2022/9295326.
18. Kwon S, Choi EK, Lee SR, et al. The left atrial low-voltage area and persistent atrial fibrillation treated with pulmonary vein isolation alone. *European Heart Journal.* 2022;43(Supplement2) https://doi.org/10.1093/eurheartj/ehac544.464.
19. Ma J, Chen Q, Ma S. Left atrial fibrosis in atrial fibrillation: Mechanisms, clinical evaluation and management. *J Cell Mol Med.* 2021;25(6): 2764-2775. https://doi.org/10.1111/jcmm.16350.
20. Yang F, Raiszaden F, Fisher J, et al. Pulmonary Vein Isolation: Making the Most of Local Vein Capture with Exit Block. *The Journal of Innovations in Cardiac Rhythm Management* 2015;6: 2078–2084. https://doi.org/10.19102/icrm.2015.060705.
21. Babak A, Kauffman CB, Lynady C, et al. Pulmonary vein capture is a predictor for long-term success of standalone pulmonary vein isolation with cryoballoon ablation in patients with persistent atrial fibrillation. *Front Cardiovasc Med.* 2024;10: 1150378. https://doi.org/10.3389/fcvm.2023.1150378.
22. Issa ZF, Miller JM, Zipes DP. Clinical Arrhythmology and Electrophysiology.1st ed. Philadelphia: Saunders; 2009:242.
23. Squara F, Liuba I, Chik W, et al. Loss of local capture of the pulmonary vein myocardium after antral isolation: prevalence and clinical significance. *J Cardiovasc Electrophysiol.* 2015;26(3): 242-250. https://doi.org/10.1111/jce.12585.

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EVALUATION OF THE ABLATION INDEX DURING CATHETER TREATMENT WITHOUT FLUOROSCOPY IN PATIENTS WITH CORONARY HEART DISEASE AND SYSTOLIC DYSFUNCTION

V.A.Amanatova[1], M.R.Khachirov[2], T.M.Uskach[1,3], D.F.Ardus[1], A.V.Vereshchagina[1], M.A.Podyanov[1], D.I.Cherkashin[1], I.R.Grishin[1], O.V. Sapelnikov[1]

[1]FSBI "Academician E.I. Chazov National Medical Research Center of Cardiology" of the MH RF, Russia, Moscow, 15A Academician Chazov str.; [2]SBHI "V.V.Veresaev City Clinical Hospital of the Moscow Department of Health", Russia, Moscow, 10 Lobbenskaya str.; [3]FSBEI of CPE "Russian Medical Academy of Continuous Professional Education" of the MH RF, Russia, Moscow, 38 Smolnaya str.

Aim. To study the ablation index (AI) in the context of catheter treatment of ventricular tachycardia (VT) without the use of fluoroscopy in patients with chronic heart failure.

Methods. Catheter ablation of VT was performed in 47 patients with coronary heart disease and chronic heart failure. Intraoperative parameters of the ablation, including the average ablation index, were assessed. The fact of arrhythmia induction after a series of radiofrequency exposures was assessed. Recurrence of VT was also assessed. The observation period was 12 months.

Results. During surgery after ablation exposure, arrhythmia induction was impossible in 100% of patients. After 12 months of observation, freedom from arrhythmia was 84,8%. Patients without recurrence of VT had a statistically significantly higher mean AI (612 [522,5; 683,5]) than with recurrence of VT (7 (15,2%) patients) (438 [416,5; 462]) (p=0,001). The possibility of predicting recurrence of VT depending on the mean AI value was also assessed. It was found that with the mean AI value greater than or equal to 473, the risk of recurrence of VT is lower (p=0,001).

Conclusions. AI can be used as a parameter for monitoring effective ablation exposure in the context of catheter ablation of VT along with other determinants currently used.

Keywords: ventricular tachycardia; ablation index; heart failure; coronary artery disease; catheter ablation

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Corresponding Author: Amanatova Valeria, E-mail: amanatova.v@yandex.ru,

V.A.Amanatova - ORCID ID 0000-0002-0678-9538, M.R.Khachirov ORCID ID 0000-0003-0180-2569, T.M.Uskach - ORCID ID 0000-0003-4318-0315, D.F.Ardus - ORCID ID 0000-0001-8305-1855, A.V.Vereshchagina - ORCID ID 0000-0001-8158-3794, M.A.Podyanov - ORCID ID 0009-0003-7069-6349, D.I.Cherkashin - ORCID ID 0000-0003-1679-1719, I.R.Grishin - ORCID ID 0000-0002-2689-2751, O.V.Sapelnikov - ORCID ID 0000-0002-5186-2474

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Ventricular tachycardia (VT) is defined as a tachycardia (rate >100 bpm) consisting of three or more consecutive complexes originating below the bifurcation of the His bundle, arising from the specialised conduction system, the ventricular myocardium, or both tissues, irrespective of atrial or atrioventricular nodal conduction. Such rhythm disturbances may occur in patients with coronary artery disease as well as in those with various cardiomyopathies. The pathophysiology of VT differs across patient populations [1, 2].

In patients with prior myocardial infarction (MI), most sustained monomorphic VTs are caused by a macro-re-entry mechanism involving the scar zone. Experimental studies have shown that the electrophysiological substrate for monomorphic VT gradually forms during the subacute phase of MI, with no difference observed between VTs induced in the subacute versus chronic phases, as both are associated with comparable sites of early presystolic activation. These sites are predominantly located in the border zone, adjacent to dense scar areas in both phases [3]. Persistent coronary occlusion usually leads to the development of a dense, transmural central scar core within the region supplied by the occluded artery, surrounded by a thin border zone where fibrous tissue and viable myocardial fibres are intricately interwoven. By contrast, early reperfusion may result in a more complex substrate characterised by non-transmural myocardial necrosis, heterogeneous scarring, and multiple channels of viable myocardium interspersed within the scar and border zones [4].

The development of VT significantly worsens both prognosis and quality of life. Implantation of an implantable cardioverter-defibrillator (ICD) can reduce mortality in patients with VT; however, this therapy does not prevent recurrence of arrhythmias. Implantable devices may, however, provide valuable data on the "burden" of ventricular arrhythmias [5, 6]. In 2022, a hypothesis was proposed suggesting a link between VT burden and mortality. Researchers considered two possible scenarios: one in which

progression of underlying heart disease increases both mortality risk and VT recurrence, and another representing a causal relationship, where disease progression increases the frequency of VT recurrence, thus creating a vicious cycle. This cycle of disease progression increasing VT burden, and in turn elevated VT burden increasing mortality risk due to cardiac pathology, illustrates a self-reinforcing loop [7].

VT accounts for approximately 25% of sudden cardiac deaths (SCD) in the general population, and in patients with cardiovascular disease this figure reaches 50% [8]. A distinct subgroup at risk of clinically significant arrhythmias is patients with chronic heart failure (CHF). The occurrence of arrhythmias in this population further aggravates the course of their disease. At the same time, given that CHF is the natural outcome of most cardiovascular pathologies, the development of ventricular arrhythmias in CHF patients is largely predictable [9]. Implantation of ICD for primary or secondary prevention of SCD is included in several contemporary guidelines [10]. However, ICD shocks may contribute to progression of CHF and impair quality of life [11-13].

The efficacy of catheter ablation (CA) depends on appropriate patient selection, procedural quality, and post-procedural management [14, 15]. Despite the availability of mapping techniques, several critical factors must be met to ensure procedural success. These include achieving transmurality and continuity of ablation lines, which requires catheter stability during energy delivery; sufficient application duration; adequate contact force of the ablation catheter with the myocardium; appropriate spacing between adjacent lesions to prevent the formation of conducting channels; and application of radiofrequency (RF) energy with sufficient power and duration. A delicate balance must be maintained, as insufficient RF delivery may result in suboptimal lesion formation, whereas excessive energy increases the risk of complications [16].

METHODS

The study was approved by the Ethics Committee of the National Medical Research Center of Cardiology named after Academician E.I. Chazov, Ministry of Health of the Russian Federation (Protocol No. 273 of the Committee meeting, 22 November 2021). A total of 47 patients with coronary artery disease (CAD) and CHF who underwent RFCA for VT were prospectively enrolled. All participants provided written informed consent. The follow-up period was 12 months.

Inclusion criteria were: moderately reduced or severely reduced left ventricular (LV) ejection fraction (EF);

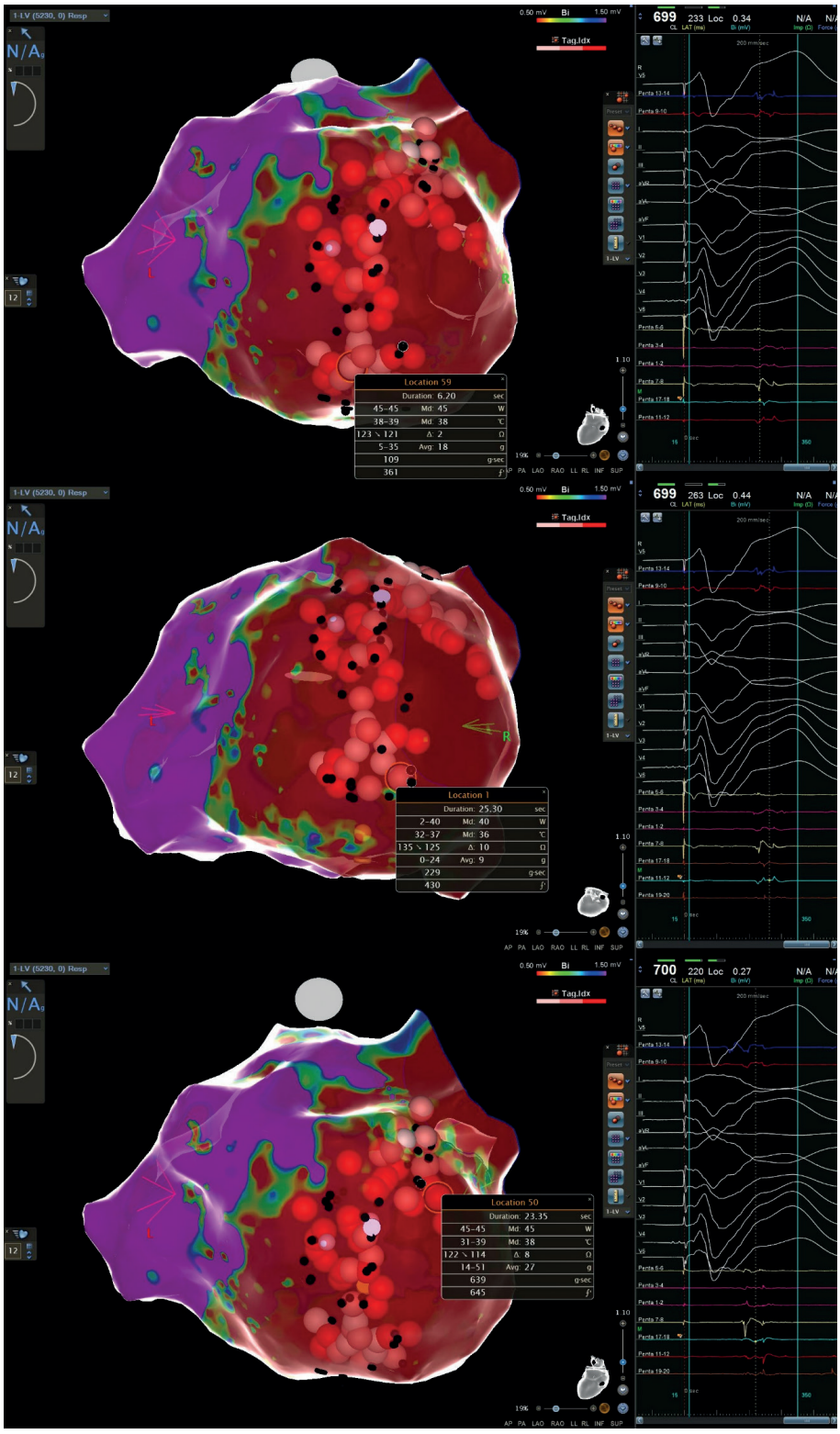

Fig. 1. Three-dimensional electroanatomical map of the left ventricle with volumetric markers indicating RF applications. Colour intensity reflects the ablation index at each site (≤400, white; 400-500, pink; >500, red).

New York Heart Association (NYHA) functional class II-III CHF; previous MI; prior revascularisation; and the presence of haemodynamically significant VT. Additional requirements were stable clinical status for at least one month prior to enrolment and receipt of optimal medical therapy for CHF for at least three months.

Exclusion criteria were: refusal to participate; NYHA functional class IV CHF; CHF decompensation at the time of enrolment; reversible causes of CHF; surgical interventions within the preceding three months; stable angina of functional class III; and non-ischaemic cardiomyopathy as the underlying cause of CHF.

Table 1.

Clinical and demographic characteristics of the patients included in the study

Parameters	Value (n=47)
Male sex, n (%)	41 (87.2)
Age, years	65 [57; 71]
BMI, kg/m²	28 [26; 30]
NYHA class II CHF, n (%)	28 (59.6)
NYHA class III CHF, n (%)	19 (40.4)
NT-proBNP, pg/mL	756 [493.5; 1106]
Overall LVEF, %	40 [34; 46]
CHFmrEF, n (%)	26 (55.3)
CHFrEF, n (%)	21 (44.7)
Arterial hypertension, n (%)	34 (72.3)
Paroxysmal AF, n (%)	24 (51.1)
Permanent AF, n (%)	4 (8.5)
Artificial rhythm, n (%)	3 (6.4)
Diabetes mellitus, n (%)	9 (19.1)
Chronic kidney disease, n (%)	9 (19.1)
History of interventions	
PCI, n (%)	38 (80.8)
CABG/LIMA graft, n (%)	9 (19.2)
ICD implantation, n (%)	26 (55.3)

Note: BMI - body mass index; NYHA class CHF - New York Heart Association functional class of chronic heart failure; CHFmrEF and CHFrEF - chronic heart failure with moderately reduced and reduced left ventricular ejection fraction (LVEF), respectively; AF - atrial fibrillation; PCI - percutaneous coronary intervention; CABG - coronary artery bypass grafting; LIMA graft - left internal mammary artery graft; ICD - implantable cardioverter-defibrillator.

Catheter Ablation Technique

The procedure was performed under endotracheal general anaesthesia. The internal jugular and femoral veins were punctured, and haemostatic introducers were placed. Through a steerable introducer, a diagnostic 10-pole catheter was advanced into the right ventricle. Transseptal puncture of the interatrial septum was performed. A diagnostic PentaRay catheter (Biosense Webster, Johnson & Johnson, USA) was advanced into the LV cavity under intracardiac echocardiographic guidance. In cases where mapping of the LV outflow tract via the transseptal approach was not feasible, retrograde access through femoral artery puncture was employed. Epicardial VT ablation was performed when epicardial arrhythmogenic foci had been confirmed during prior mapping. In these cases, pericardial puncture was carried out via a subxiphoid approach. Coronary angiography was performed intraoperatively to ensure the safety of RF delivery in proximity to coronary arteries. In certain cases, when technical issues with mapping occurred, a combined approach was used—simultaneous transseptal puncture and right femoral artery puncture.

Mapping was performed using the CARTO 3 system (Biosense Webster, Johnson & Johnson, USA) with a 22-pole diagnostic PentaRay mapping catheter (Biosense Webster, Johnson & Johnson, USA) and a Thermocool SmartTouch ablation catheter (Biosense Webster, Johnson & Johnson, USA; curve D/F) equipped with contact force sensing and ablation index (AI) measurement. Voltage thresholds for distinguishing scar tissue from viable myocardium were set at 0.3-0.8 mV. During activation mapping, the QRS morphology of clinically significant VT recorded on 12-lead ECG played a key role. In voltage mapping, late potentials (extending beyond the QRS complex) were identified on the navigation model during ventricular pacing when clinically feasible (stable haemodynamics, absence of haemodynamically unstable VT induction); otherwise, mapping was performed during sinus rhythm.

The target AI in areas of thinned myocardium (4 mm, LV aneurysmal regions) was ≤550, whereas in regions with myocardial thickness >5 mm it ranged from 700 to 800. In isthmus ablation for VT, RF delivery was applied until VT termination, followed by consolidation lesions within the target area until the endpoint of non-inducibility was achieved. For RF ablation of

Table 2.

Comparison of baseline echocardiographic parameters between patients with and without ventricular tachycardia recurrence

Parameter	Patients with VT recurrence (n=7)	Patients without VT recurrence (n=39)	p
LVEF, %	35 [25; 40]	42 [34; 46]	0,07
LV EDV, mL	170 [125; 280]	167 [135; 201]	0,6
LV ESV, mL	80 [55; 203]	79 [48; 120]	0,4
LV EDD, mm	62 [51; 75]	62 [58; 68]	0,9
LV ESD, mm	48 [38; 63]	47 [39; 53]	0,4
LV aneurysm, n (%)	1 (14,2)	7 (17,9)	0,8
LVPW thickness, mm	0,9 [0,8; 1,0]	1 [0,7; 1,0]	0,6
NT-proBNP, pg/mL	809 [647; 1566]	722 [385; 1012]	0,2

Note: LV - left ventricle; EDV - end-diastolic volume; ESV - end-systolic volume; EDD - end-diastolic diameter; ESD - end-systolic diameter; PW - posterior wall thickness.

substrate zones with late potentials, RF applications were delivered across all identified sites, with subsequent electrophysiological testing until the endpoint of non-inducibility was confirmed (Fig. 1).

Statistical Analysis

Statistical analysis was performed using Excel 2010 and STATISTICA 10 (StatSoft Inc., USA). Categorical variables are presented as absolute numbers and percentages. The following statistical methods were used: the Mann-Whitney U test. Sample parameters presented in the tables are expressed as M (SD) and Me [Lq; Uq], where M - mean, SD - standard deviation, Me - median, Lq; Uq - interquartile range. A p-value <0.05 was considered statistically significant; values of $0.05 < p < 0.10$ were interpreted as a trend.

Sensitivity and specificity of the studied parameters were also assessed using receiver operating characteristic (ROC) curve analysis. Quantitative assessment of the ROC curve was performed by calculating the area under the curve (AUC). The following scale was applied to interpret AUC values as a measure of diagnostic test performance: AUC = 0.9-1.0, excellent; 0.8-0.9, high; 0.7-0.8, good; 0.6-0.7, moderate; 0.5-0.6, poor.

RESULTS

Among the 47 patients included in the study, 87.2% were male, and the median age was 65 [57; 71] years. The CHF phenotype was predominantly CHF with moderately reduced LVEF (55.3%), although 44.7% of patients had reduced LVEF. Prior to RFCA, 26 patients underwent ICD implantation. Baseline patient characteristics are summarised in Table 1.

All patients were receiving optimal medical therapy for CHF. As antiarrhythmic therapy, all patients were prescribed amiodarone (100%). At the time of enrolment, 5 patients (10.6%) had a VT history of 6 months, 17 patients (36.2%) between 6 and 12 months, and 25 patients (53.2%) ≥12 months. Thus, the median duration of VT prior to hospitalisation was 12 months.

All procedures were performed without fluoroscopy, under intracardiac echocardiographic guidance. Intraoperative mapping was performed in all patients: stimulation mapping in 51% (n=24), activation mapping in 38.4% (n=18), and scar homogenisation in 10.6% (n=5). Access was retrograde in 8 cases (17%), transseptal in 33 (70.2%), epicardial in 4 (8.5%), and combined in 2 (4.2%). The median procedure duration was 190 [150; 227] minutes. VT was inducible in all patients at the start of the procedure. Following RF ablation, VT was rendered non-inducible in 100% of patients. Standard RF parameters were applied: RF power 40-50 W, contact force 10-25 g/cm², application time 31±10.4 - 57.65±24.3 s, and temperature 43-46 °C.

Special attention was given to analysis of the AI. During RFCA of VT in areas of thinned myocardium (post-infarction zones or border zones between viable myocardium and post-infarction scar), AI values were deliberately limited to 400-500 to minimise complications, whereas in regions of "thicker" myocardium, AI was increased to 700-800 to improve efficacy.

At 12-month follow-up, ICD interrogation and Holter monitoring were performed. VT recurrence was documented in 7 patients (15.2%), corresponding to an arrhythmia-free survival of 84.8% following RFCA. Importantly, no VT recurrences were observed in the first 6 months post-ablation.

Baseline echocardiographic parameters were compared between patients with and without VT recurrence. Overall, the groups were comparable; however, there was a trend toward lower LVEF in the recurrence group (Table 2).

AI was analysed in all patients. Those without VT recurrence (39 patients, 84.8%) had a significantly higher median AI (612.0 [522.5; 683.5]) compared with those with recurrence (7 patients, 15.2%) (438 [416.5; 462]); p=0.001 (Fig. 2). VT recurrence risk was further assessed as a function of mean AI using ROC analysis. The area under the ROC curve (AUC) for prediction of VT recurrence by mean AI was 0.886±0.049 (95% CI: 0.791-0.982) (Fig. 2). This model was statistically significant (p=0.001). The cut-off value for mean AI was 473. Mean AI ≤473 predicted a high risk of VT recurrence. Sensitivity and specificity were

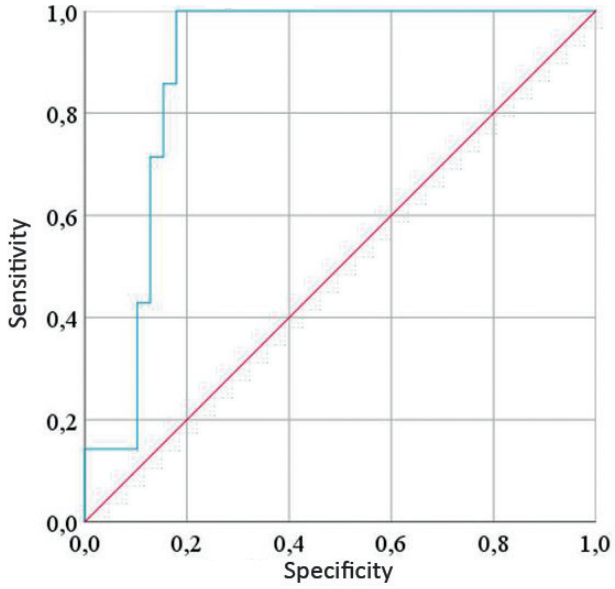

Fig. 3. ROC curve illustrating the relationship between ventricular tachycardia recurrence and mean ablation index.

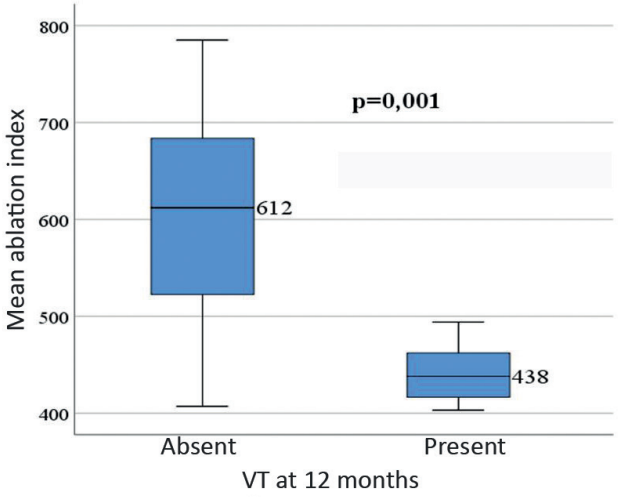

Fig. 2. Mean ablation index values in patients with and without arrhythmia recurrence during follow-up.

85.7% and 84.6%, respectively (Fig. 3). The odds of VT recurrence in patients with mean AI >473 were reduced by 1.125 (95% CI: 0.221-5.714).

DISCUSSION

The main factors contributing to improved efficacy of ablation are accurate identification of the arrhythmogenic substrate and adequate energy delivery to achieve transmurality [22]. At the preoperative stage, magnetic resonance imaging (MRI) with contrast enhancement may be performed. Fibrosis/scar zones identified by MRI are, in most cases, the sources of VT. Moreover, MRI can provide information not only on localisation of scar tissue but also on its density and transmurality. However, MRI has limitations, particularly in patients with implanted ICDs, where artefacts preclude adequate interpretation [23].

During the procedure itself, invasive mapping of the arrhythmogenic substrate is performed to identify zones of slow conduction. RF applications are then delivered to these regions. The primary objective of activation mapping is to identify the critical isthmus, which plays a key role in sustaining tachycardia. However, this approach has certain limitations. Successful mapping requires stable activation sequences and good arrhythmia tolerance, making activation mapping challenging in haemodynamically unstable arrhythmias, tachycardias with variable morphology, or those with complex or non-reproducible induction [24]. Pace-mapping can aid localisation of the VT source by endocardial stimulation at various sites, followed by comparison of the morphology of paced QRS complexes with tachycardia QRS complexes [24]. Together, these mapping methods, combined with preoperative imaging data, allow accurate localisation of the arrhythmogenic substrate for targeted RF delivery.

Several determinants of RF lesion size must also be considered intraoperatively, such as RF power and application duration. Domestic literature describes a study comparing high-power ablation (50 W) with standard-power ablation (45 W), using a standard application time of 60 s. The procedural endpoint of VT non-inducibility was achieved in 100% of patients. At 12 months, arrhythmia-free survival was 82.6% in the high-power group versus 76.2% in the standard-power group (p=0.0286). Importantly, this was the first study to evaluate the ablation index (AI) in VT ablation. The mean AI was significantly higher in the high-power group (475.4) than in the standard-power group (461.1), with borderline statistical significance (p=0.0549) [25].

In addition to conventional procedural parameters, the authors assessed mean AI, which had previously only been studied in AF ablation. They later published a follow-up article further evaluating the role of mean AI in VT treatment. This study included 63 patients with CAD referred for RFCA of VT. All patients underwent high-power ablation (50 W). Postoperatively, VT was absent in 52 patients (82.6%). The mean AI was significantly higher in the group without VT recurrence (494.9±73.3) compared with those with recurrence (383.2±44.3; p<0.0001). Each 10-unit increase in mean AI was associated with a 1.37-fold reduction in VT recurrence risk (p=0.0025; 95% CI: 1.16-1.77) [26].

Our findings were consistent with these results, demonstrating that higher mean AI values (612 [522.5; 683.5]) were associated with freedom from VT recurrence. Given the absence of reference values for AI in VT ablation, operators referred to AI thresholds established for left atrial ablation. According to the CLOSE protocol, target AI values for the left atrium are ≥550 for the anterior wall, ≥400 for the posterior wall, and ≥300 when chest pain or oesophageal temperature elevation occurs [27]. It is well known that the anterior wall of the left atrium is thicker than the posterior wall, explaining these differences in AI thresholds. These data were extrapolated to VT ablation in our study. When comparing patients with and without VT recurrence, there was a trend toward more advanced CHF in the recurrence group, which may have contributed to the use of lower AI values in this subgroup of patients.

CONCLUSION

Improving the efficacy of RFCA for VT remains an important objective in contemporary arrhythmology. The AI has already demonstrated its value in atrial fibrillation ablation alongside other determinants of lesion formation. Further studies are required to investigate AI in the context of ventricular arrhythmia ablation in order to establish reference values for different anatomical locations, to refine VT ablation protocols, and thereby to enhance procedural efficacy.

The application of higher AI values during RFCA of VT appears reasonable; however, more definitive conclusions cannot yet be drawn due to the limited number of studies available. The role of AI in ventricular arrhythmia ablation warrants further investigation with larger sample sizes and diverse study designs.

REFERENCES

1. Zeppenfeld K, Tfelt-Hansen J,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: Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC). *European Heart Journal.* 2022;43(40): 3997-4126. https://doi.org/10.1093/eurheartj/ehac262.

2. 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.org/10.15829/1560-4071-2021-4600.

3. Haris M. Haqqani MBBS(Hons), David J. Callans MD. Ventricular Tachycardia in Coronary Artery Disease. *Cardiac Electrophysiology Clinics*. 2014;6(3): 525-534.

4. Liuba I, Frankel DS, Riley MP, et al. Scar progression in patients with nonischemic cardiomyopathy and ventricular arrhythmias. *Heart Rhythm.* 2014;11(5): 755-762. https://doi.org/10.1016/j.hrthm.2014.02.012.

5. Thomas H, Diamond J, Vieco A, et al. Global Atlas of Cardiovascular Disease 2000-2016: the path to preven-

tion and control. *Glob Heart* 2018;13: 143-63. https://doi.org/10.1016/j.gheart.2018.09.511.
6. Eckart RE, Shry EA, Burke AP, et al. Sudden death in young adults: an autopsy-based series of a population undergoing active surveillance. *J Am Coll Cardiol.* 2011;58: 1254-61. https://doi.org/10.1016/j.jacc.2011.01.049
7. Samuel M, Elsokkari I, Sapp JL. Ventricular Tachycardia Burden and Mortality: Association or Causality? *Can J Cardiol.* 2022;38(4): 454-464. https://doi.org/10.1016/j.cjca.2022.01.016.
8. Deyell MW, AbdelWahab A, Angaran P, et al. 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society position statement of the management of ventricular tachycardia and fibrillation in patients with structural heart disease. *Can J Cardiol.* 2020;36: 822-36. https://doi.org/10.1016/j.cjca.2020.04.004
9. Alvarez CK, Cronin E, Baker WL, Kluger J. Heart failure as a substrate and trigger for ventricular tachycardia. *J Interv Card Electrophysiol.* 2019;56(3): 229-247. https://doi.org/10.1007/s10840-019-00623-x.
10. Galyavich AS, Tereshchenko SN, Uskach TM, et al. 2024 Clinical practice guidelines for Chronic heart failure. *Russian Journal of Cardiology.* 2024;29(11): 6162. (In Russ.) https://doi.org/10.15829/1560-4071-2024-6162.
11. Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med.* 2008;359: 1009-17. https://doi.org/10.1056/NEJMoa071098.
12. Powell BD, Saxon LA, Boehmer JP, et al. Survival after shock therapy in implantable cardioverter-defibrillator and cardiac resynchronization therapy-defibrillator recipients according to rhythm shocked. The ALTITUDE survival by rhythm study. *J Am Coll Cardiol.* 2013;62: 1674-1679 https://doi.org/10.1016/j.jacc.2013.04.083.
13. Kamphuis HC, de Leeuw JR, Derksen R, et al. Implantable cardioverter defibrillator recipients: quality of life in recipients with and without ICD shock delivery: a prospective study. *Europace*. 2003;5: 381-9. https://doi.org/10.1016/s1099-5129(03)00078-3.
14. Reddy VY, Reynolds MR, Neuzil P., et al. Prophylactic catheter ablation for the prevention of defibrillator therapy. *N Engl J Med.* 2007;357: 2657-2665. https://doi.org/10.1056/NEJMoa065457.
15. Pandian J, Kaur D, Yalagudri S, et al. Safety and efficacy of epicardial approach to catheter ablation of ventricular tachycardia - An institutional experience. *Indian Heart J.* 2017; 69 (2): 170-175. https://doi.org/10.1016/j.ihj.2016.10.010
16. Mikhaylov EN, Gasimova NZ, Ayvazyan SA, et al. Factors associated with the efficacy of atrial fibrillation radiofrequency catheter ablation: opinion of the specialists who use the "ablation index" module. *Journal of Arrhythmology.* 2020;27(3): 9-24. (In Russ.) https://doi.org/10.35336/VA-2020-3-9-24.
17. Artyukhina, EA, Satinbaev ZI Catheter ablation using the "ablation index" technology. *Annals of Arrhythmology.* 2022;19(1): 32-38 (In Russ) https://doi.org/10.15275/annaritmol.2022.1.5.
18. Liu Z, Liu L-f, Liu X-q, et al. Ablation index-guided ablation with milder targets for atrial fibrillation: Comparison between high power and low power ablation. Cardiovasc. Med. 2022:9:949918. https://doi.org/ 10.3389/fcvm.2022.94991
19. Qin X, Jiang X, Yuan Q, et al. Optimal ablation index parameters for radiofrequency ablation therapy of atrial fibrillation. *Pak J Med Sci.* 2022;38(3): 632-638.: https://doi.org/10.12669/pjms.38.3.4971.
20. Sciacca V, Vogler J, Eitel C, et al. Ablation index-guided catheter ablation of incessant ventricular tachycardia originating from the anterolateral papillary muscle. *Clin Res Cardiol.* 2022;111(5): 588-591. https://doi.org/10.1007/s00392-021-01923-x.
21. Younis A, Zilberman I, Yavin H, et al. Utility and Limitations of Ablation Index for Guiding Therapy in Ventricular Myocardium. *JACC Clin Electrophysiol.* 2023;9(8 Pt 3): 1668-1680. https://doi.org/10.1016/j.jacep.2023.03.02.
22. Pothineni NVK, Garcia FC, Santangeli P. Radiofrequency Ablation Strategies for Intramural Ventricular Arrhythmias. *Methodist Debakey Cardiovasc J.* 2021;17(1): 8-12. https://doi.org/10.14797/PEYF3776.
23. Nazarian S, Bluemke DA, Lardo AC, et al. Magnetic resonance assessment of the substrate for inducible ventricular tachycardia in nonischemic cardiomyopathy. *Circulation*. 2005;112(18): 2821-2825. https://doi.org/10.1161/CIRCULATIONAHA.105.549659.
24. Guandalini GS, Liang JJ, Marchlinski FE. Ventricular Tachycardia Ablation: Past, Present, and Future Perspectives. *JACC Clin Electrophysiol.* 2019;5(12): 1363-1383. https://doi.org/10.1016/j.jacep.2019.09.015.
25. Korolev SV, Artyukhina EA, Shabanov VV, et al. Comparative evaluation of the results of a prospective registry of high-power radiofrequency ablation of ventricular arrhythmia in patients with coronary heart disease. *Bulletin of the National Medical and Surgical Center N. I. Pirogov*. 2023;18(1): 28-35 (In Russ) https://doi.org/10.25881/20728255_2023_18_1_28.
26. Korolev SV, Artyukhina EA, Shabanov VV, et al. High-power radiofrequency ablation for ventricular tachycardia in patients with structural heart disease:one-year follow-up data from the multicenter prospective registry. *Circulatory pathology and cardiac surgery.* 2023;27(2): 66-73 (In Russ) https://doi.org/10.21688/1681- 3472-2023-2-66-73.
27. Phlips T, Taghji P, El Haddad M et al. Improving procedural and one-year outcome after contact force-guided pulmonary vein isolation: the role of interlesion distance, ablation index, and contact force variability in the 'CLOSE'-protocol. *Europace*. 2018;20(3): f419-f427. https://doi.org/10.1093/europace/eux376.

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COMPARATIVE ANALYSIS OF THREE-YEAR EFFICACY OF CATHETER ABLATION OF ATRIAL FIBRILLATION USING THE ABLATION INDEX MODULE AND THE SECOND-GENERATION CRYOBALLOON

S.N.Azizov[1], R.D.Khuziakhmetov[1], V.V.Lyashenko[2], V.A.Belov[1], A.T.Kozhenov[3]

[1]FSBI "Federal Center of Cardiovascular Surgery named after S.G.Sukhanov" of the MH RF, Russia, Perm, 35 Marshal Zhukov str.; [2]FSBI "Federal Center of High Medical Technologies» of the MH RF, Russia, Kaliningrad, 4 Kaliningradskoye Shosse; [3]SBI «Municipal Clinical Hospital No.15 named after O.M.Filatov» of Department of Health of Moscow, Russia, Moscow, 23 Veshnyakovskaya str.

Aim. To compare immediate and long-term outcomes of catheter-based atrial fibrillation (AF) treatment following pulmonary vein (PV) cryoballoon ablation (CBA) using the second-generation cryoballoon and PV radiofrequency ablation (RFA) performed on the navigation system using the contact force-sensing catheter with the AI module.

Methods. The study included 199 patients referred for PV isolation between 2018 and 2021. Patients were divided into two groups: the study group (n=110) underwent PV isolation via RFA using the catheter with the AI module; the control group (n=89) underwent PV CBA using the second-generation cryoballoon. The follow-up period was limited to 36 months, with a mean follow-up of 27.9 ± 14.2 months.

Results. The three-year efficacy of CBA and RFA using the AI module was comparable (freedom from atrial tachyarrhythmias: RFA group 0.61±0.05, CBA group 0.62±0.05 (Log-Rank test, p = 0.896)), with similar complication rates and profiles (3.6% (n=4) vs. 4.5% (n=4), p=0.759). The AF recurrence rate during the blanking period was significantly lower in the RFA group using the AI module (1.8% (n=2) vs. 9.0% (n=8) in the CBA group, p=0.045). Procedure duration was significantly shorter in the cryoablation group (RFA 92.7±20.9 min, CBA 83.9±19.6 min, p=0.005). The need for repeat intervention was comparable between groups (RFA 21.8% (n=24), CBA 30.3% (n=27), p=0.171).

Conclusion. Comparative analysis of the three-year efficacy of radiofrequency antral pulmonary vein isolation using the catheter with the "Ablation Index" (AI) module demonstrated results comparable to ablation with the second-generation cryoballoon. Furthermore, during the blanking period, the RFA group showed a statistically significant reduction in AF recurrence compared to the CBA group.

Key words: atrial fibrillation; catheter ablation; radiofrequency ablation; cryoballoon ablation; pulmonary veins

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Corresponding Author: Azizov Sardor, E-mail: azizov.s89@mail.ru

S.N.Azizov - ORCID ID 0009-0006-1678-9175, R.D.Khuziakhmetov - ORCID ID 0009-0001-2835-9571, V.V.Lyashenko - ORCID ID 0000-0002-8501-4801, V.A.Belov - ORCID ID 0000-0002-0945-8208, A.T.Kozhenov - ORCID ID 0009-0005-1750-1586

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Pulmonary vein (PV) isolation is the cornerstone of invasive treatment for atrial fibrillation (AF) [1]. Currently, the most widely used catheter-based methods for PV isolation are radiofrequency (RF) ablation and cryoballoon ablation (CBA). The majority of studies have demonstrated comparable efficacy between these approaches [2-4]. However, according to published data, RF ablation has primarily been performed with irrigated contact force-sensing catheters, without the use of the ablation index (AI; Biosense Webster, USA).

AI is a technology that automatically quantifies the extent of ablation lesion formation, calculated from three main parameters: catheter contact force, application duration, and RF power [5]. The reliability of AI values in predicting lesion depth at atrial endocardial sites was first demonstrated in experimental canine studies [6, 7]. This provided the potential, when using the Carto 3 three-dimensional mapping system (Biosense Webster, Johnson & Johnson, USA), to monitor lesion depth during catheter ablation and to reduce the risk of procedure-related complications [8-10].

Subsequently, multiple studies have compared the efficacy of RF ablation with and without the use of AI. In most of these, freedom from atrial tachyarrhythmias was significantly higher when AI guidance was employed [9, 11-13]. Thus, AI has emerged as an additional tool to enhance the efficacy of RF ablation in AF treatment.

Aim: to compare the efficacy of AF treatment between cryoballoon PV isolation performed with the Arctic Front Advance balloon (Medtronic, USA) and RF ablation performed with the SmartTouch contact force-sensing

catheter (Biosense Webster, Johnson & Johnson, USA) using AI guidance.

METHODS

A total of 199 consecutive patients referred for catheter-based PV isolation between 2018 and 2021 were enrolled. Patients were divided into two groups: the study group comprised 110 patients who underwent RF ablation with the SmartTouch catheter using AI technology, while the control group included 89 patients who underwent PV isolation with the second-generation Arctic Front Advance cryoballoon. Group allocation was based on the availability of consumables at the time of the procedure.

The primary endpoint was freedom from any atrial tachyarrhythmia (AF, atrial flutter, atrial tachycardia) during long-term follow-up (up to 36 months). Secondary endpoints included: recurrence of atrial tachyarrhythmias during the blanking period (first 3 months post-procedure), complication rates and patterns, procedure duration, and frequency of repeat ablations.

Assessment of the primary endpoint was based on the absence of symptomatic or asymptomatic atrial tachyarrhythmias lasting more than 30 seconds. Arrhythmias occurring during the blanking period were not considered recurrences when evaluating long-term procedural efficacy. Arrhythmia recurrence was documented by Holter monitoring, interrogation of implanted devices (pacemakers), and review of medical records.

Secondary endpoints were evaluated using medical documentation (procedure duration, repeat ablation rate), patient complaints, clinical status, and instrumental and laboratory findings (intra- and postoperative complications).

All patient data were anonymised and entered into a dedicated database excluding personal identifiers. All patients provided written informed consent both for participation in the study and for the AF ablation procedure, in accordance with current guidelines.

Inclusion criteria were: ECG-documented, symptomatic paroxysmal or persistent AF. Exclusion criteria were: previous PV isolation, intracardiac thrombus, thyroid dysfunction, requirement for valve or vascular cardiac surgery, inability to take oral anticoagulants, and severe renal or hepatic impairment. Baseline clinical characteristics by group are shown in Table 1.

As part of the preoperative protocol, all patients underwent multislice computed tomography of the left atrium and PVs with intravenous contrast. In patients with a PV common ostium or PV ostial diameter >28 mm, RF antral PV isolation was performed. Patients older than 40 years underwent coronary angiography.

Radiofrequency and cryoballoon ablation

All procedures were performed under local anaesthesia. After femoral vein cannulation under fluoroscopic guidance, transseptal access was obtained (double puncture in the study group for RF ablation, single puncture in the control group for cryoballoon PV isolation).

RF antral PV isolation was performed using the Carto 3 navigation system (Biosense Webster, Johnson & Johnson, USA) with a ThermoCool SmartTouch contact force-sensing catheter and the Visitag and Ablation Index modules (Biosense Webster, Johnson & Johnson, USA).

Table 1.

Clinical characteristics of the patient groups

Characteristic	RFA-AI group (n=110)	CBA group (n=89)	P
Mean age, years	64.4±7.4	62.7±7.5	0.145
Sex (M/F), %	48.2/51.8	46.1/53.9	0.766
Body mass index, kg/m^2	30.9±4.9	29.7±4.8	0.136
Paroxysmal AF, %	76.4	70.8	0.373
Persistent AF, %	23.6	29.2	
ACA*, %	5.5	4.5	0.758
Coronary artery disease, %	35.5	32.6	0.671
Myocardial infarction, %	7.3	5.6	0.639
Diabetes mellitus, %	8.2	10.1	0.637
Arterial hypertension, %	93.6	92.1	0.783
Pacemaker implantation*, %	11.8	7.9	0.478
Myocardial revascularisation*, %	11.8	11.2	0.898
LVEDV, mL	96.8 ± 25.9	90.6 ± 20.1	0.085
LVEF, %	55.2±6.1	55.8±6.3	0.589
LA volume (TTE), mL	73.9±24.5	70.2±18.2	0.458
LAVI (TTE), mL/m^2	38.0±11.2	36.9±8.9	0.738
IVS thickness, mm	13.2±3.3	13.6±2.4	0.086
LVPW thickness, mm	12.5±3.5	12.5±1.9	0.556
MR grade 0, %	33	28.1	0.224
MR grade I, %	50.5	61.8	
MR grade II, %	16.5	10.1	
sPAP, mmHg	37.9±7.3	35.7±7.5	0.163
mPAP, mmHg	20.8±8.2	20.5±6.5	0.907
LA volume (MSCT), mL	112.9±28.5	116.8±27.9	0.415
LAVI (MSCT), mL/m^2	57.8±15.1	60.5±15.1	0.288

Notes: RFA-AI - radiofrequency pulmonary vein ablation with Ablation Index guidance; CBA - cryoballoon pulmonary vein isolation; AF - atrial fibrillation; ACA* - acute cerebrovascular accident; * - in medical history; PM - pacemaker; LVEDV - left ventricular end-diastolic volume; LV - left ventricle; LVEF - left ventricular ejection fraction; LA - left atrium; TTE - transthoracic echocardiography; LAVI - left atrial volume index; IVS - interventricular septal thickness; LVPW - left ventricular posterior wall thickness; MR - mitral regurgitation; sPAP and mPAP - systolic and mean pulmonary artery pressure; MSCT - multislice computed tomography with intravenous contrast.

Ablation points were automatically annotated according to the following parameters: maximum catheter SD displacement - 3 mm; minimum stability duration - 3 s; contact force range - 4-40 g. Ablation tags were 6 mm in size, with interlesion distance ≤6 mm. PV isolation was verified with a circular Lasso catheter (Biosense Webster, Johnson & Johnson, USA). RF parameters were: power 45 W at all LA sites; irrigation rate 2 mL/min during standby and 30 mL/min during ablation; target AI 400-420 for the posterior wall and 460-500 for other LA segments.

Cryoballoon PV isolation was performed with the second-generation 28 mm Arctic Front Advance cryoballoon (Medtronic, USA). Entry and exit block of the PVs was verified with the Achieve circular diagnostic catheter (Medtronic, USA). Cryoablation was initiated after complete PV occlusion was confirmed by angiography. Freeze duration did not exceed 240 s per application. Right phrenic nerve pacing was performed during right PV isolation to monitor diaphragmatic nerve function.

The intraprocedural endpoints of effective PV isolation were: elimination of PV potentials on Achieve catheter electrodes within <75 s and absence of contrast leakage from the PV during cryoablation. When these criteria were met, no additional applications were delivered.

Postoperative period and follow-up

In the early postoperative period, all patients underwent echocardiography and Holter monitoring. Scheduled follow-up visits with mandatory ECG Holter monitoring were performed at 3, 6, and 12 months, and every 6 months thereafter. Three months after the procedure, antiarrhythmic therapy was discontinued in the absence of arrhythmia recurrence. Analysis of antiarrhythmic drug use before and after ablation was not performed in this study.

Statistical analysis

statistical analysis was performed using IBM SPSS Statistics version 27. Parametric data were assessed for normal distribution, and comparisons were made using Student's *t*-test or the Mann-Whitney test, as appropriate. Non-parametric data were compared using Fisher's exact test or Pearson's χ^2 test, depending on event counts. Freedom from atrial tachyarrhythmias was assessed by survival analysis using the Kaplan-Meier method.

The statistical significance of associations with clinical factors in survival analysis was evaluated using the Mantel-Cox log-rank test. A p-value <0.05 was considered statistically significant.

RESULTS

Intraoperative data

fluoroscopy time and duration of the left atrial stage were not evaluated, as these data were not documented in the operative protocols of the control group. Overall procedure duration was significantly shorter in the study group (Table 2). Intraoperatively, acute isolation of all PVs was achieved in all patients in both groups.

Postoperative date

The mean follow-up period was 27.9±14.2 months. By month 36, 54 of 89 patients remained under observation in the control group (34 patients with documented atrial tachyarrhythmias, one lost to follow-up) and 61 of 110 in the study group (41 patients with documented atrial tachyarrhythmias, eight lost to follow-up).

During the blanking period, AF recurrence was recorded in 8 patients in the control group and 2 patients in the study group. The incidence of recurrences during the blanking period and their distribution by AF type are presented in Table 2. In the RF ablation group with AI guidance, recurrence rates in the blanking period were significantly lower compared with the control group.

Kaplan-Meier survival analysis demonstrated freedom from atrial tachyarrhythmias of 0.62±0.05 in the control group and 0.61±0.05 in the study group (log-rank test, p=0.896) (Fig. 1). Subgroup analysis of freedom from atrial tachyarrhythmias by AF type using the Kaplan-Meier method showed values of 0.69±0.06 in the CBA group versus 0.60±0.06 in the RF AI group for paroxysmal AF (log-rank test, p=0.400) (Fig. 2), and 0.42±0.09 in the CBA group versus 0.61±0.09 in the RF AI group for persistent AF (log-rank test, p=0.173) (Fig. 3). No statistically significant differences in freedom from atrial tachyarrhythmias were found between the two treatment groups or their subgroups over the follow-up period.

Table 2.

Immediate and long-term outcomes of catheter ablation for atrial fibrillation

	RFA-AI group (n=110)	CBA group (n=89)	P
Procedure duration, min	92.7±20.9	83.9±19.6	0.005
Complications, n (%)	4 (3.6)	4 (4.5)	0.759
Recurrence of atrial tachyarrhythmias			
During the blanking period, n (%)	2 (1.8)	8 (9.0)	0.045
Overall, n (%)	43 (39.1)	34 (38.2)	0.898
In paroxysmal AF, n (%)	33 (39.3)	19 (30.2)	0.252
In persistent AF, n (%)	10 (38.5)	15 (57.7)	0.165
Repeat procedures for atrial tachyarrhythmias			
Total patients, n (%)	24 (21.8)	27 (30.3)	0.171
Procedures per patient	0.26±0.55	0.37±0.65	0.179

Repeat ablation

No statistically significant difference in the rate of repeat interventions was observed between the study and control groups. No complications resulting in death or requiring additional invasive intervention were recorded in either group. In 4 patients (4.5%) in the control group and 4 patients (3.6%) in the study group, complications such as pericardial effusion up to 10 mm (one case in each group) or post-puncture hematoma (three cases in each group) were documented, with no significant difference in the frequency or distribution of complications (p=0.759).

DISCUSSION

The present study yielded the following findings: (1) the three-year

efficacy of cryoballoon PV isolation and RF antral PV isolation with Ablation Index (AI) guidance was comparable; (2) recurrence rates during the blanking period were significantly lower in the RF ablation group; (3) procedure duration was significantly shorter in the cryoballoon group; and (4) the need for repeat interventions was similar in both groups.

Multiple studies have compared the efficacy of CBA and RF antral ablation. These investigations have used different devices, including first- or second-generation cryoballoons and RF catheters with or without contact force sensing. As technology evolved, each subsequent trial compared the latest available iterations of these catheters.

The most widely recognised study directly comparing CBA and RF ablation is the multicentre randomised FIRE and ICE trial. This study found no statistically significant difference in the primary endpoint (first documented AF recurrence >30 seconds, occurrence of atrial flutter or atrial tachycardia, initiation of antiarrhythmic therapy, or repeat AF ablation after a 90-day blanking period) between RF ablation and CBA at long-term follow-up [4]. However, secondary analyses of this trial demonstrated that patients treated with CBA had lower rates of repeat ablation, electrical cardioversion (ECV), repeat hospitalisations for any cause, and repeat hospitalisations for cardiovascular disease compared with RF ablation [14]. Importantly, this study did not stratify results by the type of RF catheter used (contact force-sensing vs non-sensing) or the generation of cryoballoon applied.

Similar findings were reported by domestic investigators who compared RF ablation with the SmartTouch contact force-sensing catheter (Biosense Webster, Johnson & Johnson, USA) and first- and second-generation Arctic Front cryoballoons (Medtronic, USA) [15]. They found no significant difference in long-term efficacy between the two methods, although, unlike the FIRE and ICE trial, the frequency of repeat procedures was comparable between groups [14, 15].

Later studies incorporated technological advances by comparing only second-generation cryoballoons with contact force-sensing RF catheters [2, 16]. For example, T.J. Buist et al. (2018) compared the second-generation cryoballoon with contact force-sensing RF catheters in terms of arrhythmia-free survival, PV reconnection after the index procedure, and repeat ablation rates. Their findings demonstrated a significant advantage of CBA: freedom from atrial arrhythmias after a single procedure was higher, repeat ablations were less frequent, and PV reconnection rates during redo procedures were lower compared with RF ablation [16].

Similarly, W. Maskoun et al. (2021) reported that CBA achieved significantly greater long-term arrhythmia-free survival than RF ablation, both with and without contact force sensing, in patients with paroxysmal AF. The repeat ablation rate was also lower in the CBA group [17]. Other studies, however, have shown comparable long-term efficacy between CBA and RF ablation but did not specifically assess secondary endpoints such as repeat interventions, hospitalisations, or ECV during the blanking period [18].

Taken together, most studies suggest that freedom from atrial tachyarrhythmias after second-generation CBA is comparable to RF ablation with contact force sensing, and in some cases superior [2, 16-18]. Repeat ablation and ECV rates, however, have generally been higher in the RF group [16, 17].

To date, no published studies have directly compared CBA with RF ablation incorporating AI guidance. Most

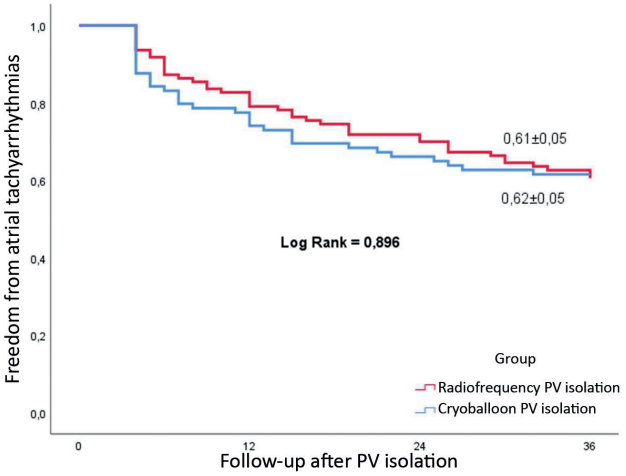

Fig. 1. Overall freedom from atrial tachyarrhythmias at 36 months of follow-up. Abbreviations: RF - radiofrequency ablation; PV - pulmonary vein.

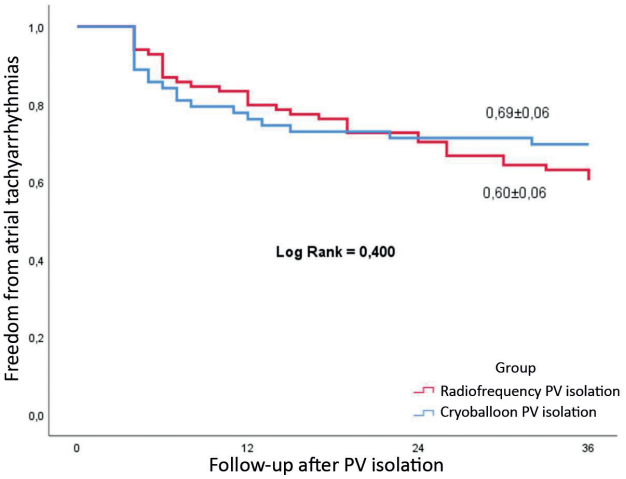

Fig. 2. Overall freedom from atrial tachyarrhythmias in patients with paroxysmal AF at 36 months of follow-up.

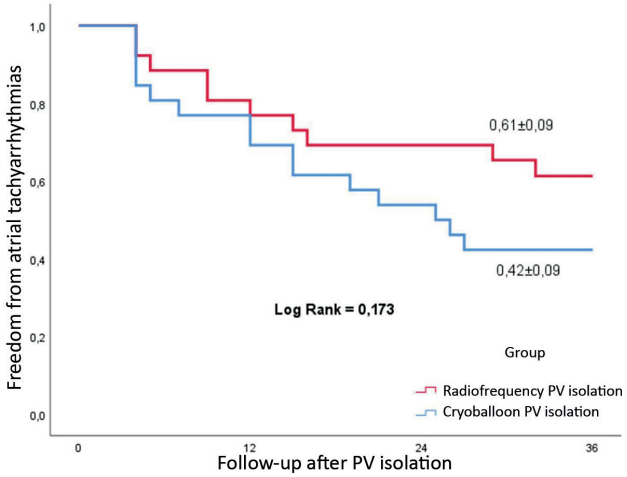

Fig. 3. Overall freedom from atrial tachyarrhythmias in patients with persistent AF at 36 months of follow-up.

have instead evaluated RF ablation with and without AI. These studies consistently showed higher arrhythmia-free survival with AI-guided ablation, with a similar safety profile [9, 11-13]. This supports the utility of AI as an effective adjunct. Theoretically, AI-guided RF ablation may yield outcomes equal to or better than CBA. In our study, where RF ablation was performed with both contact force-sensing catheters and AI, no significant difference was observed in long-term efficacy compared with CBA. However, analysis of secondary endpoints revealed discrepancies with prior studies: the need for repeat procedures was similar in both groups (21.8% [24/110] in the RF group vs 30.3% [27/89] in the CBA group, p=0.171), while recurrence rates during the blanking period were significantly lower in the RF group (1.8% [2/110] vs 9.0% [8/89], p=0.045).

Thus, the advantages of CBA (fewer repeat procedures and ECV during the blanking period), reported in prior large-scale studies [14, 16, 17], were only partially confirmed here. Although the number of ECVs performed during the blanking period could not be reliably quantified in our study, we hypothesise that the higher recurrence rate during this period in the CBA group indirectly reflects a higher need for ECV. Previous studies attributing superior or comparable long-term efficacy of CBA to more durable PV isolation and lower rates of PV reconnection compared with RF ablation [16, 17, 19-21] support this interpretation.

The introduction of AI has led to the standardisation of RF ablation by enabling operators to deliver lesions along a predefined line, with defined target AI values required for transmural atrial lesions, durable PV isolation, and minimal risk of reconnection. The predictive accuracy of AI for lesion depth has been confirmed in experimental canine models [6, 7].

Our findings regarding procedural duration are consistent with prior studies, with cryoablation being faster. Current contact force-sensing catheters have limitations in maximal power delivery, meaning that achieving target AI requires longer application times, dependent on contact force. By contrast, CBA often achieves PV isolation with a single application per vein.

Overall, the present results suggest that AI provides a valuable adjunct that improves RF ablation outcomes without requiring major engineering modifications of the catheter itself, making RF ablation comparable to CBA in terms of long-term arrhythmia-free survival, repeat ablation rates, and blanking period recurrences (a surrogate for ECV frequency). However, our study did not assess arrhythmia recurrence rates at repeat ablation, the number of ECVs during the blanking period, or perform a detailed comparative analysis of these endpoints. Further studies with larger sample sizes and robust designs are warranted to clarify these aspects.

Study limitations

Our study has several important limitations. Implantable loop recorders were not used for the detection of atrial tachyarrhythmias. Recurrence of AF in the postoperative period was assessed by Holter monitoring, interrogation of implanted devices (pacemakers), and review of medical records. The study design was non-randomised and single-centre, and postoperative pharmacological therapy was not systematically evaluated.

CONCLUSION

A comparative analysis of three-year outcomes demonstrated that radiofrequency antral pulmonary vein isolation with Ablation Index guidance yielded results comparable to those of second-generation cryoballoon ablation. Notably, during the blanking period, the RF group showed a statistically significant reduction in atrial tachyarrhythmia recurrences compared with the CBA group.

REFERENCES

1. Van Gelder IC, Rienstra M, Bunting KV, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2024;45(36): 3314-3414. https://doi.org/10.1093/eurheartj/ehae176.

2. Squara F, Zhao A, Marijon E, et al. Comparison between radiofrequency with contact force-sensing and second-generation cryoballoon for paroxysmal atrial fibrillation catheter ablation: A multicentre european evaluation. *Europace.* 2015;17: 718-724. https://doi.org/10.1093/europace/euv060.

3. Jourda F, Providencia R, Marijon E, et al. Contact-force guided radiofrequency vs. Second-generation balloon cryotherapy for pulmonary vein isolation in patients with paroxysmal atrial fibrillation-a prospective evaluation. *Europace.* 2015;17: 225-231. https://doi.org/10.1093/europace/euu215.

4. Kuck KH, Brugada J, Furnkranz A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med.* 2016;374: 2235-2245. https://doi.org/10.1056/NEJMoa1602014.

5. Mikhaylov EN, Gasimova NZ, Ayvazyan SA, et al. Factors associated with the efficacy of atrial fibrillation radiofrequency catheter ablation: opinion of the cialists who use the "ablation index" module. *Journal of Arrhythmology*. 2020;27(3): 9-24. (In Russ.). https://doi.org/10.35336/VA-2020-3-9-24.

6. Nakagawa H., Ikeda A., Govari A., et al. Prospective study to test the ability to create RF lesions at predicted depth and diameter using a new formula incorporating contact force, radiofrequency power and application time (force-power-time index) in the beating canine heart. *Heart Rhythm*. 2014;11: S548.

7. Das M, Loveday JJ, Wynn GJ, et al. Ablation index, a novel marker of ablation lesion quality: prediction of pulmonary vein reconnection at repeat electrophysiology study and regional differences in target values. *Europace.* 2017;19: 775- 83. https://doi.org/10.1093/europace/euw105.

8. Ullah W, Hunter RJ, Finlay MC, et al. Ablation Index and Surround Flow Catheter Irrigation: Impedance-Based Appraisal in Clinical Ablation. *JACC Clin Electrophysiol.* 2017;3(10): 1080-1088. https://doi.org/10.1016/j.jacep.2017.03.011.

9. Hussein A, Das M, Chaturvedi V, et al. Prospective use of Ablation Index targets improves clinical outcomes following ablation for atrial fibrillation. *J Cardiovasc Electro-*

physiol. 2017;28(9): 1037- 1047. https://doi.org/10.1111/jce.13281.
10. Phlips T, Taghji P, El Haddad M, et al. Improving procedural and oneyear outcome after contact force-guided pulmonary vein isolation: the role of interlesion distance, ablation index, and contact force variability in the 'CLOSE'-protocol. *Europace.* 2018;20(FI_3): f419-f427. https://doi.org/10.1093/europace/eux376.
11. Solimene F, Schillaci V, Shopova G, et al. Safety and efficacy of atrial fibrillation ablation guided by ablation index module. *J Interv Card Electrophysiol.* 2019;54: 9-15.
12. Casella M, Dello Russo A, Riva S, et al. An ablation index operator-independent approach to improve efficacy in atrial fibrillation ablation at 24-month follow-up: a single center experience. *J Interv Card Electrophysiol.* 2019;57: 241-9.
13. Ioannou A, Papageorgiou N, Lim WY, et al. Efficacy and safety of ablation index-guided catheter ablation for atrial fibrillation: an updated meta-analysis. *Europace.* 2020;22: 1659-1671.
14. Kuck KH, Furnkranz A, Chun KR, et al. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. *European heart journal.* 2016;37(38): 2858-65.
15. Chichkova T.Yu., Mamchur S.E., Ivanitsky E.A., et al. Comparison of effectiveness of radiofrequency ablation and cryoablation of atrial fibrillation based on the experience of two clinical centers. *Journal of Arrhythmology.* 2017;(88): 30-35. (In Russ.).
16. Buist, TJ, Adiyaman A, Smit JJJ, et al. Arrhythmia-free survival and pulmonary vein reconnection patterns after second-generation cryoballoon and contact-force radiofrequency pulmonary vein isolation. *Clin Res Cardiol*. 2018;107: 498-506. https://doi.org/10.1007/s00392-018-1211-9.
17. Maskoun W, Abualsuod A, Habash F, et al. Cryoballoon vs radiofrequency ablation of atrial fibrillation: insights from the Veterans Healthcare System. *J Interv Card Electrophysiol. 2021;*62: 531-538. https://doi.org/10.1007/s10840-020-00927-3.
18. Matta M, Anselmino M, Ferraris F, Scaglione M, Gaita F. Cryoballoon vs. radiofrequency contact force ablation for paroxysmal atrial fibrillation: a propensity score analysis. *J Cardiovasc Med (Hagerstown).* 2018;19(4): 141-147. https://doi.org/10.2459/JCM.0000000000000633.
19. Reddy VY, Sediva L, Petru J, et al. Durability of pulmonary vein isolation with cryoballoon ablation: results from the sustained PV isolation with arctic front advance (SUPIR) study. *J Cardiovasc Electrophysiol.* 2015;26: 493-500.
20. Aryana A, Singh SM, Mugnai G, et al. Pulmonary vein reconnection following catheter ablation of atrial fibrillation using the second-generation cryoballoon versus open-irrigated radiofrequency: results of a multicenter analysis. *J Interv Card Electrophysiol.* 2016;47(3): 341-348. https://doi.org/10.1007/s10840-016-0172-z.
21. Andrade JG, Khairy P, Dubuc M. Catheter cryoablation: biology and clinical uses. *Circ Arrhythm Electrophysiol.* 2013;6(1): 218-27. https://doi.org/10.1161/CIRCEP.112.973651.

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THE EFFECT OF ATRIAL PACING ON THE RISK OF ATRIAL TACHYARRHYTHMIAS IN PATIENTS WITH DUAL-CHAMBER CARDIAC PACEMAKERS: A PILOT STUDY

I.B.Lukin, D.V.Federiakin, D.Iu.Gridiakina, M.H.Karaagach

FSBI «Tver State Medical University» of the MH RF, Russia, Tver, 4 Sovetskaya str.

Aim. To evaluate the effect of atrial pacing (AP) on the development of atrial extrasystoles and episodes of supraventricular tachycardia in patients with dual-chamber cardiac pacemakers.

Methods. The study included 97 patients who underwent implantation of dual-chamber cardiac pacemakers. The analysis of 169 control examinations in the period from 1 to 20 months after surgery was carried out. The parameters of atrial stimulation, group atrial extrasystoles, and episodes of supraventricular tachycardia were evaluated. The initial data was processed in Microsoft Excel and Access, statistical analysis was performed in Jupyter Notebook (Python 3.x).

Results. A moderate positive correlation was established between atrial extrasystoles and episodes of supraventricular tachycardia ($p=0.623$, $p<0.001$). In the AP group ≥ 91%, there was a decrease in the frequency of AT/AF >24 hours ($p = 0.060$). Logistic regression showed a significant reduction in the risk of AT/AF >24 hours with AP 51 - 90% (odds ratio 0.31, $p=0.002$).

Conclusion. High level of atrial stimulation may reduce the risk of prolonged episodes of supraventricular tachycardia, however, the effect of atrial stimulation of cardiac pacemaker on episodes of atrial extrasystoles has not reached statistical significance.

Key words: electrocardiostimulation; atrial stimulation; atrial fibrillation; atrial extrasystole; dual-chamber pacemaker; cardiac pacemaker.

Conflict of interest: none.

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Corresponding Author: Lukin Ilya, E-mail: prlukin@gmail.com

I.B.Lukin - ORCID ID 0000-0003-1871-2754, D.V.Federiakin - ORCID ID 0000-0003-0993-5315, D.Iu.Gridiakina - ORCID ID 0009-0007-3510-2102, M.H.Karaagach ORCID ID 0009-0004-5420-601X

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Atrial fibrillation (AF) is one of the most common arrhythmias observed in patients with implanted pacemakers (PMs). AF increases the risk of serious complications such as stroke, heart failure, and all-cause mortality. Importantly, long episodes of AF (lasting more than 24 hours) are most strongly associated with stroke risk [1].

According to the European Society of Cardiology (ESC), the risk of AF in patients with atrioventricular (AV) block and sinus node dysfunction (SND) increases with insufficient atrial pacing [1]. The introduction of adaptive atrial pacing (AP) algorithms is one of the approaches to rhythm disorder prevention and to reducing the incidence of prolonged AF episodes [2-4].

Despite a considerable body of research, the impact of AP on AF risk remains a subject of debate. On the one hand, AP can improve haemodynamics, enhance atrioventricular synchrony, and prevent pathological myocardial remodelling [5]. On the other hand, excessive AP may promote atrial premature contractions (APCs), which in turn increase the likelihood of AF development [6, 7].

We previously published our data on the performance of supraventricular tachycardia prevention algorithms in patients with implanted PMs [8]. The objective of the pres-

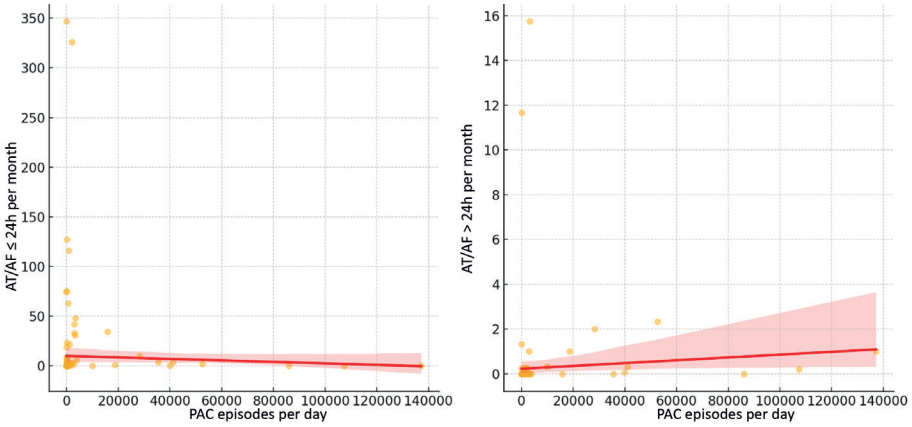

Fig. 1. Analysis of the relationship between PACs and AT/AF lasting no more than 24 hours (a) and more than 24 hours (b). Here and below, PACs = grouped premature atrial contractions; * - it should be noted that the programmer also counts PACs during AF; AT/AF = atrial tachyarrhythmias/atrial fibrillation.

ent study is to evaluate the effect of AP on the risk of AF and APCs in patients who underwent implantation of dual-chamber pacemakers.

METHODS

Study design

This study is a retrospective cohort analysis conducted at the Tver State Medical University Clinic. It included patients who underwent implantation of dual-chamber PMs between January 2022 and August 2024, with a programmed basic pacing rate of 60 bpm.

Inclusion criteria:

- implantation of a dual-chamber PM;
- available data on AP;
- follow-up period of at least 1 month.

Exclusion criteria:

- patients with cardiac resynchronization therapy (CRT) or implantable cardioverter-defibrillators (ICDs);
- insufficient data on atrial tachyarrhythmias (ATs) and/or AF, or AP;
- patients with permanent AF;
- patients with severe structural heart disease requiring surgical correction;
- patients who underwent catheter ablation of ATs prior to inclusion or during follow-up.

Information on antiarrhythmic and other pharmacological therapy was not included in the analysis. Significant baseline clinical differences between groups that could affect the results were not anticipated. Assessment of AP and atrial tachyarrhythmia episodes was based on data obtained from the Medtronic programmer. In Medtronic programmers, atrial tachyarrhythmias are designated as AT/AF; therefore, in this study the same designation (AT/AF) is used. The following parameters were analysed: percentage of AP, number of atrial premature contraction (APC) clusters, and incidence of AT/AF episodes lasting ≤24 hours and >24 hours (AT/AF ≤24 and AT/AF >24, respectively).

The number of grouped atrial premature contractions (APCs) was assessed per day according to the formula:

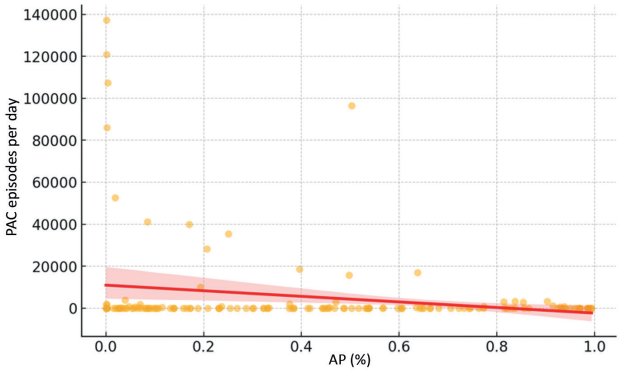

Fig. 2. Analysis of the relationship between atrial pacing and episodes of atrial extrasystole. Here and below, AP = atrial pacing.

Date/Time	Duration hh:mm:ss		Rate (bpm) Max A	Max V
10.03.2025 15:32	17:20:12	Suspended...	> 400	183

High-rate ventricular episodes : **0**

Pacing (% of total):		Event counters	
A pacing	< 0,1%	Single PVCs	23
V pacing	60,1%	PVC runs	1
Reduced VP+	On	PAC runs	79659

Fig. 3. Report data from the programmer of patient E. (see explanation in the text).

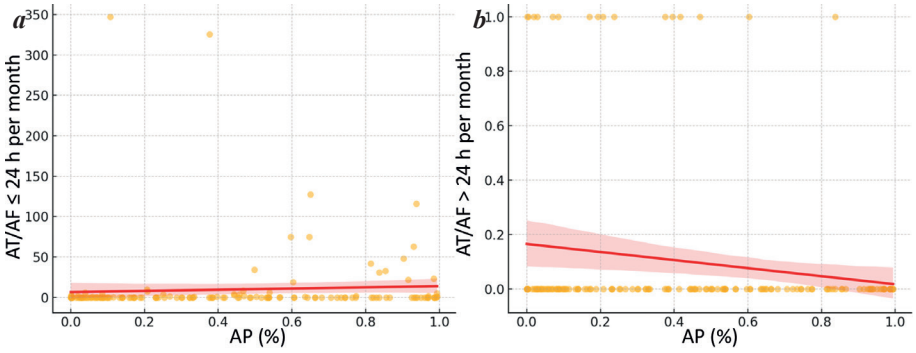

Fig. 4. Analysis of the relationship between atrial pacing and AT/AF episodes lasting no more than 24 hours (a) and more than 24 hours (b).

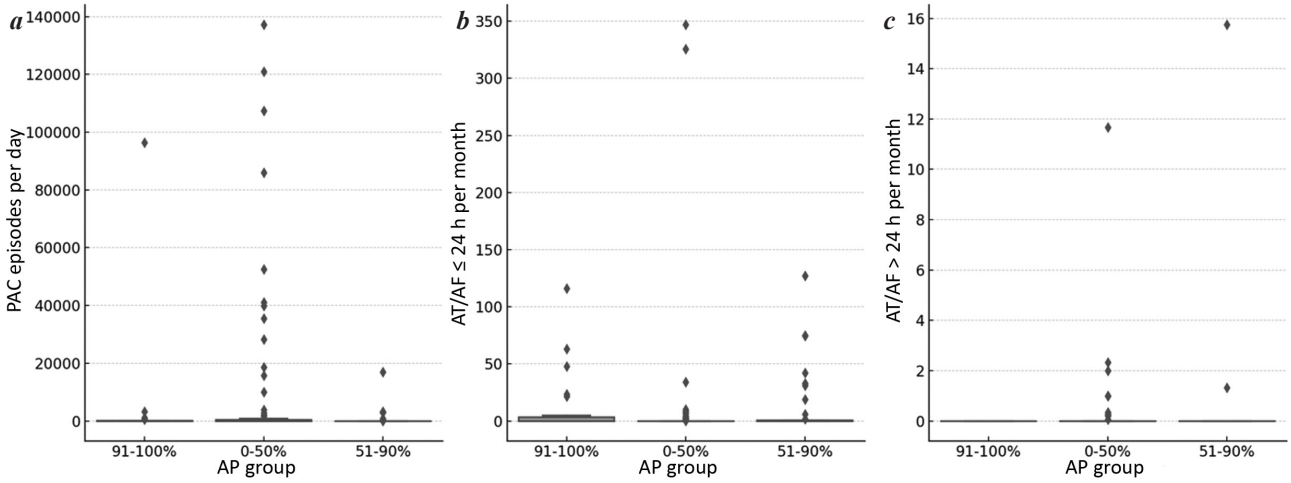

Fig. 5. Comparative analysis of the frequency of grouped PACs (a), AT/AF episodes lasting no more than 24 hours (b), and more than 24 hours (c), depending on the level of AP (AP 0-50%, AP 51-90%, AP 91-100%).

Number of APC episodes per day = Number of APC episodes during the observation period / Observation period, days.

The number of AT/AF episodes lasting no more than 24 hours and more than 24 hours was recalculated as the number of episodes per month. The recalculation was performed using the following formula:
Number of AT/AF episodes per month = Number of AT/AF episodes during the observation period×30 / Observation period, days.

Single PACs were not evaluated, as the programmer of this model did not include the corresponding function.

In the first stage, the effect of PACs on the development of AT/AF episodes lasting no more than 24 hours and more than 24 hours was assessed. In the second stage, the effect of atrial pacing (AP) on the number of recorded grouped PACs and on the development of AT/AF≤24 and AT/AF>24 was evaluated.

Subsequently, patients were divided into three groups according to the percentage of AP: 0-50% (AP 0-50%), 51-90% (AP 51-90%), 91-100% (AP 91-100%) and the impact of AP on the number of PACs per day, AT/AF≤24 and AT/AF>24 per month was assessed in each group.

Statistical analysis

Patient data were processed using Microsoft Access and Excel. Data analysis was performed with Jupyter Notebook software (Python 3.x). Categorical variables were compared using the chi-square test (χ^2), and continuous variables using Student's t-test or the Mann-Whitney U test. Correlation analysis was conducted using Spearman's correlation coefficient (ρ). Logistic regression was applied to assess predictors of AT/AF. Statistical significance was set at $p < 0.05$.

RESULTS

General characteristics of the study population

The study included 97 patients, of whom 44.3% were men. The mean age at the time of surgery was 68.8 ± 14.3 years. In 32% of cases, a Medtronic DR pacemaker was implanted, and in 68% a Vitatron device. The mean follow-up period was 6.68 ± 4.42 months (ranging from 1 to 20 months). The indications for pacemaker implantation were distributed as follows: AV block - 33.0% of patients (n=32), sinus node dysfunction (SND) - 21.6% (n=21), and a combination of AV block and SND - 44.3% (n=44). A history of paroxysmal AF was diagnosed in 33.0% of patients.

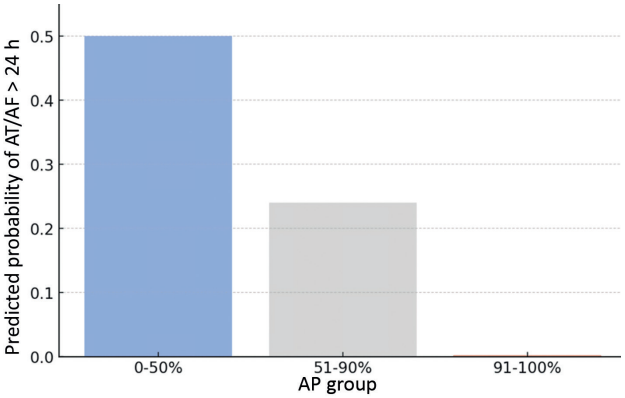

Fig. 6. Probability of AT/AF episodes >24 h depending on the level of AP (results of Firth logistic regression, 95% CI).

Association Between PAC Episodes and AT/AF

Figure 1 shows the correlation analysis, which demonstrated a moderate positive association between the frequency of grouped PACs and AT/AF episodes recorded during pacemaker data analysis. Spearman's correlation coefficient $\rho = 0.623$ ($p < 0.001$) indicates a moderate positive relationship between daily PACs and short episodes of AT/AF ≤24 hours, while $\rho = 0.443$ ($p < 0.001$) points to a moderate positive relationship between daily PACs and prolonged episodes of AT/AF >24 hours. Both results are highly statistically significant, confirming the association between an increased frequency of grouped PACs and a higher likelihood of AT/AF. However, the less pronounced correlation with prolonged episodes (>24 hours) may suggest the influence of additional factors contributing to the chronification of arrhythmia. These findings support the hypothesis regarding the importance of atrial activity control and timely correction of PACs in patients with dual-chamber PMs, which may help reduce the risk of clinically significant AT/AF episodes.

Analysis of the Impact of AP on PAC Episodes

Figure 2 presents a scatter plot illustrating the relationship between AP level and the frequency of daily PAC episodes. Spearman's coefficient $\rho = -0.067$ ($p = 0.752$) indicates no significant association. Linear regression (red line) shows a trend toward a slight decrease in the number of PAC episodes with increasing atrial pacing; however, this does not reach statistical significance. The wide dispersion of values, especially at low levels of AP, indicates considerable variability among patients. The absence of a clear linear trend, confirmed by a low coefficient of determination ($R^2 = 4.6\%$), highlights the limited explanatory power of the model. This suggests the need for a larger sample size and inclusion of additional parameters for a more accurate assessment of the effect of AP on PACs.

It is noteworthy that in some patients, the programmer recorded a very high number of "grouped PACs"—more than 100,000 episodes per day. A detailed examination revealed that this was related to PAC detection algorithms, since such a high number of PACs was observed during episodes of AF. Figure 3 demonstrates programmer data from patient E. during an AF paroxysm. Over 17 hours and 20 minutes of monitoring, 79,659 PAC episodes were recorded, which extrapolates to more than 110,000 per day. Throughout the entire monitoring period, AF was continuously present. Holter monitoring performed during the same time interval also confirmed AF. This situation clearly highlights certain limitations regarding PAC detection in programmer data.

Analysis of the impact of AP on the development of AT/AF

Figure 4 presents graphs of the relationship between AP and the monthly frequency of atrial tachyarrhythmia episodes.

In Figure 4a (AT/AF ≤24 h), no clear linear association between AP and short-term AT/AF episodes is observed. The regression line shows only a weak trend toward a reduction in AT/AF ≤24 h with increasing atrial pacing, but this effect is minimal. Spearman's coefficient:

ρ = -0.087, p = 0.324 (not statistically significant). The wide scatter of values suggests variability in the data and possible influence of additional factors. The absence of a clear association between short AT/AF episodes and the percentage of AP may indicate either the predominance of other mechanisms in their occurrence or an insufficient sample size.

In Figure 4b (AT/AF >24 h), a negative correlation was found between AP and the frequency of long-lasting AT/AF episodes. The regression line demonstrates a moderately expressed decrease in the frequency of AT/AF >24 h with increasing AP. Spearman's coefficient: ρ = -0.312, p = 0.002 (statistically significant). A high level of atrial pacing (AP ≥91%) shows a trend toward reduced risk of long-lasting AT/AF episodes, which is confirmed by the statistically significant correlation (ρ = -0.312, p = 0.002).

Analysis of differences between groups depending on AP level

Figure 5 presents the results of a comparative analysis of patient groups stratified by AP level with respect to grouped PACs, AT/AF ≤24 h, and AT/AF >24 h. The Kruskal-Wallis test was used to assess differences.

The number of PAC episodes per day did not show a significant association with AP level (H = 0.57, p = 0.752), and the differences between groups were not statistically significant. This confirms the absence of a clear effect of AP on PACs in the studied cohort.

AT/AF ≤24 h showed a tendency to increase with higher AP levels, but the differences between groups did not reach statistical significance (H = 4.27, p = 0.118). This may indicate that short-term AT/AF episodes are less sensitive to changes in AP level.

AT/AF >24 h demonstrated a tendency toward reduction in the AP 91-100% group; however, p > 0.05 (H = 5.62, p = 0.060). This may suggest a possible protective effect of high AP in preventing long-lasting AT/AF episodes. At the same time, statistical significance was not achieved, which warrants further investigation in a larger sample.

Analysis of the impact of AP on the risk of prolonged AT/AF based on firth logistic regression

To assess the effect of AP on the risk of prolonged AT/AF episodes, Firth logistic regression was performed. The predicted probability plot demonstrated a reduction in the risk of AT/AF >24 h with increasing AP, with the lowest probability observed in the AP 91-100% group (Fig. 6).

For the AP 51-90% group (compared with the reference group AP 0-50%): β = -1.154, p = 0.002 (statistically significant). The odds ratio of 0.31 indicates a marked reduction in the likelihood of AT/AF >24 h, confirming the protective effect of moderate AP.

For the AP 91-100% group (compared with the reference group AP 0-50%): β = -6.052, p = 0.151 (not statistically significant). Although there was a pronounced reduction in the risk of AT/AF >24 h, the result did not reach statistical significance due to the small sample size.

DISCUSSION

The results obtained demonstrate that a high AP burden may reduce the risk of long (>24h) supraventricular tachycardia episodes, although its effect on PACs was not significant. These findings are consistent with those of B.L. Wilkoff et al. (2003), who showed that maintaining sinus rhythm with a high percentage of AP can reduce the risk of prolonged AF episodes [9].

Previous studies have pointed to potential mechanisms underlying the protective effect of AP. For example, J.B. Thambo et al. (2016) reported that atrial pacing improves haemodynamics and reduces atrial remodelling [7]. Conversely, C.A. Morillo et al. (2021) noted that excessive atrial pacing may promote arrhythmia in predisposed patients [10]. Our results support this dual role of atrial pacing: in the AP 51-90% group, a significant reduction in the risk of AT/AF>24h was observed (hazard ratio 0.31, p = 0.002), whereas in the AP 91-100% group, statistical significance was not reached (p = 0.060), which may be explained by the limited sample size.

Correlation analysis confirmed a moderate association between PACs and AT/AF episodes (ρ = 0.623, p<0.001), consistent with A.M. Gillis et al. (2017), who demonstrated that atrial extrasystoles may act as triggers for AF onset [2]. However, despite this association, atrial pacing did not have a significant impact on grouped PAC frequency (p = 0.752), supporting the hypothesis of the multifactorial nature of AT/AF mechanisms.

Study limitations

Despite the significant findings obtained, this study has several limitations. Its retrospective design does not allow for control over confounding factors during follow-up; the limited sample size constrains the strength of final conclusions; and no analysis was performed of concomitant factors such as structural heart disease, comorbidities, antiarrhythmic and other pharmacological therapy, left atrial volume, or alternative pacemaker algorithms. In addition, the relatively short observation period precludes assessment of long-term outcomes.

To confirm the present findings and enable their translation into clinical practice, further research is required. This should include prospective studies with longer follow-up periods, multivariable analyses incorporating additional parameters (e.g., echocardiography, 24-hour Holter monitoring, comorbidities), and investigations of different pacing algorithms (comparing device models and their specific programming strategies for AF prevention). Such studies would allow for a more precise definition of optimal pacing parameters and support the development of individualised pacemaker programming approaches aimed at AF prevention in patients with diverse cardiac conditions.

CONCLUSION

It may be assumed that atrial pacing exerts a potential protective effect against prolonged episodes of supraventricular tachyarrhythmias and atrial fibrillation. However, definitive confirmation requires further research with larger sample sizes and the application of multivariable analyses that incorporate additional parameters such as left atrial volume, concomitant cardiovascular comorbidities, and alternative pacemaker algorithms.

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): 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. European Heart Journal. 2021;42(5): 373-498 https://doi.org/10.1093/eurheartj/ehaa612.
2. Gillis AM, Morillo CA, Kus T, et al. Pacing and atrial fibrillation. Heart Rhythm. 2017;14(4): 631-639. https://doi.org/10.1016/j.hrthm.2016.11.003.
3. Gillis AM, Sutton R, Morillo CA, et al. Pacing mode and atrial fibrillation prevention. Circulation. 2019;140(14): 1030-1043. https://doi.org/10.1161/CIRCULATIONAHA.118.037720.
4. Sweeney MO, Bank AJ, Nsah E, et al. Atrial pacing and atrial fibrillation: Clinical outcomes. Circulation. 2018;137(8): 806-815. https://doi.org/10.1161/CIRCULATIONAHA.117.031792.
5. Carlson MD, Ip J, Messenger JC, et al. Long-term effects of atrial pacing on atrial fibrillation incidence. Journal of the American College of Cardiology. 2019;73(9): 1117-1126. https://doi.org/10.1016/j.jacc.2018.12.036.
6. Lamas GA, OrAB EJ, Stambler BS, et al. The Mode Selection Trial in Sinus Node Dysfunction. New England Journal of Medicine. 2002;347(24): 1837-1847. https://doi.org/10.1056/NEJMoa021328.
7. Thambo JB, Ploux S, Labrousse L, et al. Atrial-based pacing strategies to prevent atrial fibrillation. Journal of Cardiovascular Electrophysiology. 2016;27(3): 351-359. https://doi.org/10.1111/jce.12891.
8. Lukin IB. Algorithms for the prevention and treatment of supraventricular tachycardia in patients with implanted pacemakers: case series. Journal of Arrhythmology. 2022;29(4): e9-e14 (In Russ.) https://doi.org/10.35336/VA-2022-4-12.
9. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing and atrial fibrillation prevention. Journal of the American College of Cardiology. 2003;41(3): 432-438. https://doi.org/10.1016/S0735-1097(02)02720-9.
10. Morillo CA, Connolly SJ, Pogue J, et al. Atrial pacing and atrial fibrillation: insights from clinical trials. Europace. 2021;23(2): 225-235. https://doi.org/10.1093/europace/euaa231.

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FOLLOW-UP OF A CHILD WITH KEARNS-SAYRE SYNDROME AND IMPLANTED PACEMAKER: A CASE REPORT

A.Y.Bokach, N.S.Igembekov, Zh.E.Serikova
Multi-profile hospital No.2 in Karaganda, Kazakhstan, Karaganda, 23 Krylova str.

A clinical case of a child with a rare mitochondrial disease, Kearns-Sayre syndrome, who had a pacemaker implanted due to the development of complete atrioventricular block, is presented for the first time in the Republic of Kazakhstan. The issues of complex diagnostics and management tactics are discussed.

Key words: mitochondrial myopathy; severe neurological deficit; atrioventricular block of the third degree in children; children; implantation of a pacemaker in children

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Corresponding Author: Serikova Zhaniya, E-mail: m.zhaneka@mail.ru

A.Y.Bokach - ORCID ID 0009-0002-3058-6906, N.S.Igembekov - ORCID ID 0009-0007-9974-8164, Zh.E.Serikova - ORCID ID 0009-0008-3324-0066

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Kearns-Sayre Syndrome (KSS) is a rare mitochondrial disorder, first described in 1958 by Thomas Kearns and George Pomeroy Sayre in their publication “Retinitis pigmentosa, external ophthalmoplegia, and complete heart block” [1]. The disease is characterised by the classical triad of symptoms: onset before the age of 20 years, chronic progressive external ophthalmoplegia, and pigmentary retinopathy [2]. A distinctive feature of KSS is the high prevalence of cardiac conduction disturbances, which significantly influence the prognosis of the disease.

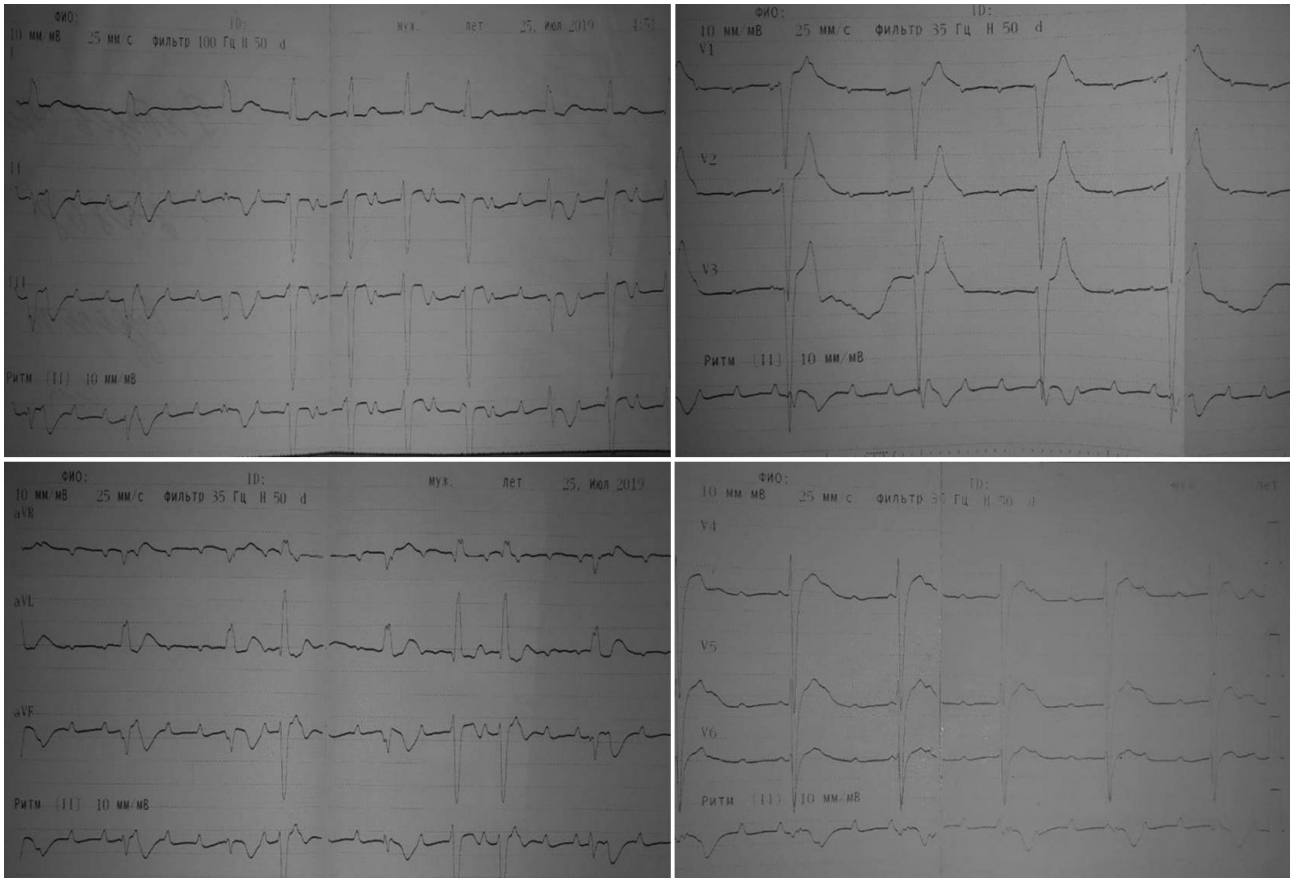

Fig. 1. Electrocardiogram of a patient with third-degree atrioventricular block.

Epidemiological data indicate a prevalence of 1-3 cases per 100,000-125,000 population [3-5]. Approximately 90% of KSS cases are sporadic and are caused by large deletions of mitochondrial DNA (mtDNA) ranging from 1.1 to 10 kilobases. The most common is the so-called “standard deletion” - a loss of 4,977 base pairs, accounting for more than one-third of all cases [6,7]. The aetiological factors responsible for these deletions remain unclear.

Patients with KSS frequently present with conduction abnormalities, ranging from PR-interval prolongation to complete atrioventricular (AV) block. These disturbances are associated with a high risk of stroke and sudden cardiac death [4], which underscores the need for timely implantation of a pacemaker (PM). This article presents a clinical case of PM implantation in a 10-year-old patient with KSS. According to the literature, fewer than 10 cases of this syndrome have been reported in the post-Soviet space since the 20th century. The described case is the first documented in Kazakhstan.

The patient was a 10-year-old boy, born from the second pregnancy. The first pregnancy ended with the death of the child on the first day of life due to sepsis. The second pregnancy occurred 6 months later and was complicated by pre-eclampsia with a threat of miscarriage during most of the gestational period. He was delivered at 40 weeks, weighing 3550 g and measuring 53 cm in length. Family history on the paternal side included systemic lupus erythematosus in the grandmother, hand tremor in an aunt and her daughter; the maternal family history was unremarkable.

From the age of 3 years, the patient presented with eyelid ptosis, visual impairment, headaches, unsteady gait, and developmental delay (both mental and physical). From the age of 8 years, muscle weakness and tremor of the limbs developed. At 10 years and 11 months, complete AV block occurred (Fig. 1). A dual-chamber PM with active-fixation endocardial leads was implanted; the generator was positioned in the left subclavian region (Figs. 2, 3). Laboratory tests revealed hypokalaemia, hyperglycaemia, and elevated transaminases; creatine phosphokinase levels were within the normal range. Echocardiography showed left ventricular (LV) ejection fraction (EF) of 50-54% without other abnormalities.

At the age of 14 years, molecular genetic testing using long-fragment PCR identified a deletion of approximately 7000 base pairs (positions 1650-16,565) in a heteroplasmic state (~70% mutant copies), confirming the diagnosis of Kearns-Sayre syndrome.

Later that year, the patient was urgently hospitalised in the intensive care unit with multiple episodes of vomiting with mucus, marked weakness, lethargy, dyspnoea, and fever of 38.7 °C. On admission, his condition was assessed as coma grade I-II. Laboratory results: lactate 6.1 mmol/L; marked leukocytosis with neutrophilia and lymphopenia; D-dimer 4164.4 ng/mL; C-reactive protein 12.75 mg/L; NT-proBNP 17,499.8 pg/mL; procalcitonin 1.56 ng/mL; glucose 16.2 mmol/L. Blood cultures showed no microbial growth. On physical examination, there was pharyngeal hyperaemia and purulent follicular tonsillitis.

ECG revealed atrial fibrillation with paroxysms of non-sustained ventricular tachycardia. An elevated pacing threshold of the right ventricle was noted, with an episode of pacing failure and a minimal heart rate of 46 bpm; after increasing the pacing amplitude, effective capture was restored. Echocardiography demonstrated severe diffuse LV systolic dysfunction (EF 20-25%), without chamber dilation or valvular abnormalities.

In the intensive care setting, vasopressor, antibiotic, detoxification, and hypoglycaemic therapy was initiated. Infectious-toxic myocarditis was suspected. Despite treatment, the patient’s condition continued to deteriorate, culminating in cardiac arrest. Resuscitation was performed for 35 minutes without success. The patient died at the age of 14 years and 11 months from progressive cardiovascular failure. The parents declined autopsy.

DISCUSSION

Patients with KSS are characterised by increased susceptibility to infectious diseases, attributable to multi-

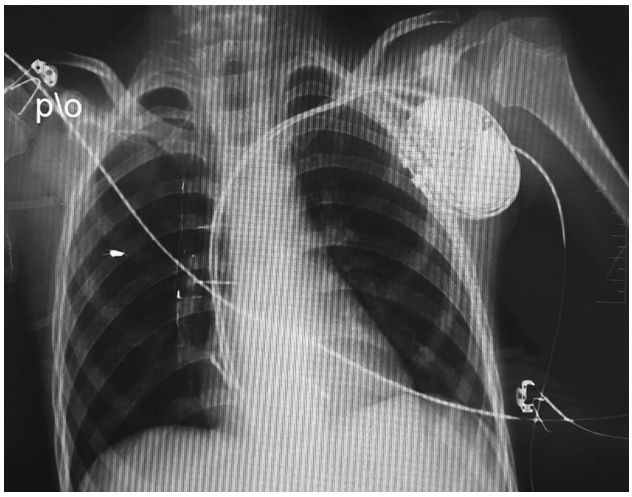

Fig. 2. Chest radiograph of a patient after pacemaker implantation.

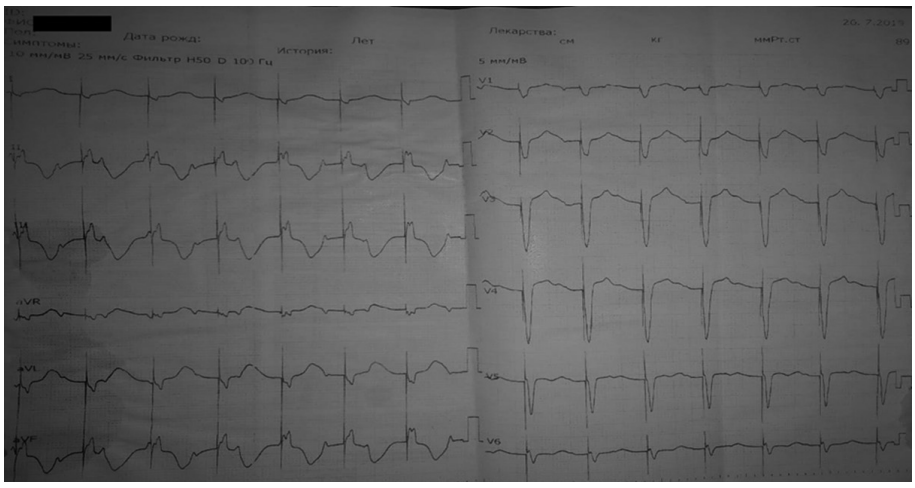

Fig. 3. Electrocardiogram of a patient after pacemaker implantation.

system mitochondrial dysfunction and impaired immune responses. In the present case, acute tonsillitis likely triggered an infectious-toxic myocarditis, which subsequently led to acute heart failure and death.

Currently, there are no pharmacological treatments for mitochondrial diseases supported by high-level evidence. The main therapeutic strategies focus on reducing excessive free radical production and enhancing adenosine triphosphate synthesis, both of which are critical for improving mitochondrial metabolism and the cellular energy balance.

Monitoring of patients with mitochondrial disorders should include regular electrocardiography, echocardiography, Holter monitoring, audiometry, and endocrine assessment [8], given the unpredictable disease course and the potential for progression to AV block [9].

Considering the high risk of complete AV block, ventricular arrhythmias, and sudden cardiac death in patients with KSS, implantation of an implantable cardioverter-defibrillator (ICD) should be considered [10]. In the case described, pacemaker implantation was performed before genetic confirmation of the diagnosis. An ICD was not implanted initially due to the lack of clear recommendations for primary prevention of sudden cardiac death in this patient category [11]. Pacemaker telemetry did not reveal life-threatening arrhythmias, LV ejection fraction remained above 40%, and no LV hypertrophy was present, all of which supported the choice of pacemaker over ICD [12].

According to the literature, among 15 children with KSS followed between 2007 and 2019, 11 underwent pacemaker implantation, and one with non-sustained ventricular tachycardia received an ICD. The mean age of patients with conduction disturbances was 13.7 years. Four patients died at a mean age of 14.7±2.6 years; however, no cases of sudden death were documented. Two deaths were due to heart failure, in one case combined with septic shock; in these patients, LV dysfunction had developed before pacemaker implantation. Other reported causes of death included pancreatitis and unidentified factors [13]. Details of these fatal outcomes were not specified.

Modern approaches to the management of patients with KSS emphasise the need for multidisciplinary care involving cardiologists, geneticists, endocrinologists, and neurologists. Early diagnosis and close monitoring allow timely detection of progressive conduction disturbances and help prevent severe complications, including sudden cardiac death. The question of prophylactic ICD implantation or cardiac resynchronisation therapy devices with defibrillator function remains an area of ongoing research and requires further clinical validation.

The patient's parent provided written informed consent for publication of these data.

CONCLUSION

Patients with Kearns-Sayre syndrome (are prone to the development and progression of conduction system abnormalities, which necessitates regular and thorough cardiological monitoring. Early diagnosis enables frequent electrocardiography and Holter monitoring to ensure timely decisions regarding implantation of pacemakers, ICDs, or cardiac resynchronisation therapy devices with a defibrillator function. At present, cases of prophylactic implantation of such devices immediately following the diagnosis of KSS have not been described, highlighting an important area for further investigation.

REFERENCES

1. Kearns TP, Sayre GP. Retinitis pigmentosa, external ophthalmophegia, and complete heart block: unusual syndrome with histologic study in one of two cases. *AMA Arch Ophthalmol.* 1958;60(2): 280-9.
2. Shemesh A, Margolin E. Kearns-Sayre Syndrome. [Updated 2023 Jul 17]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482341/
3. Finsterer J. Kearns-Sayre Syndrome. Orpha.net. 2021-09-01. Available from: https://www.orpha.net/en/disease/detail/480?name=ORPHA480&mode=orpha
4. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US) National Library of Medicine 8600 Rockville Pike, Bethesda, MD 20894 U.S. Department of Health and Human Services National Institutes of Health. Last updated December 1, 2011. Available from: https://medlineplus.gov/genetics/condition/kearns-sayre-syndrome/#frequency
5. Zhu Q, Chen C, Yao J. Kearns-Sayre syndrome with a novel large-scale deletion: a case report. BMC Ophthalmol. 2022 Jan 24;22(1):35. https://doi.org/10.1186/s12886-021-02224-7.
6. Vlasenko SV, Ponomarenko EN, Kushnir GM, et al. Clinical case study of Kearns-Sayre syndrome: diagnosis, methods of treatment. *Neuromuscular Diseases.* 2018;8(3):51-57. (In Russ.) https://doi.org/10.17650/2222-8721-2018-8-3-51-57
7. Tsang SH, Aycinena ARP, Sharma T. Mitochondrial Disorder: Kearns-Sayre Syndrome. *Adv Exp Med Biol*. 2018;1085: 161-162. https://doi.org/10.1007/978-3-319-95046-4_30.
8. Saldaña-Martínez A, Muñoz ML, Pérez-Ramírez G, et al. Whole sequence of the mitochondrial DNA genome of Kearns Sayre Syndrome patients: Identification of deletions and variants. *Gene*. 2019;688: 171-181. https://doi.org/10.1016/j.gene.2018.11.085.
9. Rashbaeva GS, Kabaev UT, Abdrakhmanov AS, et al. Clinical protocols of the Ministry of Health of the Republic of Kazakhstan, Cardiac conduction disorder, 2014. Available from: https://diseases.medelement.com/disease (In Russ.).
10. Wiseman K, Gor D, Udongwo N, et al. Ventricular arrhythmias in Kearns-Sayre syndrome: A cohort study using the National Inpatient Sample database 2016-2019. Pacing Clin Electrophysiol. 2022 Dec;45(12):1357-1363. https://doi.org/1010.1111/pace.14607.
11. Kharbouch H, Boussaadani B, Fellat I, et al. Kearns Sayre syndrome: a rare etiology of complete atrioventricular block in children (case report). *Pan Afr Med J.* 2021;40: 154. https://doi.org/10.11604/pamj.2021.40.154.24281.
12. Groh WJ, Bhakta D, Tomaselli GF et al. 2022 HRS expert consensus statement on evaluation and manage-

ment of arrhythmic risk in neuromuscular disorders. *Heart Rhythm.* 2022;19(10): e61-e120. https://doi.org/10.1016/j.hrthm.2022.04.022.
13. Di Mambro C, Tamborrino PP, Silvetti MS, et al. Progressive involvement of cardiac conduction system in paediatric patients with Kearns-Sayre syndrome: how to predict occurrence of complete heart block and sudden cardiac death? *Europace*. 2021 ;23(6): 948-957. d https://doi.org/10.1093/europace/euaa335.

https://doi.org/10.35336/VA-1467

BALANCING BETWEEN CLINICAL EFFICACY AND ECONOMIC EXPEDIENCY: CHOOSING A DEVICE FOR CARDIAC RESYNCHRONIZATION THERAPY

D.A.Zorin[1,2], A.A.Nechepurenko[2], A.A.Demidov[1], O.N. Dyakova[1], N.N.Ilov[1,2], N.P.Zorina[3], K.N.Ivankova[1]

[1] FSBEI of HE Astrakhan State Medical University, MH RF, Russia, Astrakhan, 121 Bakinskaya str;

[2] FSBI "Federal Center for Cardiovascular Surgery" of the MH RF, Russia, Astrakhan, 4 Pokrovskaya Roscha str;

[3]SBHO AR «City polyclinic №10», Russia, Astrakhan, 26 Silikatnaya str.

The article focuses on the analysis of device selection for cardiac resynchronization therapy based on the stratification of sudden cardiac death risk. Various diagnostic methods and clinical-anamnestic data are considered, along with their role in predicting arrhythmogenic events and making implantation decisions. Differences in implantation approaches for patients with ischemic and non-ischemic cardiomyopathy are discussed, emphasizing the importance of a combined risk assessment and the use of prognostic models. Unresolved issues related to optimal patient selection, timing for evaluating CRT effectiveness, and potential implantation strategies considering both economic and clinical factors are also reviewed.

Key words: chronic heart failure; ventricular tachyarrhythmias; sudden cardiac death; implantable cardioverter-defibrillator; cardiac resynchronization therapy

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Corresponding author: Zorin Dmitry, E-mail: dimusechek1997@gmail.com

D.A.Zorin - ORCID ID 0000-0001-7167-4713, A.A.Nechepurenko - ORCID ID 0000-0001-5722-9883, A.A.Demidov - ORCID ID 0000-0001-7179-5101, O.N. Dyakova - ORCID ID 0000-0001-7444-530X, N.N.Ilov - ORCID ID 0000-0003-1294-9646, N.P.Zorina - ORCID ID 0009-0003-8451-9837, K.N.Ivankova - ORCID ID 0009-0005-2111-0684
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According to epidemiological studies, chronic heart failure (CHF) affects 1-2% of the adult population in developed countries. In Russia, the prevalence of CHF has increased significantly in recent years: from 4.9% to 10.2% between 1998 and 2014. At the turn of the 21st century, in the European part of Russia, the prevalence of CHF of any New York Heart Association (NYHA) functional class was 7.0%, with severe forms of CHF (NYHA class III-IV) diagnosed in 2.1% of the population [1].

A particularly challenging category in terms of cardiovascular risk assessment and prediction of adverse events are patients with reduced left ventricular ejection fraction (LVEF). It has been demonstrated that when LVEF falls below 35%, such patients enter a high-risk group for sudden cardiac death (SCD) [2] and death due to acute decompensation of cardiac function, with SCD accounting for 15-20% of all fatal cases [3, 4].

SCD is primarily caused by the development of ventricular tachyarrhythmias (VT), which can be effectively terminated by implantable cardioverter-defibrillator (ICD) therapy. The device acts through antitachycardia pacing or shock delivery [5]. Therefore, ICD implantation is recommended for all patients with heart failure with reduced ejection fraction (HFrEF) who belong to the high-risk group for SCD, as well as for patients who have already survived an SCD episode or have had documented sustained VT. While the clinical rationale for ICD implantation as secondary prevention is beyond doubt in the professional community, the issue of selecting patients with HFrEF for interventional primary prevention of SCD increasingly becomes the subject of active discussion and debate [6].

It should be remembered that ICD implantation provides access to life-saving therapy but does not prevent the occurrence of arrhythmic events in the future. By contrast, another interventional treatment for CHF—cardiac resynchronisation therapy (CRT), indicated in HFrEF patients with a wide QRS complex on the electrocardiogram (ECG)—not only improves LV contractility [7], reduces the likelihood of repeated CHF hospitalisations [8], and enhances quality of life [9], but also has the potential to modify arrhythmic risk [10]. The principle of CRT is to correct atrioventricular and interventricular dyssynchrony by combining endocardial stimulation of the right ventricle with epicardial stimulation of the LV, synchronised with atrial systole. A positive response to CRT is considered a favourable prognostic marker [7]. Given that a responder to CRT may no longer meet the indications for ICD implantation, the question arises whether to implant a CRT-P (CRT with pacemaker function only) or a CRT-D (CRT with defibrillator function).

The problem of selecting the type of CRT device depending on the presence or absence of a defibrillator function is highly relevant due to the need to balance clinical efficacy, safety, economic feasibility, and individual patient characteristics. This underscores the demand for research in this field.

CRT - INDICATIONS AND RESPONSE PATTERNS TO THERAPY

The main indications for CRT are LVEF ≤35% and QRS duration ≥150 ms in the presence of left bundle branch block (LBBB) morphology. CRT is also indicated in patients with a wide QRS complex without LBBB morphology, although these indications carry a lower level of evidence [11]. In patients with HFrEF, interventricular and intraventricular conduction disturbances, including LBBB, are observed in approximately 30% of cases [12]. Current national and international guidelines recognise CRT as a highly effective treatment for such patients, as it has been shown to improve contractile function, reduce symptoms, enhance quality of life, and decrease both mortality and hospitalisation rates in patients with CHF [11].

It is well known that LBBB is an unfavourable marker that worsens prognosis in patients with CHF [12]. This is attributed to the development of interventricular dyssynchrony, in which right ventricular contraction occurs before left ventricular systole. The resulting interventricular and intraventricular dyssynchrony arises from the propagation of the electrical signal through the interventricular septum, leading to early activation of the septal region of the LV, while a zone of delayed activation appears in the posterior-basal wall of the LV. This mechanical mismatch causes presystolic stretching of the late-activated regions, which, in line with the Frank-Starling mechanism, augments systolic contraction. Consequently, systolic stress, tension, and myocardial oxygen consumption increase in the late-activated areas and decrease in the early-activated regions. The subsequent loss of contractile efficiency leads to the development of heart failure [13].

The response criteria for CRT described in the literature can be classified into several main categories:

- Clinical response - improvement in CHF functional class according to NYHA, improved quality of life.
- Echocardiographic (Echo) response - increase in LVEF, reduction in LV end-systolic volume (LVESV), reduction in mechanical dyssynchrony.
- Electrocardiographic response - narrowing of the QRS complex by ≥10 ms.

These response categories influence the achievement of various endpoints, including reduced hospitalisations, lower all-cause and cardiovascular mortality, and decreased arrhythmic risk [14].

As a clinical response criterion, improvement in CHF functional class according to NYHA is traditionally considered. In a study by Toshiko Nakai et al. [15], patients were assessed by both clinical and echocardiographic criteria. Those who showed improvement in NYHA class demonstrated better clinical outcomes after implantation, particularly regarding CHF-related hospitalisations and cardiovascular mortality.

The effect of electrocardiographic response was examined in a meta-analysis by George Bazoukis et al. [16], which found that narrowing of the QRS complex after CRT implantation was associated both with improvement in NYHA class and with a reduction in LVESV. QRS duration is undoubtedly a prognostic marker that increases the likelihood of response; however, QRS width on ECG is closely linked to LV volumetric parameters as measured by Echo. According to R.A. Stewart et al., each 10 ms increase in QRS duration was associated with an 8.3% increase in LV myocardial mass, a 9.2% increase in LV end-diastolic volume, and a 7.8% increase in LVESV [17]. In a study by N. Yamamoto et al., a modified QRS duration index—defined as the ratio of QRS duration to LV end-diastolic volume—significantly increased the probability of CRT response in patients with an "intermediate" QRS width (120-149 ms) on ECG [9].

The "gold standard" of a positive haemodynamic response is considered an increase in LVEF by ≥5% or a reduction in LVESV by ≥15%. These changes have a proven effect on all-cause mortality, arrhythmic risk, and cardiovascular mortality [14, 18].

It is important to emphasise that the effect of CRT is not limited to improving LV contractile function and CHF functional class. It also includes a reduction in myocardial electrical heterogeneity, which may contribute to lowering arrhythmic risk. For example, a decrease in LVESV and an increase in LVEF are associated not only with improved functional indices but also with a reduced likelihood of developing VT. In a study by N.N. Ilov et al., a reduction in LVESV by ≥15% and an increase in LVEF by ≥5% significantly decreased the risk of ventricular arrhythmias [4].

These results were corroborated in the PREDICT-CRT study, where haemodynamic response was associated with reduced all-cause mortality [18]. However, it should be noted that a direct correlation between changes in individual haemodynamic parameters and a reduction in VT risk is not always observed. For example, in a study by V.A. Kuznetsov et al. [19], which assessed the impact of response to CRT based on NYHA class, LVEF, and LVESV on overall mortality, concordance between response criteria was found to be low, and only the echocardiographic parameter (LVESV) demonstrated a moderate inverse correlation with mortality.

The impact of positive LVESV dynamics on cardiovascular mortality has been confirmed in further studies [18, 20]. Nevertheless, as shown by A. Van der Heijden et al., although the probability of VT decreased over a 5-year follow-up in patients with a "super-response" in LVESV, there were no statistically significant differences between responders and non-responders to CRT [20]. Similarly, M. Linhart et al., contrary to the above findings, did not demonstrate an effect of CRT on the occurrence of VT, noting that only the presence of myocardial scar was a significant predictor [21]. T. Nakamura et al. also reported no association between CRT response and VT occurrence [22].

These observations highlight that the efficacy of CRT in reducing life-threatening arrhythmias depends not only on the degree of improvement in contractile function but also on its impact on the electrical properties of the myocardium and the presence of substrate for VT.

In the absence of a haemodynamic response to CRT, a proarrhythmic effect may instead be observed, associated with progressive dispersion of repolarisation. This is supported by studies showing that lack of reverse remodelling was associated with increased VT incidence. M. Cvijić et al. [23] demonstrated that reverse remodelling reduces myocardial electrical heterogeneity, whereas in the ab-

sence of response to CRT, progressive repolarisation dispersion occurs. A published meta-analysis (8,000 patients) showed that the incidence of ventricular arrhythmias was 24% higher in patients with CRT non-response compared with those with implanted ICDs [24].

Thus, CRT demonstrates the ability to reduce SCD risk in the presence of a pronounced haemodynamic response and absence of substrate for VT, but requires close monitoring to prevent potential adverse effects in non-responders. A reduction in arrhythmic risk may therefore be regarded as a favourable effect of CRT response..

CRT-D OR CRT-P?

It seems logical to assume that in patients with a high probability of haemodynamic response to CRT, implantation of a device without a defibrillator function (CRT-P) would be reasonable, as this would help to avoid the well-known adverse events associated with ICDs and reduce treatment costs. However, this assumption is not always supported by clinical trial data.

For instance, results from the Swedish registry comparing patients with CRT-P and CRT-D demonstrated that those receiving CRT-D had lower 1- and 3-year all-cause and cardiovascular mortality [25]. The authors noted that patients who received CRT-P were older and had higher LVEF, which may have partly influenced the outcomes. Increased mortality in the CRT-P group was attributed to causes of death that an ICD would not have been able to prevent.

These findings are corroborated by the COMPANION trial, in which CRT-D reduced the risk of death by 24%. Similar results were observed in the REVERSE study, where CRT-D lowered 5-year mortality by 65% [26, 27]. A likely explanation for these results is the reduction in SCD in the CRT-D group. Nevertheless, a significant factor when interpreting these data is the aetiology of heart failure. For example, a subgroup analysis of the DANISH trial, which included patients with non-ischaemic HFrEF, showed that CRT-D did not reduce all-cause mortality [28].

Russian clinical guidelines do not yet provide specific recommendations for choosing between CRT-P and CRT-D. European guidelines suggest a somewhat broader approach, indicating that CRT-D should be more strongly considered in younger patients and in those with a likely proarrhythmic substrate, particularly when confirmed by gadolinium-enhanced cardiac MRI. However, they emphasise that clear criteria do not currently exist, and device selection should be individualised for each patient [29].

Thus, the decision regarding the choice of device for CRT remains complex and requires consideration of multiple factors, including patient age and preferences, the aetiology of heart failure, and the expected haemodynamic response to therapy. Importantly, the presence of a proarrhythmic substrate remains a decisive factor, as it significantly increases the likelihood of SCD.

SEARCH FOR THE SUBSTRATE OF VENTRICULAR TACHYCARDIA

The risk of SCD is determined by the presence of an anatomical substrate (myocardial hypertrophy, post-infarction cardiosclerosis, fibrosis) and electrophysiological changes (enhanced automaticity, triggered activity, dispersion of refractory periods) [9]. Identifying the potential substrate of VT remains a key task in SCD risk stratification.

Instrumental methods can provide additional information about the presence of a substrate and help decide on ICD implantation. Routine ECG diagnostics can be used to search for a potential substrate. On ECG analysis, dispersion of refractory periods can be assessed, manifested as QT interval prolongation/shortening [30] or changes in the interval from the T-wave peak to its end [31]. Other potential ECG markers of substrate include signs of early ventricular repolarisation [32] and LV hypertrophy [6]. It is noted that combining several markers significantly increases the prognostic value of ECG criteria, even in patients with LVEF >35% [33].

Transthoracic Echo, in addition to assessing LVEF, provides information on structural cardiac changes such as chamber volumes, wall thickness, LV mass, and regional wall motion abnormalities [34, 35]. Promising newer Echo techniques include tissue Doppler and two-dimensional strain imaging. Studies have shown that assessing longitudinal, radial, and circumferential myocardial strain, global longitudinal strain, and mechanical dispersion can improve diagnostic accuracy for VT substrate [36].

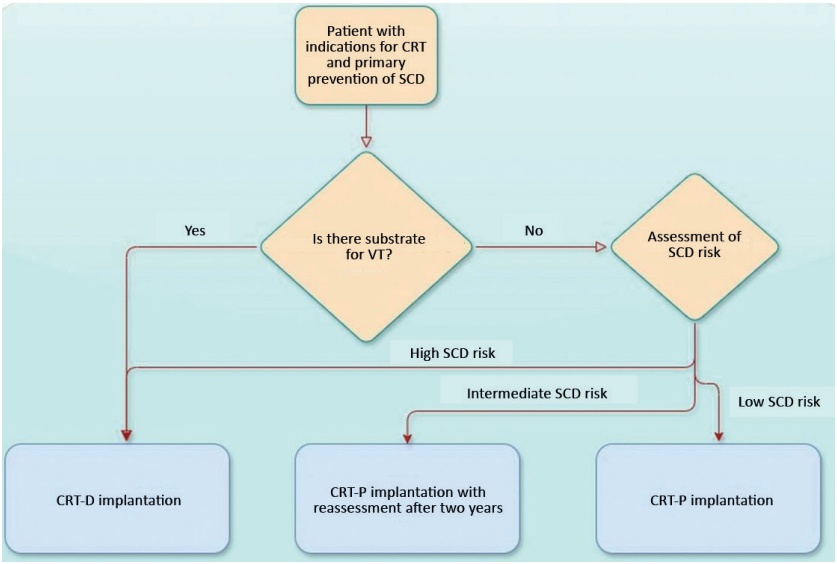

Fig. 1. Algorithm for device selection, where CRT - cardiac resynchronisation therapy; VT - ventricular tachycardia; SCD - sudden cardiac death.

Cardiac MRI with late gadolinium enhancement (LGE) occupies an important place in detecting potential VT substrate. Clinical guidelines recommend using this method as an additional factor when deciding on ICD implantation [37]. Gadolinium-based contrast accumulates in fibrotic tissue and visualises arrhythmogenic substrate [38]. Studies in patients with ischaemic cardiomyopathy (ICM) indicate that the presence of LGE zones is associated with increased risk of all-cause mortality and arrhythmic events [39]. A study

by colleagues in Penza confirmed the well-established link between LGE and SCD risk [40]. It is noted that when LGE exceeds 14% of LV myocardial mass, there is a direct correlation with ICD therapies.

Instrumental methods thus provide important information on anatomical and electrophysiological substrate, aiding ICD decision-making. Confirmed presence of a VT substrate should undoubtedly be a decisive factor for device implantation. However, these methods have limitations: they are not always absolutely precise, require substantial costs, and are not universally available. Therefore, it is important to consider not only diagnostic test results but also multiple other factors such as clinical data, history, and comorbidities [41].

The effectiveness of ICD use in patients with ICM is unquestionable. The predictive value of coronary artery disease for SCD is confirmed by a meta-analysis by Vikash Jaiswal et al., including data from 13 randomised studies [42]. Naturally, patients with ICM have high SCD risk due to the likely presence of VT substrate. Formation of arrhythmogenic substrate is related to peri-infarct zones surrounding scar tissue. These zones, containing partially viable cardiomyocytes, create electrical anisotropy, facilitating re-entry mediated VT [40, 43].

By contrast, the evidence base for ICD use in patients with non-ischaemic cardiomyopathy (NICM) is less convincing. Although the DANISH, DEFINITE, and SCD-HeFT trials demonstrated reduced SCD risk in ICD patients, they did not show a statistically significant effect on all-cause mortality [44-46]. This is attributed to the relatively lower proportion of SCD in overall mortality in these cohorts. It can reasonably be assumed that the substrate for VT in NICM is less extensive. Experimental data indicate that LV fibrosis in NICM patients significantly increases SCD risk [47]. Fibrotic zones with delayed conduction, increased automaticity, and myocardial refractory dispersion create conditions for VT. Thus, the presence of VT substrate appears to be the key factor for deriving maximum benefit from ICD implantation [48].

Experts agree that a single-factor approach is ineffective for this problem. Improved SCD risk stratification is possible only through a combined assessment method incorporating multiple predictors and the development of prognostic models.

Of particular interest is the use of prognostic scoring systems such as the MADIT-ICD Benefit Score, ESTIMATED Score, SCD-HeFT score analysis, and the Seattle Heart Failure Model [49-52]. These tools incorporate numerous factors to improve stratification of SCD risk and all-cause mortality in patients with HFrEF. Their analysis includes both predictors of VT substrate from available instrumental and laboratory studies, and clinical-anamnestic data [32]. Such models allow estimation of the benefit of ICD implantation by comparing SCD risk with all-cause mortality for an individual patient. The higher the probability of SCD, the greater the benefit of ICD therapy [49-51].

Particular attention should be paid to the MADIT-ICD Benefit Score, developed in 2020 from data from the largest MADIT trials (MADIT II, MADIT-CRT, MADIT-RIT, and MADIT-RISK). It is one of the most comprehensive prognostic models, created from a registry of over 4,500 patients. The calculator proposed by the authors incorporates predictors of VT and non-arrhythmic death. Predictors of VT include: male sex, age <75 years, heart rate (HR) >75 bpm, systolic blood pressure (SBP) <140 mmHg, LVEF ≤25%, and history of unstable VT, myocardial infarction, and atrial arrhythmias [49].

The calculator allows prediction of the likelihood of VT or non-arrhythmic death, assessing the potential benefit of ICD implantation. ROC analysis with external validation demonstrated high accuracy of the models: C-statistics of 0.75 for VT prediction and 0.67 for non-arrhythmic death. Within this context, the use of prognostic scales in patients with implanted CRT devices is of particular interest. As an independent factor influencing CRT outcomes, CRT itself was added to the MADIT-ICD Benefit Score and the Seattle Heart Failure Model, although separate analysis of CRT patients is available only from MADIT trial data [49, 52].

According to the MADIT-CRT analysis, treatment with CRT-D compared to ICD alone was associated only with a reduced risk of non-arrhythmic mortality [53]. A separate analysis excluding patients from MADIT-II showed similar results [49]. However, these studies also demonstrated that patients with QRS morphology consistent with LBBB experienced significant reduction in life-threatening arrhythmias, largely due to improved LV function and remodelling, confirming the positive effect of CRT on arrhythmic risk [54]. Yet, applying this model to assess ICD benefit in Russian patients yielded unsatisfactory results, underlining the need for local studies in this field [55].

UNRESOLVED PRACTICAL ISSUES AND PERSPECTIVES FOR THEIR RESOLUTION

It may be assumed that the presence of predictors of a positive response to CRT, an expected life expectancy of more than one year, and a low risk of SCD provide grounds for implanting a CRT-P device. However, despite the proven efficacy of CRT, according to various data, 30-40% of patients do not achieve the expected benefit from therapy [8, 56]. Factors reducing the likelihood of response to CRT include advanced CHF of high functional class, ICM with probable scarring in the pacing area, a baseline QRS complex that is insufficiently wide, or morphology not consistent with LBBB. Additional factors that may impair the probability of response include atrial fibrillation, chronic kidney disease, and baseline right ventricular dysfunction [57].

Equally important is determining the optimal follow-up period after implantation, after which the effects of CRT should be evaluated and further management decisions made to improve patient outcomes. In a study by T.V. Chumarnaya et al. [58], it was demonstrated that one year is sufficient in most cases to assess the clinical response, while reverse LV remodelling may continue for up to 24 months. Other studies also identify 12 months as adequate for CRT evaluation [59]. Based on these findings, a 24-month period after implantation reliably differentiates responders from non-responders, allowing subsequent treatment strategies to be defined.

An additional factor that could improve the efficacy of CRT-P is the use of conduction system pacing. In

this surgical approach, the lead is placed conventionally in the target vein of the coronary sinus to stimulate the LV, while another is implanted into the interventricular septum to capture the conduction system using the "stylet-driven" method, without dedicated delivery systems. The patients' response is assessed after two years. This strategy pursues two objectives: first, significantly increasing the probability of CRT response, as reflected in the LOT-CRT trial [60]; and second, if no response is observed after the maximum observation period, the option remains to implant a dual-chamber ICD with a DF-1 connector. In such cases, a shock lead is placed, while the previously implanted lead into the conduction system can be used for ventricular pacing, narrowing the QRS complex, potentially preventing CHF progression due to dyssynchrony, and avoiding LV pacing which, according to studies, increases the risk of VT in non-responders [24]. Possible limitations of this strategy include the risk of venous occlusion after initial implantation, the need for re-intervention in some non-responders after two years, and the technical skills required to place the lead into the conduction system.

Despite the large number of studies dedicated to predicting the probability of response to CRT, existing pre-implantation assessment algorithms remain imperfect, limiting their routine use in clinical practice. Nevertheless, the economic justification of CRT-P implantation as first-line therapy in patients with HFrEF is beyond doubt. CRT-P is more accessible in Russia due to its inclusion in the basic programme of mandatory health insurance. According to the Resolution of the Government of the Russian Federation of 27 December 2024, No. 1940 "On the Programme of State Guarantees of Free Medical Care to Citizens for 2025 and for the Planned Period of 2026 and 2027," reimbursement for CRT-P implantation amounts to 532,230 rubles, whereas CRT-D costs 1,281,144 rubles. This suggests a potential economic advantage from the more targeted use of CRT-D, reducing the number of such devices implanted under conditions of limited availability. An important clarification is that this strategy should be limited to patients with an indication for CRT and no evidence of VT substrate, confirmed by imaging modalities such as Echo, cardiac MRI with gadolinium, or invasive intracardiac electrophysiological study [3]. The algorithm for selecting between CRT-P and CRT-D is illustrated in Fig. 1. However, confirmation of this hypothesis requires further studies aimed at stratifying SCD risk in patients with indications for CRT.

CONCLUSION

The inclusion of funding for CRT device implantation in the basic programme of the Mandatory Health Insurance Fund has made CRT more accessible in our country, further emphasizing the relevance of the issue under discussion. It is likely that when selecting the optimal device for CRT, it is necessary to assess not only the baseline risk of SCD but also the probability of response to CRT and the potential for arrhythmic risk modification during therapy. The search for predictors and the development of prognostic systems aimed at evaluating such outcomes represent one of the priority tasks of contemporary cardiology, requiring prospective clinical studies that include domestic cohorts of patients with HFrEF.

REFERENCES

1. Polyakov DS, Fomin IV, Belenkov YuN, et al. Chronic heart failure in the Russian Federation: what has changed over 20 years of follow-up? Results of the EPOCH-CHF study. *Kardiologiia*. 2021;61(4): 4-14 (in Russ.). https://doi.org/10.18087/cardio.2021.4.n1628.

2. Vaduganathan M, Patel RB, Michel A, et al. Mode of Death in Heart Failure With Preserved Ejection Fraction. *J Am Coll Cardiol.* 2017;69: 556-69. https://doi.org/10.1016/j.jacc.2016.10.078.

3. Ilov NN, Palnikova OV, Stompel DR, et al. Risk stratification of sudden cardiac death in heart failure patients: is left ventricular ejection fraction alone sufficient? *Russian Journal of Cardiology.* 2021;26(1): 3959. (In Russ.). https://doi.org/10.15829/1560-4071-2021-3959.

4. Ilov NN, Palnikova OV, Stompel DR, et al. Clinical Predictors of Occurrence of Ventricular Tachyarrhythmias in Patients with Reduced Left Ventricle Ejection Fraction. Results of Single-Center Prospective Study. Kardiologiia. 2021;61(5): 32-40 (in Russ.). https://doi.org/10.18087/cardio.2021.5.n1480.

5. Revishvili ASh, Shlyahto EV, Popov SV, et al. Klinicheskie rekomendacii po primeneniyu kardioverterov-defibrillyatorov. In. Klinicheskie rekomendacii po provedeniyu elektrofiziologicheskih issledovanij, kateternoj ablyacii i primeneniyu implantiruemyh antiaritmicheskih ustrojstv. (Ed. Revishvili ASh, Shlyahto EV, Popov SV, et al.). Moscow 2017: 55-86 (in Russ.) ISBN 978-5-9500922-0-6.

6. Zaman S, Goldberger JJ, Kovoor P. Sudden Death Risk-Stratification in 2018-2019: The Old and the New. *Heart Lung Circ*. 2019;28: 57-64. https://doi.org/10.1016/j.hlc.2018.08.027.

7. Postol AS, Neminushchiy NM, Antipov GN, 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.

8. Glikson M, Israel C, Denmark C, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *EHJ.* 2021: 1-94. https://doi.org/10.1093/eurheartj/ehab364.

9. Yamamoto N, Noda T, Nakano M, et al. Clinical utility of QRS duration normalized to left ventricular volume for predicting cardiac resynchronization therapy efficacy in patients with "mid-range" QRS duration. *Heart Rhythm*. 2024;21: 855-62. https://doi.org/10.1016/j.hrthm.2024.02.019.

10. Amara N, Boveda S, Defaye P, et al. Implantable cardioverter-defibrillator therapy among patients with non-ischaemic vs. ischaemic cardiomyopathy for primary prevention of sudden cardiac death. *Europace.* 2018;20: 65-72. https://doi.org/10.1093/europace/euw379.

11. Galyavich A.S., Tereshchenko S.N., Uskach T.M. et al. 2024 Clinical practice guidelines for Chronic heart failure. *Russian Journal of Cardiology.* 2024;29(11): 6162. (In Russ.). https://doi.org/10.15829/1560-4071-2024-6162.

12. Wallentin L, Stenestrand U, Tabrizi F, et al. Influence of left bundle branch block on long-term mortality in a population with heart failure. *EHJ.* 2007:2449-55. https://doi.org/10.1093/eurheartj/ehm262.
13. Moustafa AT, Tang ASL, Khan HR. Conduction system pacing on track to replace CRT ? Review of conduction system pacing. *Front Cardiovasc Med.* 2023: 1-12. https://doi.org/10.3389/fcvm.2023.1220709.
14. Ilov NN, Stompel DR, Palnikova OV, et al. 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
15. Nakai T, Ikeya Y, Kogawa R, et al. What Are the Expectations for Cardiac Resynchronization Therapy ? A Validation of Two Response Definitions. *Journal of clinical medicine* 2021;10(3): 514. https://doi:10.3390/jcm10030514.
16. Bazoukis G, Naka KK, Alsheikh-Ali A, et al. Association of QRS narrowing with response to cardiac resynchronization therapy - a systematic review and meta-analysis of observational studies. *Heart Failure Reviews* 2020;25: 745-56. https://doi.org/10.1007/s10741-019-09839-5.
17. 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.
18. Stankovic I, Belmans A, Prinz C, et al. The association of volumetric response and long-term survival after cardiac resynchronization therapy *European Heart Journal - Cardiovascular Imaging.* 2017;18(10): 1109-17. https://doi.org/10.1093/ehjci/jex188.
19. Kuznetsov V.A., Soldatova A.M., Enina T.N. et al. Does the lack of left ventricular reverse remodeling always mean non - response to cardiac resynchronization therapy? *Terapevticheskii arkhiv.* 2019;91: 10-5 (in Russ.). https://doi.org/10.26442/00403660.2019.12.000102.
20. van der Heijden AC, Höke U, Thijssen J, et al. Super-responders to cardiac resynchronization therapy remain at risk for ventricular arrhythmias and benefit from defibrillator treatment. *European Journal of Heart Failure*. 2014;16: 1104-11. https://doi.org/10.1002/ejhf.152.
21. Linhart M, Doltra A, Acosta J, et al. Ventricular arrhythmia risk is associated with myocardial scar but not with response to cardiac resynchronization therapy. *EP Europace.* 2020;22: 1391-400. https://doi.org/10.1093/europace/euaa142.
22. Nakamura T, Fukuzawa K, Kiuchi K et al. Ventricular arrhythmia events in heart failure patients with cardiac resynchronization therapy with or without a defibrillator for primary prevention. *J Arrhythmia*. 2022;38: 1056-62. https://doi.org/10.1002/joa3.12795.
23. Cvijić M, Antolič B, Klemen L, et al. Repolarization heterogeneity in patients with cardiac resynchronization therapy and its relation to ventricular tachyarrhythmias. *Heart Rhythm.* 2018;15: 1784-90. https://doi.org/10.1016/j.hrthm.2018.06.023.
24. Deif B, Ballantyne B, Almehmadi F, et al. Cardiac resynchronization is pro-arrhythmic in the absence of reverse ventricular remodelling: a systematic review and meta-analysis. *Cardiovascular Research*. 2018;114(11): 1435-44. https://doi.org/10.1093/cvr/cvy182.
25. Schrage B, Lund LH, Melin M, et al. Cardiac resynchronization therapy with or without defibrillator in patients with heart failure. *EP Europace*. 2022;24: 48-57. https://doi.org/10.1093/europace/euab233.
26. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *The New England journal of medicine.* 2004;350(21): 2140-50. https://doi.org/10.1056/NEJMoa032423.
27. Linde C, Abraham WT, Gold MR et al. Randomized Trial of Cardiac Resynchronization in Mildly Symptomatic Heart Failure Patients and in Asymptomatic Patients With Left Ventricular Dysfunction and Previous Heart Failure Symptoms. *JACC.* 2008;52(23): 1834-43. https://doi.org/10.1016/j.jacc.2008.08.027.
28. Kober L, Thune JJ, Nielsen JC et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *The New England journal of medicine*. 2016;375: 1221-30. https://doi.org/10.1056/NEJMoa1608029.
29. 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: 3427-520. https://doi.org/10.1093/eurheartj/ehab364.
30. Ramalho D, Freitas J. Drug-induced life-threatening arrhythmias and sudden cardiac death: A clinical perspective of long QT, short QT and Brugada syndromes. *Revista Portuguesa de Cardiologia.* 2018;37: 435-46. https://doi.org/10.1016/j.repc.2017.07.010.
31. Tse G, Gong M, Wong WT, et al. The T(peak) - T(end) interval as an electrocardiographic risk marker of arrhythmic and mortality outcomes: A systematic review and meta-analysis. *Heart Rhythm.* 2017;14: 1131-7. https://doi.org/10.1016/j.hrthm.2017.05.031.
32. Pranata R, Yonas E, Vania R, et al. Electrocardiographic early repolarization is associated with future ventricular arrhythmia after acute myocardial infarction-Systematic Review and Meta-Analysis. *Journal of Arrhythmia.* 2019;35: 626-35. https://doi.org/10.1002/joa3.12196.
33. Aro AL, Reinier K, Rusinaru C, et al. Electrical risk score beyond the left ventricular ejection fraction: prediction of sudden cardiac death in the Oregon Sudden Unexpected Death Study and the Atherosclerosis Risk in Communities Study. *European Heart Journal.* 2017;38: 3017-25. https://doi.org/10.1093/eurheartj/ehx331.
34. van der Bijl P, Delgado V, Bax JJ. Imaging for sudden cardiac death risk stratification: Current perspective and future directions. *Progress in cardiovascular diseases.* 2019;62: 205-11. https://doi.org/10.1016/j.pcad.2019.04.005.
35. Chatterjee S, Bavishi C, Sardar P et al. Meta-analysis of left ventricular hypertrophy and sustained arrhythmias. *American Journal of Cardiology.* 2014;114: 1049-52. https://doi.org/10.1016/j.amjcard.2014.07.015.
36. Golukhova E.Z., Bulaeva N.I., Mrikaev D.V. et al. Prognostic value of left ventricular global longitudinal strain and mechanical dispersion by speckle tracking echocardiography

in patients with ischemic and nonischemic cardiomyopathy: a systematic review and meta-analysis. *Russian Journal of Cardiology*. 2022;27(3S): 5034 (in Russ.). https://doi.org/10.15829/1560-4071-2022-5034.
37. 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. *European Heart Journal.* 2022;43: 3997-4126. https://doi.org/10.1093/eurheartj/ehac262.
38. Golukhova EZ, Aleksandrova SA, Berdibekov BS. Predictive role of quantification of myocardial fibrosis using delayed contrast-enhanced magnetic resonance imaging in nonischemic dilated cardiomyopathies: a systematic review and meta-analysis. *Russian Journal of Cardiology.* 2021;26: 189-97 (in Russ.). https://doi.org/10.15829/1560-4071-2021-4776.
39. Shlevkov NB, Zhambeev AA, Gasparyan AZ, et al. Characteristic of fibrotic myocardial lesions associated with life-threatening ventricular tachyarrhythmias in patients with ischemic and non-ischemic cardiomyopathies. *Terapevticheskii arkhiv.* 2018;90(9): 42-7 (in Russ.). https://doi.org/10.26442/terarkh201890942-47.
40. Bazylev V.V., Ushakov R.Yu., Durmanov S.S. 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/10.35336/VA-1260.
41. Narins CR, Aktas MK, Chen AY, et al. Arrhythmic and Mortality Outcomes Among Ischemic Versus Nonischemic Cardiomyopathy Patients Receiving Primary ICD Therapy. *JACC Clinical Electrophysiology.* 2022;8: 1-11. https://doi.org/10.1016/j.jacep.2021.06.020.
42. 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. *Current Problems in Cardiology.* 2024;49: 102198. https://doi.org/10.1016/j.cpcardiol.2023.102198.
43. Burke AP, Virmani R. Pathophysiology of acute myocardial infarction. *Medical Clinics of North America*. 2007;91(4): 553-72; ix. https://doi.org/10.1016/j.mcna.2007.03.005.
44. Køber L, Thune JJ, Nielsen JC, et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. *The New England Journal of Medicine*. 2016;375: 1221-30. https://doi.org/10.1056/NEJMoa1608029.
45. Kadish A, Dyer A, Daubert JP et al. Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy. *The New England Journal of Medicine*. 2004;350: 2151-8. https://doi.org/10.1056/NEJMoa033088.
46. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *The New England Journal of Medicine*. 2002;346: 877-83. https://doi.org/10.1056/NEJMoa013474.
47. Gulati A, Jabbour A, Ismail TF, et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA* 2013;309: 896-908. https://doi.org/10.1001/jama.2013.1363.
48. Gold MR, Daubert J-C, Abraham WT, et al. Implantable Defibrillators Improve Survival in Patients With Mildly Symptomatic Heart Failure Receiving Cardiac Resynchronization Therapy. *Circulation Arrhythmia and Electrophysiology.* 2013;6: 1163-8. https://doi.org/10.1161/CIRCEP.113.000570.
49. Younis A, Goldberger JJ, Kutyifa V, et al. Predicted benefit of an implantable cardioverter-defibrillator: the MADIT-ICD benefit score. *European Heart Journal* 2021;42: 1676-84. https://doi.org/10.1093/eurheartj/ehaa1057.
50. 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. *Canadian Journal of Cardiology.* 2020;36: 1121-9. https://doi.org/10.1016/j.cjca.2019.11.009.
51. Reeder HT, Shen C, Buxton AE, et al. Joint Shock/Death Risk Prediction Model for Patients Considering Implantable Cardioverter-Defibrillators. *Circulation Cardiovascular Quality and Outcomes*. 2019;12: e005675. https://doi.org/10.1161/CIRCOUTCOMES.119.005675.
52. 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.
53. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *The New England Journal of Medicine.* 2009;361: 1329-38. https://doi.org/10.1056/NEJMoa0906431.
54. Goldenberg I, Aktas MK, Zareba W, et al. QRS Morphology and the Risk of Ventricular Tachyarrhythmia in Cardiac Resynchronization Therapy Recipients. *JACC Clinical Electrophysiology.* 2024;10: 16-26. https://doi.org/10.1016/j.jacep.2023.09.018.
55. Ilov NN, Boytsov SA, Nechepurenko A.A. Whether to implant a defibrillator or not? The Possibility of Using the MADIT-ICD Benefit Score Calculator in Real Practice. *Kardiologiia.* 2024;64(2): 27-33. (in Russ.). https://doi.org/10.18087/cardio.2024.2.n2447.
56. Mei DA, Gerra L, Imberti JF, et al. Cardiac resynchronization therapy (CRT) nonresponders in the contemporary era : A state-of-the-art review. *Heart Rhythm*. 2024: 1-11. https://doi.org/10.1016/j.hrthm.2024.05.057.
57. Cleland J, Freemantle N, Ghio S, et al. Predicting the Long-Term Effects of Cardiac Resynchronization Therapy on Mortality From Baseline Variables and the Early Response. *JACC*. 2008;52. https://doi.org/10.1016/j.jacc.2008.04.036.
58. Chumarnaya TV, Lyubimtseva TA, Solodushkin SI et al. Evaluation of the long-term effectiveness of cardiac resynchronization therapy. *Russian Journal of Cardiology*. 2021;26(7): 4531 (in Russ.). https://doi.org/10.15829/1560-4071-2021-4531.
59. Szabó KM, Tóth A, Nagy L, et al. Add-on Sacubitril/Valsartan Therapy Induces Left Ventricular Remodeling in Non-responders to Cardiac Resynchronization Therapy to a Similar Extent as in Heart Failure Patients Without Resynchronization. *Cardiology and Therapy.* 2024;13: 149-61. https://doi.org/10.1007/s40119-023-00346-1.
60. Jastrzębski M, Moskal P, Huybrechts W, et al. Left bundle branch-optimized cardiac resynchronization therapy (LOT-CRT): Results from an international LBBAP collaborative study group. *Heart Rhythm*. 2022;19: 13-21.

https://doi.org/10.1016/j.hrthm.2021.07.057.
61. Strauss DG. Differentiation between left bundle branch block and left ventricular hypertrophy: Implications for cardiac resynchronization therapy. *Journal of Electrocardiology.* 2012;45: 635-9. https://doi.org/10.1016/j.jelectrocard.2012.09.001.

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METHODS OF ANESTHESIOLOGICAL SUPPORT IN THE ELECTROPHYSIOLOGICAL LABORATORY

V.I.Steklov[1], E.A.Kim[1], M.V.Emelianenko[2], S.O.Lependin[1], F.G.Rzaev[3]

[1]Central Military Clinical Hospital named after P.V. Mandryka of the Ministry of Defense of the Russia, Russia, Moscow, 8a Bolshaya Olenya str; [2]Clinical City Hospital named after M.P. Konchalovsky, Russia, Moscow, Zelenograd, 2 Kashtanovaya str; [3]Clinical City Hospital named after I.V. Davydovsky, Russia, Moscow, 11 Yauzskaya str.

The article presents modern methods of anesthetic aids used in the case of such interventional and surgical interventions as implantation of a pacemaker, cardiac resynchronization therapy, cardioverter defibrillator and catheter ablation. The advantages, disadvantages and problematic issues of anesthesia are discussed depending on the type of intervention and the patient's condition. Based on the analyzed data, it is concluded that anesthesia during interventions in patients with arrhythmological profile is a global practice and emphasizes the positive impact of anesthesia methods on the quality and safety of procedures performed.

Key words: pacemaker; cardiac resynchronization therapy; cardioverter defibrillator; catheter ablation; anesthesia

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Corresponding Author: Steklov Vladimir, E-mail:vsteklov@yandex.ru

V.I.Steklov - ORCID ID 0000-0001-6790-9401, E.A.Kim - ORCID ID 0000-0002-9427-3207, M.V. Emelianenko - ORCID ID 0000-0002-9919-2203, S.O.Lependin - ORCID ID 0000-0001-8670-8787, F.G.Rzaev - ORCID ID 0000-0002-4094-7771

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In recent decades, there has been a marked increase in the number of procedures performed on the cardiac conduction system. Contemporary interventional catheter-based technologies, employing radiofrequency current, cryoablation, electroporation, and methods of electrocardiotherapy - including implantation of permanent pacemakers (PPM), implantable cardioverter-defibrillators (ICD), and devices for cardiac resynchronisation therapy (CRT) - have assumed a leading role in the management of various cardiac arrhythmias and conduction disorders, congestive heart failure, as well as in the primary and secondary prevention of sudden cardiac death (SCD) [1].

The implantation of cardiac rhythm management devices, catheter ablation (CA), and electrical cardioversion constitute interventions that require anaesthetic support. The principal objectives of anaesthetic management in the electrophysiology laboratory are the suppression of conscious perception, autonomic and nociceptive blockade, muscle relaxation, and the monitoring and, if necessary, substitution of vital functions.

At present, there are no clearly defined recommendations regarding the methods of pharmacological sedation, the agents of choice, or their dosing regimens tailored to the specific procedural requirements of particular arrhythmias. This article provides a comparative analysis of the published literature on the efficacy and safety of various anaesthetic strategies in the setting of arrhythmias, including general, regional, and infiltration anaesthesia, supplemented by pharmacological sedation or total intravenous anaesthesia [1, 2].

In light of the above, the objective of this study was to analyse the problem of anaesthetic management in patients with arrhythmias and conduction disorders undergoing interventional and surgical procedures.

DEFINITION AND CLASSIFICATION OF ANAESTHETIC METHODS

Most interventions involving the cardiac conduction system (implantation of an antiarrhythmic device, intracardiac electrophysiological study, electrical cardioversion, and catheter ablation [CA]) may be accompanied by general discomfort and painful sensations, while patient immobility is required to enhance the safety and quality of the procedure (particularly when using three-dimensional mapping and navigation systems). In global medical practice, various anaesthetic approaches are employed: local (infiltration, regional block), general (inhalational and non-inhalational anaesthesia, with respiratory support or complete substitution of external respiration), as well as combined and multimodal techniques [3].

Sedation, although a component of general anaesthesia, has in contemporary practice become widely applied as a stand-alone method during a variety of therapeutic and diagnostic procedures - both invasive and non-invasive - where it is necessary to ensure the patient's psychological comfort, alleviate agitation, maintain a required position, or in the context of intensive care [4].

Sedation (from the Latin sedatio - "calming"; also referred to as pharmacological sleep or medically induced coma) is defined as an artificially induced state achieved

by the administration of sedative agents, characterised by a controlled reduction or absence of consciousness, with preserved protective reflexes, adequate spontaneous breathing, and responsiveness to external physical stimuli [5]. Other authors define sedation more broadly as a combination of pharmacological and non-pharmacological measures aimed at ensuring the patient's physical and psychological comfort during medical procedures [6].

Pharmacological sedation (PS) attenuates the endocrine-metabolic stress response, improves the balance between oxygen delivery and consumption, and thereby contributes to a reduced incidence of intra- and postoperative complications [7].

Depending on the depth of wakefulness (consciousness), the following levels of PS are distinguished:

1. Minimal (anxiolysis) or mild (superficial) sedation: the patient remains awake and in verbal contact with the physician, though perception, cognitive function, and coordination may be impaired.
2. Moderate sedation: characterised by depression of consciousness. The patient responds to verbal commands or light tactile stimulation and is capable of cooperation. Airway support is not required, spontaneous ventilation remains adequate, and cardiovascular function is preserved.
3. Deep sedation: verbal contact with the patient is lost; the patient is asleep but responds to strong (painful) stimuli. Airway support may be required, with possible impairment of spontaneous ventilation and cardiovascular function.
4. General anaesthesia (GA): consciousness is completely suppressed for the duration of the intervention using intravenous hypnotics or inhalational anaesthetics. External respiration is maintained by mechanical ventilation [8].

Approaches to anaesthetic management in the electrophysiology laboratory may therefore vary - from anxiolysis to general anaesthesia with full substitution of respiratory function - depending on the type of arrhythmia and the nature of the intervention.

ANAESTHETIC MANAGEMENT DURING PACEMAKER IMPLANTATION

The initial stages of implanting electronic devices for electrotherapy required thoracotomy; however, since the late 1980s this procedure has become minimally invasive and is now performed without general anaesthesia [9]. In routine practice it is carried out under local infiltration anaesthesia. In recent years, there has been increasing application of serratus anterior plane block (SAPB), blockade of the intercostobrachial and intercostal nerves from the third to the sixth, as well as of the long thoracic nerve (PECS II block), performed under ultrasound guidance in the setting of mild or moderate pharmacological sedation (PS) [10, 12].

Authors have reported the feasibility and effectiveness of SAPB in providing anaesthesia/analgesia during subcutaneous ICD implantation, enabling a reduction in the requirement for sedation and a shorter procedural duration. Results from a single-centre study demonstrated that local anaesthesia with sedation is a safe and feasible option for cardiac rhythm management device implantation, including complex procedures such as ICD and cardiac resynchronisation therapy defibrillator (CRT-D) implantation [13]. At the same time, this approach cannot be relied upon as a stand-alone method owing to the technical features of regional blockade and pharmacological sedation or GA cannot be excluded. In our view, SAPB at present can be considered an adjunctive component within a multimodal anaesthetic strategy.

For PS, the benzodiazepine sedative midazolam is most commonly used at a dose of 2-4 mg, or 1-2 mg in patients aged over 75 years and weighing less than 70 kg, in combination with an opioid analgesic - fentanyl (50-100 μg), nalbuphine (0.27 ± 0.05 mg/kg), or other opioid agents. The advantages of midazolam over other benzodiazepines had already been recognised in the 1980s: rapid onset of action, short duration after bolus administration, and the ability to induce anterograde amnesia. These properties provide broad opportunities for use in invasive interventions, eliminating procedure-related discomfort, while the rapid elimination of midazolam ensures adequate spontaneous respiration [14, 15]. The report by D. J. Fox and colleagues confirmed the safety and efficacy of this sedation method in the implantation of more than 500 ICD and CRT devices [16].

In current practice, alongside midazolam, 1% propofol solution is increasingly used during cardiac rhythm management device implantation [17]. Continuous intravenous administration of propofol provides rapid recovery, reduced postoperative nausea and vomiting, and shorter post-anaesthesia recovery times [18]. However, T. Trouvé-Buisson and colleagues, in a study involving 269 patients undergoing cardiac electronic device implantation and lead extraction under propofol, reported respiratory complications in 19% of cases, including hypoxia (86%), apnoea (30%), and aspiration (2%) [19].

In a retrospective analysis of 197 ICD or CRT implantations using propofol and midazolam, K. Pandya and colleagues found that these agents, administered for moderate sedation, induced hypotension in 25% of ICD patients and in 56% of CRT patients, with correction of arterial blood pressure using inotropes required in 10% of ICD procedures and in 24% of CRT procedures [20].

ANAESTHETIC MANAGEMENT DURING CARDIAC RESYNCHRONISATION THERAPY DEVICE IMPLANTATION

Among the most vulnerable patients in the electrophysiology laboratory are candidates for CRT. These patients typically present with advanced heart failure, severe impairment of left ventricular systolic function, and mechanical dyssynchrony resulting from bundle branch block with a QRS duration exceeding 130-150 ms. All these factors, together with the longer procedural time required for positioning the left ventricular lead into the target vein of the coronary sinus, substantially increase the risk of intraoperative complications.

Initially, during CRT implantation, the left ventricular lead was fixed epicardially to the lateral wall of the left ventricle, which necessitated thoracotomy under GA. Today, however, epicardial leads are in most cases successfully placed through the venous system of the heart without thoracotomy and without GA [21].

Many investigators have demonstrated that performing the procedure under local anaesthesia is safer and

does not adversely affect the procedural outcome. Thus, in a retrospective analysis of 341 CRT implantations performed under GA, hypotension occurred in 43% of cases, compared with only 4% of cases when local anaesthesia combined with mild or moderate PS was used. Inotropic support was required to correct hypotension in one-quarter of patients [22]. Another study yielded similar results: hypotension occurred more frequently in patients undergoing GA (26% versus 4%), who also more frequently required inotropic agents and anticholinergics [23].

Deep sedation may be necessary during CRT implantation in restless or agitated patients, in those who continue to experience pain despite local anaesthesia, or in cases where patients cannot tolerate prolonged supine positioning due to comorbidities. In such situations, midazolam or fentanyl may be administered to alleviate symptoms and improve patient comfort. Importantly, no significant differences in the length of hospital stay were observed with respect to the anaesthetic technique used [24].

ANAESTHETIC MANAGEMENT DURING SUBCUTANEOUS CARDIOVERTER-DEFIBRILLATOR IMPLANTATION

In the 1970s, Mieczysław Mirowski and colleagues developed the first implantable defibrillator which, despite numerous design limitations, successfully fulfilled its intended function in 97% of cases. In 1980, the first human implantation of an ICD was performed [25].

Anaesthetic management for ICD implantation is generally similar to that for pacemaker or CRT device implantation. When intraoperative ICD testing is required, deep sedation with propofol combined with fentanyl is typically used [16, 26].

Implantation of a subcutaneous ICD (S-ICD) requires different anaesthetic management, as the device is positioned subcutaneously along the left anterior axillary line. Placement of the shock electrode involves creating a subcutaneous tunnel parallel to the left sternal border. Extensive tunnelling and defibrillator testing with determination of the shock threshold necessitate either a deep level of sedation or GA [27]. However, anaesthetic management has received limited attention in the published results of two large clinical trials [28]. According to some authors, patients undergoing the procedure under moderate or deep PS experienced pain and discomfort during tunnelling and ICD testing, which required deepening of anaesthesia but without the use of muscle relaxants or mechanical ventilation. To relieve postoperative pain, local anaesthetics were infiltrated subcutaneously at the end of the procedure [29].

The standard approach to S-ICD implantation often requires GA or deep sedation under the supervision of an anaesthesiologist. More recently, serratus anterior plane block under ultrasound guidance, in combination with parasternal blockade, has been employed to provide anaesthesia/analgesia and reduce the need for sedation during S-ICD implantation [10-13].

Thus, most procedures for the implantation of electronic antiarrhythmic devices can today be performed under local anaesthesia with varying levels of PS, without the need for GA with muscle relaxation and mechanical ventilation. In certain patients (particularly undergoing CRT or ICD implantation), administration of 1% propofol as part of anaesthetic management may lead to intraoperative hypotension and/or depression of spontaneous respiration. Such cases necessitate continuous, careful monitoring of the patient's condition by the attending anaesthesiologist and represent an additional psychological burden for the medical staff.

ANAESTHETIC MANAGEMENT DURING CATHETER ABLATION OF ARRHYTHMIAS

Anaesthesia for catheter ablation of atrial fibrillation

over time, catheter ablation (CA) of atrial fibrillation (AF) has evolved from an experimental procedure into a first-line therapy, as evidenced by numerous publications [30]. During CA, electrical isolation of the pulmonary veins from the left atrium is achieved using either radiofrequency current or cryothermal energy [31]. Since AF ablation is associated with painful sensations and requires the patient to remain supine and immobile for an extended period, it is considered appropriate to perform this procedure under GA with mechanical ventilation (MV) or under total intravenous anaesthesia (TIVA) with spontaneous respiration. An ideal anaesthetic technique that fully satisfies both operator and patient has yet to be established.

Several publications, based on large clinical datasets, have shown that GA with MV is associated with higher procedural success rates and shorter procedural duration compared with moderate sedation using midazolam (Dormicum) and fentanyl (88% versus 69%, $p<0.001$; and 2.4±1.4 versus 3.6±1.1 hours, $p<0.001$) [32]. The authors suggested that the absence of muscular contractions and controlled ventilation during GA + MV facilitated more stable positioning of the ablation catheter during energy delivery. With respect to complication rates, these were low and comparable between AF ablation performed under GA with MV and that performed under moderate or deep pharmacological sedation (PS) in combination with opioids.

Other investigators have likewise reported that AF ablation under GA + MV demonstrated better tolerability, more positive patient perception of the procedure, higher therapeutic efficacy, and improved quality of life compared with moderate or deep sedation with spontaneous respiration [31]. Another small randomised study indicated that patients undergoing AF ablation under intravenous anaesthesia with spontaneous respiration had higher arterial $PaCO_2$ levels on blood gas analysis, whereas complication and recurrence rates did not differ compared with GA + MV [34].

A meta-analysis and systematic review of studies comparing AF ablation outcomes under GA + MV versus intravenous anaesthesia with spontaneous respiration concluded that CA performed with GA + MV yielded superior procedural results. However, no significant differences were observed between the two groups in terms of procedural duration or fluoroscopy time [35].

Nevertheless, alongside its advantages, GA also has drawbacks. Potential limitations of GA during AF ablation include the absence of intraoperative patient feed-

back, the need for inotropic support in certain patients, an increased risk of phrenic nerve injury, and higher costs [36]. An interesting study conducted by J. S. Goode Jr. and colleagues (2006) compared methods of ventilatory support between controlled MV and high-frequency jet ventilation (HFJV), demonstrating that HFJV provided greater stability of the posterior left atrial wall, thereby facilitating catheter ablation [37].

Among pharmacological agents used during AF ablation, propofol and the combination of midazolam with fentanyl are most frequently employed. The most commonly administered opioids are remifentanil and fentanyl [35].

The principal drawbacks of propofol include respiratory depression and hypotension, difficulty in maintaining optimal catheter stability due to disturbances in spontaneous respiration, longer procedural and fluoroscopy times, and a higher incidence of arrhythmia recurrence. In 2011, H. Kottkamp and colleagues conducted a prospective observational study of 650 patients who underwent AF ablation under deep sedation with midazolam and fentanyl followed by propofol infusion. In this cohort, severe hypotension occurred in 2.3% of patients, 15% required vasopressors, 1.5% developed severe hypoxia, and 1.2% required mechanical ventilation with positive end-expiratory pressure [38].

Q. Liu and colleagues (2011) reported a dose-dependent relationship between propofol and arrhythmia inducibility. Their study documented cases of supraventricular tachycardia transforming into ventricular tachycardia, as well as suppression of the electrophysiological properties of the cardiac conduction system under the influence of propofol. Furthermore, clinically relevant doses of propofol were shown to suppress potassium, sodium, and calcium channels in cardiomyocytes and to shorten action potential duration. The authors concluded that propofol exerts a cumulative negative effect on the cardiac conduction system [39].

Improved respiratory homeostasis and favourable long-term procedural outcomes have been associated with the use of non-invasive ventilation (NIV) during deep sedation with propofol in high-risk patients, such as those with obstructive sleep apnoea, elevated body mass index, or prolonged procedural duration [40]. The methods of respiratory support in the anaesthetic management of such interventions warrant a separate review due to their complexity and specific requirements.

A relatively new sedative agent, dexmedetomidine (an α_2-adrenoceptor agonist with a short half-life), is characterised by dose-dependent sedative effects, mild analgesia, and less pronounced respiratory depression compared with propofol [41]. In a 2014 study, J. S. Cho and colleagues concluded that dexmedetomidine combined with remifentanil, compared with midazolam plus remifentanil, provided deeper sedation, less respiratory depression, superior analgesia, and greater operator satisfaction during AF ablation - even at lower therapeutic doses of remifentanil [42]. However, the potential adverse effects of dexmedetomidine include bradycardia, conduction disturbances, and hypotension.

Taken together, these studies indicate that the optimal anaesthetic approach for AF ablation remains unresolved. In most investigations, the choice has been between GA with mechanical ventilation, TIVA, or superficial to moderate pharmacological sedation of varying depth with spontaneous respiration, sometimes combined with non-invasive ventilatory support.

GA with mechanical ventilation necessitates tracheal intubation, use of advanced equipment for continuous monitoring of vital parameters, and administration of muscle relaxants. By contrast, TIVA with preserved spontaneous respiration does not necessarily require intubation and mechanical ventilation as obligatory components. However, given the duration and invasiveness of AF ablation, the accumulation of sedative and analgesic agents, and the comorbidity of patients, this possibility cannot be entirely excluded. Nevertheless, patients may remain able to purposefully respond to verbal commands during CA. In all cases, the marked depression of consciousness associated with sedative use mandates continuous monitoring of respiratory parameters, haemodynamics, and depth of sedation [7].

Recent data from a meta-analysis and systematic review by N. Pang and colleagues (2022) compared GA with mechanical ventilation/deep sedation (DS) with TIVA or superficial to moderate sedation with spontaneous respiration in AF ablation, analysing procedural and clinical outcomes [43]. Notably, the authors grouped together patients who underwent GA with mechanical ventilation and those who received DS (defined in domestic practice as TIVA with preserved spontaneous respiration). They emphasised that GA with mechanical ventilation and DS achieve a similar depth of sedation, sufficient to maintain patient immobility. The main distinctions lay in airway management and anaesthetic dosing; however, when airway reflexes were not preserved during DS, the same level of respiratory support was provided as under GA with mechanical ventilation. Therefore, these patients were included within a single analytical group.

It is important to note that this meta-analysis was conducted in accordance with the Cochrane standards of evidence-based medicine: heterogeneity between studies was assessed using the I^2 statistic and Cochran's Q test; sensitivity analyses, including meta-regression, were performed in cases of high heterogeneity; and publication bias was evaluated using funnel plots and Egger's test. These methodological considerations warrant a more detailed review of the findings.

In this study, the authors analysed trials including 2,418 patients conducted across centres in China, the United Kingdom, and other countries. The mean age of participants, predominantly male (70.5%), was 61.2 years. In all studies, radiofrequency energy was used to achieve pulmonary vein isolation, with additional ablation performed where necessary.

The meta-analysis demonstrated that GA with MV or DS was associated with a lower recurrence rate following AF ablation ($p = 0.03$) compared with superficial or moderate sedation with spontaneous respiration.

The study also examined costs and complications according to anaesthetic modality. No significant differences were found between the two groups in procedural duration ($p = 0.35$) or fluoroscopy time ($p = 0.60$), whereas ablation

time was shorter in the GA + MV/DS group ($p = 0.008$). The overall complication rate and the incidence of serious adverse events were not statistically different between the two groups ($p = 0.07$ and $p = 0.94$, respectively).

On the basis of their findings, the authors concluded that GA + MV/DS may reduce the risk of AF recurrence after ablation without increasing complication rates, and may shorten ablation time, although no statistical differences were observed in other procedural parameters compared with light/moderate sedation with spontaneous respiration. Summarising the findings of the reviewed studies, the authors emphasised the significant role of anaesthesiologists in electrophysiology laboratory procedures [44].

Similar conclusions are supported by the results of a survey of 479 anaesthesiologists and cardiologists on the topic of anaesthetic support for minimally invasive cardiac procedures. In this survey, 92% of respondents indicated that the involvement of anaesthesiologists increases patient satisfaction with the procedure. However, integration of anaesthesiologists into cardiology practice remains slow: only 66% of respondents reported increased participation of anaesthesiologists in minimally invasive procedures [45].

In our view, GA and DS with mechanical ventilation or non-invasive ventilatory support are the preferred anaesthetic strategies during AF ablation, particularly in cases where prolonged procedures are anticipated in elderly and/or comorbid patients. The involvement of anaesthesiologists in minimally invasive cardiac procedures enhances safety and improves the quality of care.

More recently, inhalational anaesthesia (inhalational sedation) has been increasingly applied during radiofrequency AF ablation. The principal advantage of inhalational anaesthesia is its reliable hypnotic effect, provided by effective and safe halogenated anaesthetics such as isoflurane and sevoflurane. Inhalational anaesthesia may be administered either via a laryngeal mask or tracheal intubation [44]. Its advantages include controllability (stable concentrations without haemodynamic instability, and the ability to increase, reduce, or discontinue gas administration within seconds), the low toxicity of isoflurane (not metabolised in the body and excreted via the lungs), and rapid recovery. The principal drawback of inhalational anaesthesia is the high cost of technical maintenance and its insufficient analgesic effect, often requiring the administration of supplementary agents.

Anaesthetic management during catheter ablation of supraventricular tachycardia

the primary objective of sedation during electrophysiological study (EPS) and ablation for supraventricular tachycardia (SVT) is to achieve an appropriate balance between patient comfort and a level of sedation that still permits arrhythmia induction. CA for SVT is generally performed under TIVA with mild to moderate sedation, using benzodiazepines and opioids while maintaining spontaneous respiration. In particular clinical situations - such as in agitated patients, those who continue to report pain despite local anaesthesia, patients unable to tolerate prolonged supine positioning, or those with significant comorbidities - the procedure may be carried out under GA with MV or DS.

It should be noted that any degree of sedation reduces arrhythmia inducibility. Unlike propofol and dexmedetomidine, benzodiazepines combined with opioids exert less influence on the electrophysiological properties of the conduction system, including those of the accessory pathway [44-46]. Dexmedetomidine suppresses the automaticity of the sinoatrial node and has a negative dromotropic effect on AV conduction. These actions account for the reduced inducibility of SVT during EPS and CA [47]. For this reason, the use of dexmedetomidine in this patient category within the electrophysiology laboratory is not recommended.

Anaesthetic management during catheter ablation of ventricular arrhythmias

when selecting sedation strategies for CA of ventricular arrhythmias (VA), several factors must be considered, including patient age, comorbidities, access approach (endocardial and/or epicardial ablation), risk of airway obstruction, and patient preference. GA or DS provides patient comfort, facilitates epicardial access, and creates optimal conditions for catheter manipulation during mapping and ablation, particularly in prolonged procedures. However, the main drawback of GA/DS is the potential suppression of VA. The elimination of psychological stress and the associated changes in autonomic tone under GA/DS may reduce the spontaneous manifestation of catecholamine-dependent VA and the inducibility of re-entrant VT. Inhalational anaesthetics (sevoflurane, isoflurane) prolong action potential duration and ventricular refractoriness, while dexmedetomidine decreases sympathetic tone [44]. For these reasons, the use of such agents during CA should be avoided [48].

As noted previously, patients receiving dexmedetomidine demonstrated a significant reduction in the overall frequency of ventricular arrhythmias (OR 0.35, 95% CI 0.16-0.76) and a marked reduction in VT risk compared with controls (OR 0.25, 95% CI 0.08-0.80, $I^2 = 20\%$) [49].

Moreover, most anaesthetic agents used for sedation and analgesia reduce myocardial contractility and blood pressure, with the risk of worsening haemodynamic instability during VT, sometimes necessitating vasopressor support. Notably, the use of agents such as propofol in VA patients with severe left ventricular dysfunction may cause profound hypotension during CA. The use of such anaesthetics must therefore be strictly justified. Nevertheless, the effects of propofol on the electrophysiological properties of the heart are complex, and in some cases suppression of VA may be beneficial - for example, in terminating ventricular tachycardia or suppressing ventricular electrical storm [50].

Another disadvantage of GA/DS with muscle relaxants is the increased risk of phrenic nerve injury, since pharmacological muscle relaxation hampers identification of the phrenic nerve during epicardial ablation [51].

No definitive consensus has been reached regarding the optimal sedation strategy during CA in patients with idiopathic VA (premature ventricular contractions and/or ventricular tachycardia). In many centres, CA in this setting is performed under mild sedation with benzodiazepines. In some patients with idiopathic VT, however, administration of these agents negatively affects arrhythmia inducibility.

For this reason, in our practice we endeavour to avoid their use and resort to mild or moderate sedation only in selected clinical situations [52].

CONCLUSION

Thus, during pacemaker implantation and CA for AF, supraventricular arrhythmias, and ventricular arrhythmias, the following principles should be observed: the involvement of anaesthesiologists in minimally invasive cardiac procedures enhances the quality and safety of care. Patients undergoing arrhythmia-related interventions require thorough preoperative assessment to determine the optimal sedation and analgesia strategy, with an anaesthetic plan tailored to the individual. Comorbidities (such as morbid obesity, chronic respiratory disease), chronic use of psychoactive drugs and/or opioid analgesics for pain management, and similar factors should be decisive in favour of GA with mechanical ventilation (GA + MV).

It is prudent to avoid GA and deeper levels of sedation in patients undergoing pacemaker implantation (with the exception of subcutaneous implantable cardioverter-defibrillators [S-ICDs]); adequate local or regional anaesthesia is critical for patient comfort. CA for supraventricular arrhythmias or idiopathic ventricular tachycardia, particularly when the arrhythmia is suspected to be catecholamine-sensitive or was non-inducible during a prior procedure, should likewise be performed with minimal anaesthesia.

In the absence of formal indications for GA + MV, moderate or deep sedation (e.g. propofol infusion, midazolam, fentanyl) combined with non-invasive ventilatory support and intensive monitoring of vital functions may be used in haemodynamically stable patients with various arrhythmias when a prolonged procedure or more invasive approaches (such as epicardial access) are anticipated. GA + MV or DS with ventilatory support remain the preferred anaesthetic strategies during CA for AF and epicardial ablation of ventricular arrhythmias, particularly when lengthy procedures are expected in elderly and/or comorbid patients.

It should also be noted that, according to recent studies, anaesthetic choice is determined primarily by patient characteristics and institutional factors, without significant impact on long-term outcomes such as AF recurrence or complication rates.

REFERENCES

1. Bokeria LA, Revishvili ASh. Interventsionnaya i khirurgicheskaya aritmologiya: sovremennoe sostoyanie, problemy i perspektivy razvitiya. *Meditsinskaya tekhnika*. 2002;6: 7-8. (In Russ.)
2. Palmisano P, Ziacchi M, Angeletti A, et al. The Practice of Deep Sedation in Electrophysiology and Cardiac Pacing Laboratories: Results of an Italian Survey Promoted by the AIAC (Italian Association of Arrhythmology and Cardiac Pacing). *J Clin Med*. 2021;10(21): 5035. https://doi.org/10.3390/jcm10215035.
3. Potievskaya VI, Zabolotskikh IB, Gridchik IE, et al. Sedation of patients in intensive care units. Guidelines. *Russian Journal of Anesthesiology and Reanimatology*. 2023;(5): 624. (In Russ.). https://doi.org/10.17116/anaesthesiology20230516.
4. Lü F, Lin J, Benditt DG. Conscious sedation and anesthesia in the cardiac electrophysiology laboratory. *J Cardiovasc Electrophysiol*. 2013;24(2): 237-245. https://doi.org/10.1111/jce.12001.
5. Essandoh MK, Mark GE, Aasbo JD, et al. Anesthesia for subcutaneous implantable cardioverter-defibrillator implantation: Perspectives from the clinical experience of a U.S. panel of physicians. *Pacing Clin Electrophysiol.* 2018;41(7): 807-816. https://doi.org/10.1111/pace.13364.
6. Anesthesiology: national guidelines: a short edition / edited by A.A. Bunyatyan, V.M. Mizikov. Moscow: GEOTAR-Media, 2020. 656 p. (In Russ.). ISBN 978-5-9704-5709-2.
7. Walsh TS, Kydonaki K, Antonelli J, et al. Staff education, regular sedation and analgesia quality feedback, and a sedation monitoring technology for improving sedation and analgesia quality for critically ill, mechanically ventilated patients: a cluster randomised trial. *Lancet Respir Med*. 2016;4(10):807-817. https://doi.org/10.1016/S2213-2600(16)30178-3.
8. Kozlov IA. Modern approaches to sedation in intensive care units. *Meditsinskij alfavit.* 2013;1(38): 2232. (In Russ.).
9. Fitzpatrick AP, Lesh MD, Epstein LM, et al. Electrophysiological laboratory, electrophysiologist-implanted, nonthoracotomy-implantable cardioverter/defibrillators. *Circulation*. 1994;89(6): 2503-2508. https://doi.org/10.1161/01.cir.89.6.2503.
10. Zhang Y, Min J, Chen S. Analgesic Efficacy of Regional Anesthesia of the Hemithorax in Patients Undergoing Subcutaneous Implantable Cardioverter-Defibrillator Placement. *J Cardiothorac Vasc Anesth*. 2021;35(11): 3288-3293. https://doi.org/10.1053/j.jvca.2021.02.052.
11. Szamborski M, Janc J, Leśnik P, et al. Ultrasound-Guided Pectoserratus Plane Block and Superficial Serratus Anterior Plane Block for Subcutaneous Implantable Cardioverter-Defibrillator Implantation: A Comparative Study. *Med Sci Monit*. 2023;29: e940541. Published 2023 Jul 21. https://doi.org/10.12659/MSM.940541.
12. Uran C, Giojelli A, Borgogna DA, et al. Ultrasound-guided serratus anterior plane block combined with parasternal block in subcutaneous implantable cardioverter defibrillator implantation: Results of a pilot study. *Pacing Clin Electrophysiol*. 2020;43(7): 705-712. https://doi.org/10.1111/pace.13944.
13. Ziacchi M, Bisignani G, Palmisano P, et al. Serratus anterior plane block in subcutaneous implantable cardioverter defibrillator implantation: A case-control analysis. *J Cardiovasc Electrophysiol.* 2019;31: 144-149. https://doi.org/10.1111/jce.14293.
14. Sumin SA. Midazolam: opportunities and prospects for use in intensive care. *Medical alphabet*. 2017;3(29): 47-52. (In Russ.).
15. Miśkowiec D, Kasprzak JD, Wejner-Mik P, et al. Conscious sedation during cryoballoon ablation of atrial fibrillation: a feasibility and safety study. *Minerva Cardioangiol*. 2018;66(2): 143-151. https://doi.org/10.23736/

S0026-4725.17.04505-4
16. Fox DJ, Davidson NC, Bennett DH, et al. Safety and acceptability of implantation of internal cardioverter-defibrillators under local anesthetic and conscious sedation. *Pacing Clin Electrophysiol.* 2007;30: 992-997. https://doi.org/10.1111/j.1540-8159.2007.00816.x.
17. Marquié C, Duchemin A, Klug D, et al. Can we implant cardioverter defibrillator under minimal sedation?. *Europace*. 2007;9(7): 545-550. https://doi.org/10.1093/europace/eum060.
18. Kaya E, Südkamp H, Lortz J, et al. Feasibility and safety of using local anaesthesia with conscious sedation during complex cardiac implantable electronic device procedures. *Sci Rep.* 2018;8(1): 7103. https://doi.org/10.1038/s41598-018-25457-x.
19. Trouvé-Buisson T, Arvieux L, Bedague D, et al. Anaesthesiological support in a cardiac electrophysiology laboratory: a single-centre prospective observational study. *Eur J Anaesthesiol.* 2013 Nov;30(11): 658-63. https://doi.org/10.1097/EJA.0b013e3283626095.
20. Pandya K, Patel MB, Natla J, et al. Predictors of hemodynamic compromise with propofol during defibrillator implantation: a single center experience. *J Interv Card Electrophysiol.* 2009;25(2): 145-151. https://doi.org/10.1007/s10840-008-9355-6.
21. Shatalov KV, Serguladze SY, Abdurazakov MA, et al. Cardiac resynchronization therapy: alternative methods of left ventricular electrode implantation. *Minimally Invasive Cardiovascular Surgery*. 2024;3(3): 39-49. (In Russ.).
22. Pfau G, Schilling T, Kozian A, et al. Outcome after implantation of cardiac resynchronization/defibrillation systems in patients with congestive heart failure and left bundle-branch block. *J Cardiothorac Vasc Anesth*. 2010;24(1): 30-36. https://doi.org/10.1053/j.jvca.2009.07.009
23. Theron P, Guha K, Mantziari L, et al. General anesthesia versus sedation for implantation of a biventricular pacing device for cardiac resynchronization therapy. *J Cardiothorac Vasc Anesth.* 2014;28: 280-284. https://doi.org/10.1053/j.jvca.2013.07.008.
24. Looi KL, Lee AS, Cole K, et al. Conscious sedation and analgesia use in cardiac device implantation. *Int J Cardiol.* 2013;168(1): 561-563. https://doi.org/10.1016/j.ijcard.2013.01.167.
25. Ladeev AYu, Marochkov AV, Dmitrieva VN. The history of the creation and development of implantable cardioverter defibrillators. *Surgery news.* 2016;24(4): 317-327. (In Russ) https://doi.org/10.18484/2305-0047.2016.4.317.
26. Sayfo S, Vakil KP, Alqaqa'a A, et al. A retrospective analysis of proceduralist-directed, nurse-administered propofol sedation for implantable cardioverter-defibrillator procedures. *Heart Rhythm*. 2012;9(3): 342-346. https://doi.org/10.1016/j.hrthm.2011.10.009.
27. Cappato R, Smith WM, Hood MA, et al. Subcutaneous chronic implantable defibrillation systems in humans. *J Interv Card Electrophysiol.* 2012;34(3): 325-332. https://doi.org/10.1007/s10840-012-9665-6.
28. Burke MC, Gold MR, Knight BP, et al. Safety and Efficacy of the Totally Subcutaneous Implantable Defibrillator: 2-Year Results From a Pooled Analysis of the IDE Study and EFFORTLESS Registry. *J Am Coll Cardiol.* 2015;65(16): 1605-1615. https://doi.org/10.1016/j.jacc.2015.02.047.
29. Essandoh MK, Portillo JG, Weiss R, et al. Anesthesia care for subcutaneous implantable. *J Clin Anesth.* 2016;31: 53-59. https://doi.org/10.1016/j.jclinane.2015.11.009.
30. Blomström-Lundqvist C, Gizurarson S, Schwieler J, et al. Effect of Catheter Ablation vs Antiarrhythmic Medication on Quality of Life in Patients With Atrial Fibrillation: The CAPTAF Randomized Clinical Trial. *JAMA*. 2019;321(11): 1059-1068. https://doi.org/10.1001/jama.2019.0335.
31. Hoffmann E, Straube F, Wegscheider K, et al. Outcomes of cryoballoon or radiofrequency ablation in symptomatic paroxysmal or persistent atrial fibrillation. *Europace*. 2019;21(9): 1313-1324. https://doi.org/10.1093/europace/euz155.
32. Di Biase L, Conti S, Mohanty P, et al. General anesthesia reduces the prevalence of pulmonary vein reconnection during repeat ablation when compared with conscious sedation: results from a randomized study. *Heart Rhythm.* 2011;8(3): 368-372. https://doi.org/10.1016/j.hrthm.2010.10.043.
33. Stašková K, Bulava A, Tesařík R, et al. Radiofrequency catheter ablation of atrial fibrillation performed under general anesthesia: results of a unicentric randomized trial. *Vnitr Lek.* 2017;63(3): 163-169.
34. Firme EB, Cavalcanti IL, Barrucand L, et.al. Curative ablation of atrial fibrillation: comparison between deep sedation and general anesthesia. *Rev Col Bras Cir*. 2012;39(6): 462-468. https://doi.org/10.1590/s0100-69912012000600004.
35. Li Ka Hou C, Sang T, Chan C, et al. Anesthesia use in catheter ablation for atrial fibrillation: a systematic review and meta-analysis of observational studies. *Heart Asia*. 2019;11(2): e011155. https://doi.org/10.1136/heartasia-2018-011155.
36. Gerstein NS, Young A, Schulman PM, et al. Sedation in the Electrophysiology Laboratory: A Multidisciplinary Review. *J Am Heart Assoc.* 2016;5(6): e003629. https://doi.org/10.1161/JAHA.116.003629.
37. Goode JS Jr, Taylor RL, Buffington CW, et al. High-frequency jet ventilation: utility in posterior left atrial catheter ablation. *Heart Rhythm.* 2006;3(1): 13-19. https://doi.org/10.1016/j.hrthm.2005.09.013.
38. Kottkamp H, Hindricks G, Eitel C, et al. Deep sedation for catheter ablation of atrial fibrillation: a prospective study in 650 consecutive patients. *J Cardiovasc Electrophysiol.* 2011;22(12): 1339-1343. https://doi.org/10.1111/j.1540-8167.2011.02120.x.
39. Liu Q, Kong AL, Chen R, et al. Propofol and arrhythmias: two sides of the coin. *Acta Pharmacol Sin.* 2011 Jun;32(6): 817-23. https://doi.org/10.1038/aps.2011.42
40. Vevecka A, Schwab C, Forkmann M, et al. Predictive Factors and safety of noninvasive mechanical ventilation in combination with propofol deep sedation in left atrial ablation procedures. *Am J Cardiol.* 2019;124(2): 233-238. https://doi.org/10.1016/j.amjcard.2019.04.013.
41. Sairaku A, Yoshida Y, Hirayama H, et al. Procedural sedation with dexmedetomidine during ablation of atrial fibrillation: a randomized controlled trial. *Europace*. 2014;16(7): 994-999. https://doi.org/10.1093/europace/eut363.

42. Cho JS, Shim JK, Na S, et al. Improved sedation with dexmedetomidine-remifentanil compared with midazolam-remifentanil during catheter ablation of atrial fibrillation: a randomized, controlled trial. *Europace*. 2014;16(7): 1000-6. https://doi.org/10.1093/europace/eut365.
43. Pang N, Gao J, Zhang N, et al. Comparison of the Different Anesthesia Strategies for Atrial Fibrillation Catheter Ablation: A Systematic Review and Meta-Analysis. *Cardiol Res Pract*. 2022;2022: 1124372. https://doi.org/10.1155/2022/1124372.
44. Yildiz M, Yilmaz Ak H, Oksen D, et al. Anesthetic Management In Electrophysiology Laboratory: A Multidisciplinary Review. *J Atr Fibrillation*. 2018;10(5):1775. https://doi.org/10.4022/jafib.1775.
45. Nelson EW, Woltz EM, Wolf BJ, et al. A Survey of Current Anesthesia Trends for Electrophysiology Procedures. *Anesth Analg*. 2018;127(1): 46-53. https://doi.org/10.1213/ANE.0000000000003376.
46. Kovoor P, Porter R, Uther JB, Ross DL. Efficacy and safety of a new protocol for continuous infusion of midazolam and fentanyl and its effects on patient distress during electrophysiological studies. *Pacing Clin Electrophysiol*. 1997;20(11): 2765-2774. https://doi.org/10.1111/j.1540-8159.1997.tb05434.x
47. Khan ZP, Ferguson CN, Jones RM. alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. *Anaesthesia*. 1999;54(2): 146-165. https://doi.org/10.1046/j.1365-2044.1999.00659.x
48. Terao Y, Higashijima U, Toyoda T, et al. The effects of intravenous anesthetics on QT interval during anesthetic induction with sevoflurane. *J Anesth*. 2016;30(6): 929-934. https://doi.org/10.1007/s00540-016-2252-8.
49. Zhong Q, Kumar A, Deshmukh A, Bennett C. Dexmedetomidine Reduces Incidences of Ventricular Arrhythmias in Adult Patients: A Meta-Analysis. *Cardiol Res Pract*. 2022;2022: 5158362. https://doi.org/10.1155/2022/5158362.
50. Shannon K, Saltzman D, Li I, et al. Ventricular tachycardia converts to sinus rhythm after administration of propofol. *Am J Emerg Med.* 2021;48: 377.e1-377.e3. https://doi.org/10.1016/j.ajem.2021.04.028.
51. Patel S, Deng J, Zubair A, et al. Sedation Versus General Anesthesia for Ablation of Ventricular Arrhythmias: A Systematic Review and Meta-Analysis. *Ann Card Anaesth*. 2025;28(2):119-127. https://doi.org/10.4103/aca.aca_229_24.
52. Polovinka VS, Demyanenko AV, Steklov VI, et al. Innovative methods of treatment of ventricular arrhythmias of the heart. *Military Medical Journal*. 2014;335(11): 44-52. (In Russ). https://doi.org/10.17816/RMMJ74301.

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NOVEL ELECTROCARDIOGRAPHIC RISK PREDICTORS OF SUDDEN CARDIAC DEATH

D.A.Stepanov[1], A.A.Tatarinova[1], A.P.Nemirko[2], L.A.Manilo[2]

FSBI "Almazov National Medical Research Centre" of the MH RF, Russia, Saint-Petersburg, 2 Akkuratova str.; [2]FSAEIHE Saint Petersburg State Electrotechnical University "LETI" named after V.I.Ulyanov (Lenin), Russia, Saint Petersburg, 5 Professor Popov str., lit. F.

Among studies addressing ECG-based risk stratification for sudden cardiac death and life-threatening ventricular arrhythmias, novel approaches to ECG data analysis and derived markers of myocardial electrical instability are of particular interest. Notably, metrics obtained through vector-based, frequency-domain, and nonlinear ECG analysis have demonstrated significant value as predictors of high-risk ventricular arrhythmias and sudden cardiac death.

Key words: electrocardiography; sudden cardiac death; ventricular tachycardia; ventricular fibrillation; heart rate variability; global electric heterogeneity; periodic repolarization dynamics; entropy of repolarization

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Corresponding Author: Danila Stepanov, E-mail: daniel36611b@gmail.com

D.A.Stepanov - ORCID ID 0000-0001-7032-8800, A.A.Tatarinova - ORCID ID 0000-0001-5955-2529, A.P.Nemirko - ORCID ID 0000-0001-6459-626X, L.A.Manilo - ORCID ID 0000-0002-8796-5299

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Sudden cardiac death (SCD) remains one of the most pressing challenges in contemporary healthcare. According to current understanding, its most common cause is the occurrence of life-threatening ventricular arrhythmias (VA), including sustained ventricular tachycardia (VT) and ventricular fibrillation (VF).

The modern approach to VA research considers a comprehensive "arrhythmic profile" comprising the arrhythmic substrate, determined by the underlying cardiac disease, clinical, electrocardiographic, and electrophysiological characteristics (including the precipitating (trigger) factors), and ECG-derived markers of myocardial electrical instability (MEI). ECG-based MEI markers can reflect various mechanisms of arrhythmogenesis - both substrate-related and trigger-related, and are intended to improve the prediction of life-threatening VA.

A recent review dedicated to ECG MEI markers proposed their classification into two groups: established and novel markers. The first group markers are widely recognized by researchers and clinicians, have been extensively studied (including meta-analyses), and in some cases incorporated into clinical guidelines [1]. Meanwhile, novel markers enabled by advances in information technologies and computational power allow extraction of previously inaccessible ECG information. As such, novel ECG markers warrant further investigation to evaluate their clinical applicability.

The aim of the present review is to analyze studies focusing on selected novel ECG MEI markers as predictors of life-threatening VA and SCD, examining the underlying hypotheses, methodological aspects of their assessment, and nuances in clinical interpretation.

Table 1.

Strategy for searching publications in scientometric databases for the period 2014-2025

Language	Search tools	Keyword combinations	
English	PubMed, Google Scholar, Scopus	Main	(SCD OR Sudden cardiac death OR Sudden arrhythmic death) AND (ECG OR Electrocardiography OR Electrocardiographic) AND (New OR Novel) AND (Markers OR Predictors)
		Clarifying	(Ventricular AND (Arrhythmia OR Dysrhythmia)) AND (ECG OR Electrocardiography OR Electrocardiographic) AND (New OR Novel) AND (Markers OR Predictors)
		Clarifying	(SCD OR Sudden cardiac death OR Sudden arrhythmic death) AND (Entropy OR Nonlinear dynamics OR Frequency OR Transform OR <дополнительные уточняющие ключевые слова>)
		Clarifying	<Название заболевания> AND <Название нового ЭКГ-маркера>

This review covers research published between 2015 and 2025. Core search strategy is presented in Table 1. Within the scope of this work, the novel ECG MEI markers are categorized into three groups based on their approach to analysis of recorded ECG signal and derived data:

Analysis of diagnostically relevant parameters directly measured from the ECG. Here, the temporal dynamics of quantitative indices are evaluated and correlated with VA/SCD risk. Of particular interest is a set of novel vectorcardiographic (VCG) parameters collectively termed Global Electrical Heterogeneity (GEH) [5-12]:

- Spatial QRST angle - the 3D angle between the depolarization and repolarization vector loops, analogous to the well-known frontal QRST angle, a recognized MEI marker.
- Spatial ventricular gradient (SVG) vector magnitude and sum absolute QRST integral (SAI QRST) - indices reflecting heterogeneity in myocardial depolarization and repolarization.

Frequency-domain analysis of ECG parameters related to ventricular repolarization. This includes time-frequency transformation of time series of angles between successive T-wave axes, or direct analysis of T-wave frequency content. Parameters are assessed both relative to threshold values and as trends. Two frequency-based ECG markers are of particular interest:

- Periodic Repolarization Dynamics (PRD) - low-frequency (<0.1 Hz) power spectral density of a time series of angles between successive T-wave axes, evaluated from a 20-minute ECG recording [13-15].
- f99 index - the frequency at which the normalized spectral energy of the T wave reaches 99% [16, 18, 19].

Nonlinear analysis of ECG parameters (RR, QT intervals). This approach assesses the presence and degree of nonlinear components against deterministic and stochastic components of a time series. Notable nonlinear ECG markers include entropy-based measures (e.g., heart rate variability (HRV) entropy, repolarization entropy) and fractal methods such as detrended fluctuation analysis (DFA):

- Combinations of linear (statistical and frequency-domain) and nonlinear (entropy-based, fractal) HRV indices, analyzed using machine learning algorithms (e.g., k-nearest neighbors, support vector machines) for risk stratification or prediction of VA/SCD [27-36].
- Nonlinear indices of the repolarization phase calculated from sequences of selected ECG intervals [37, 42].

PROPERTIES OF LINEAR AND NONLINEAR SYSTEMS

Key properties of linear systems include additivity (the system's response to a composite input equals the sum of its responses to each component), homogeneity (the system's response is proportional to the input magnitude), and invariance (temporal changes in the input produce corresponding temporal changes in the output). These properties significantly simplify the study, modeling, and prediction of linear system behavior.

In contrast, the defining feature of nonlinear systems, as the name implies, is the absence of these properties, enabling the emergence of phenomena such as chaotic behavior (high sensitivity to initial conditions), multistability (presence of multiple stable states), emergence (appearance of properties absent in individual elements), scale invariance and self-similarity (retention or repetition of structural patterns across scales), temporal evolution of states, self-organization, and adaptability.

Such properties complicate the investigation and prediction of nonlinear system behavior considerably. However, by employing numerical measures of chaoticity - such as entropy, Lyapunov exponents, fractal dimension, phase portraits, and others - it is possible to assess certain properties of a dynamic system from its time series, obtaining important prognostic parameters.

NONLINEAR AND FRACTAL PROPERTIES OF THE CARDIOVASCULAR SYSTEM

Multiple levels of organization and richness of component interactions that inherently confer nonlinear behavior characterize biological systems. The cardiovascular (CV) system is no exception, exhibiting nonlinear properties at all organizational levels: from the single myocardiocyte (dependence of response to a stimulus on the current phase of the action potential), to the heart as an organ (loss of Frank-Starling law linearity in pathologically elevated preload), to the CV system as a whole (complex neurohor-

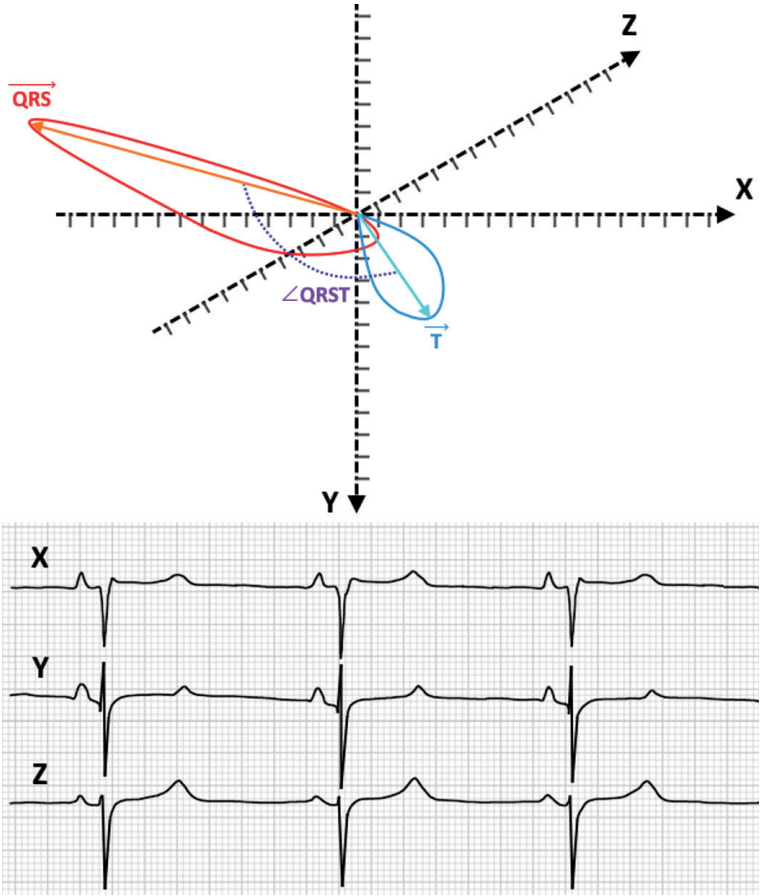

Fig. 1. GEH parameters: spatial QRST angle between QRS and T wave loops in three-dimensional space.

monal regulation of blood pressure and heart rate mediated by feedback loops).

Another important property of many biological systems is fractality - self-similarity and recurrence across different scales. In the CV system, this property manifests both structurally and functionally. Examples include fractal-like branching of the conduction system and the hierarchically interconnected operation of feedback control loops from cellular to systemic level.

CV biosignals (ECG, HRV and others) under certain conditions can be viewed as generated by deterministic chaos, where apparently irregular fluctuations conceal deterministic nonlinear components [2, 3].

The dynamic system generating these signals evolves over time in such a way that current-state analysis enables forecasting of future state, such behavior known as iterative. This forms the basis for studying and predicting physiological system dynamics using a set of nonlinear parameters measured at the present or prior time points.

It can therefore be assumed that the nonlinear, dynamic, iterative and fractal nature of processes within the CV system determines the properties of the biosignals it generates. While nonlinear system behavior can be described using linear methods in a process known as linearization, this requires the system to be near an equilibrium point - for example, the analysis of resting ECG recordings. These constraints support the rationale for exploring novel MEI markers obtained via nonlinear analysis. Nonlinear indices offer greater precision and reliability in extracting information from signals originating from inherently chaotic, dynamic sources, despite their increased computational complexity.

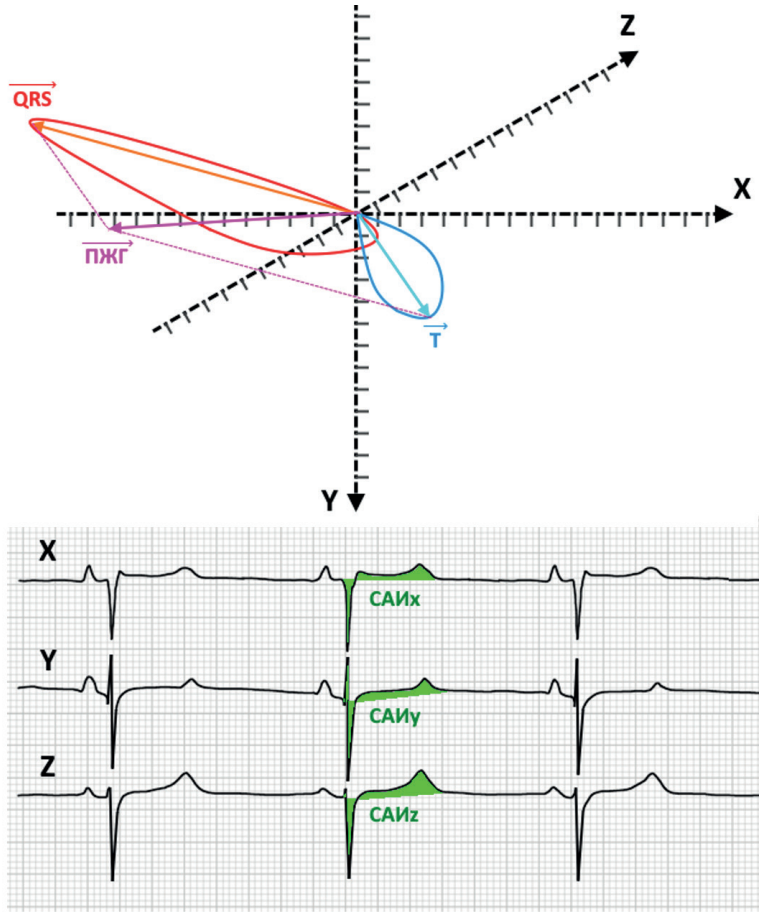

Fig. 2. GEH parameters: SVG vector (sum of QRS and T vectors in three-dimensional space) and its scalar analog SAI (total area under QRST curve).

ANALYSIS OF DIRECTLY MEASURED ECG PARAMETERS

Numerous temporal and amplitude-based parameters can be directly measured from the raw ECG signal. This group includes various intervals, many of which are already recognized as established markers of myocardial electrical instability, as well as VCG features (vectors, angles, areas) that have yielded several novel MEI markers.

The assessment of myocardial electrical activity and its spatiotemporal dynamics in normal and pathological states is of particular interest for stratifying the risk of life-threatening VA and SCD. These dynamics can be described geometrically in terms of vectors, angles, and areas. Well-known examples of such descriptors include the electrical axes of the QRS complex, P and T waves. Differences in vector orientations are quantitatively expressed as angles, the most familiar being the frontal QRST angle. While these vectors and angles can be readily calculated in the frontal plane from a standard 12-lead ECG, their three-dimensional assessment is more feasible using ECG recorded in a VCG system (most commonly Frank leads system) or transformed into such system, as reflected in the calculation methods for this group of indices.

Global electrical heterogeneity parameters

in the 1930s, Wilson et al. introduced the concept of the SVG - a vector directed toward the myocardial region with the shortest action potential duration. This index reflects the axis of maximal electrical heterogeneity in the heart, but its calculation complexity historically limited its clinical adoption [4]. In 2010, Tereshchenko et al. expanded this concept by introducing the SAI QRST parameter. This parameter is calculated as the sum of the absolute values of areas under QRST curve, averaged over 5 minutes, in three orthogonal leads. The authors hypothesized that changes in SAI QRST reflect the spatiotemporal heterogeneity of myocardial electrical activity. In a healthy heart, synchronous depolarization wave propagation ensures mutual cancellation of opposing electrical fields in different myocardial regions, whereas electrical heterogeneity - such as that arising from ischemia or fibrosis - leads to uncompensated potentials, altering the SAI of the QRS complex. Similarly, heterogeneity of repolarization (e.g., due to ischemia or electrolyte imbalances) manifests as differences in the temporal and amplitude characteristics of repolarization among myocardial segments, producing changes in the SAI of the T wave. Integrating over the entire QRST interval allows assessment of heterogeneity contributions from both depolarization and repolarization.

In a pilot study, a low SAI QRST was associated with a more than threefold increase in the risk of life-threatening VA; however, this finding was not replicated in a subsequent

study in which elevated, not reduced, SAI emerged as the risk marker. These contradictory results were likely attributable to differences in the clinical characteristics of the study populations [5-7].

Subsequently, the group of VCG parameters comprising the spatial QRST angle [8], SVG vector magnitude, and SAI QRST became collectively known as GEH parameters (Figs 1 and 2).

In a large, long-term population-based study based on the ARIC database, Perez-Alday et al. (2019) investigated the prognostic value of GEH parameters for SCD over a mean follow-up of 24,4 years. Based on the analysis of 577 SCD events recorded (3,7% of the cohort), the authors proposed a biphasic model of SCD risk stratification: in the short term, the significant predictor was an SVG vector directed toward the ventricular outflow tracts, indicating the presence of myocardial regions with a short refractory period - a potential VA substrate; in the long term, greater predictive value was found for an SVG vector directed toward the LV and a wide QRS-T angle, reflecting LV remodeling as a chronic arrhythmic substrate [9].

Further work focused on developing an SCD risk score based on GEH indices. Waks et al. (2016) conducted a study combining cohorts from the ARIC and CHS studies. Over a median follow-up of 14 years, 486 SCD events occurred (7,56%). Proportional (PR) and competing risk (CR) models were constructed, incorporating demographic characteristics, cardiovascular history and risk factors, established ECG indices (heart rate, QTc duration, QRS width, LV hypertrophy, intraventricular conduction abnormalities), and longitudinal changes in the GEH parameters. Across all models, GEH indices retained independent prognostic value; inclusion of LVEF did not significantly alter the correlations. The most robust predictors were the spatial QRS-T angle, SAI QRST, and SVG vector magnitude. A risk calculator based on these findings was made available in the supplementary materials of the original article [10].

Subsequently, Waks et al. investigated the prognostic utility of GEH parameters in patients with structural heart disease in the multicenter retrospective GEHCO study [11]. The primary endpoint was appropriate ICD therapy delivery for sustained VT. Over a median follow-up of 4 years, 541 patients (≈5% annually) reached the endpoint. Four CR models were developed: model 1 including demographic variables only, model 2 adding cardiovascular risk factors, model 3 adding device characteristics and model 4 additionally incorporating established ECG markers (heart rate, QRS width, QTc duration).

Given the previously observed inconsistent association of SAI QRST with arrhythmic risk, additional analysis was performed for subgroups by IHD status. After full adjustment (model 4), the spatial QRS-T angle, SVG vector direction, and SVG magnitude were significantly associated with the primary endpoint. Notably, arrhythmic risk correlated directly with QRST angle and SVG direction, and inversely with SVG magnitude. In IHD patients, elevated SAI QRST correlated with increased risk, whereas in non-IHD patients, lower SAI QRST was the risk marker. These findings were consistent with earlier observations that a superior-posterior SVG direction and wide QRS-T angle indicate elevated arrhythmic risk. The authors hypothesized that nonuniform SAI-VA risk correlation was caused by the underlying substrate for electrical heterogeneity. In IHD, electrical heterogeneity is driven by localized ischemia - manifesting as increased SAI, higher SVG magnitude, and vector orientation toward the arrhythmogenic substrate, whereas in non-ischemic etiologies, diffuse myocardial remodeling and fibrosis dominate, replacing electrically active myocardium and thus decreasing both SAI and SVG magnitude, without specific directional changes (described as the vector pointing «toward the entire LV»).

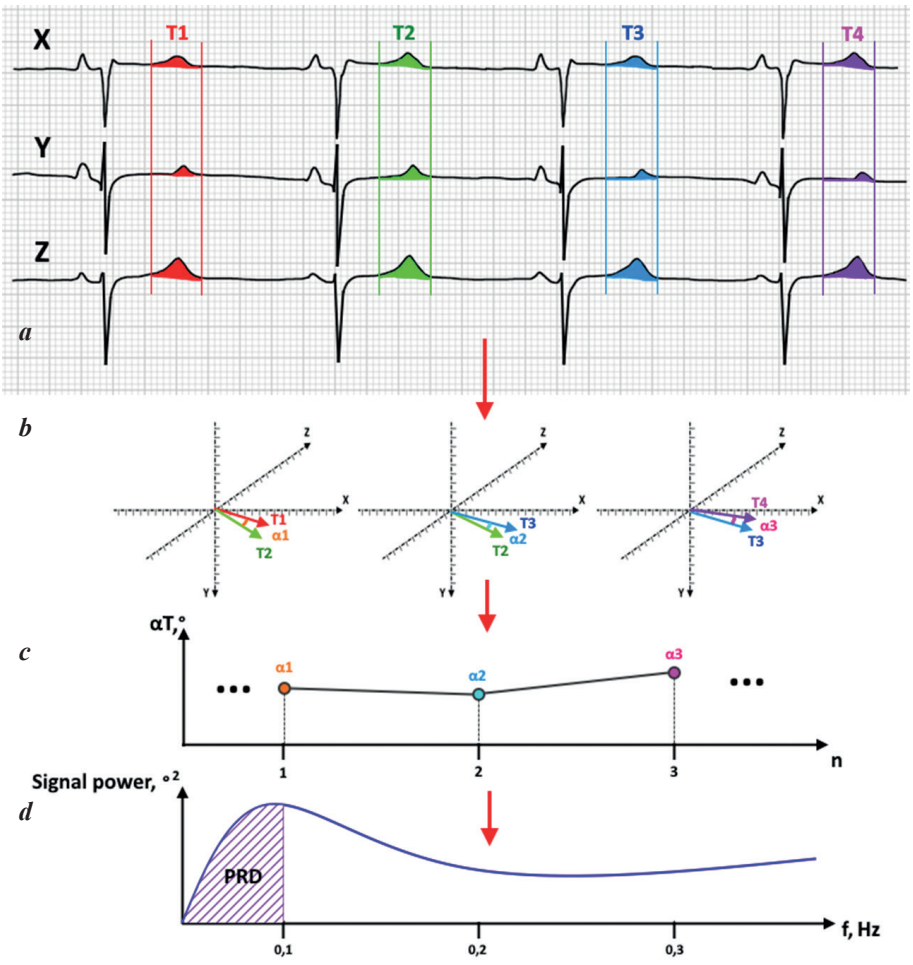

Fig. 3. PRD calculation: a - ECG in orthogonal lead system and T wave extraction; b - T wave electrical axis vectors and angles between them; c - time series of angles between T wave vectors (αT); d - power spectrum obtained by Fourier transform of angle time series. PRD is defined as power below 0,1 Hz.

These observations emphasize the necessity of accounting for myocardial disease etiology when developing GEH-based risk models. Study limitations included the lack of standardized ICD programming protocols, absence of postmortem ICD analysis in deceased patients to determine arrhythmic events immediately preceding death, and the debated validity of using ICD therapy delivery as a surrogate endpoint for SCD - concerns also noted in earlier studies [12].

VCG markers exemplify a concept discovered ahead of its time: introduced in the 1930s, they remained largely unused in clinical practice due to calculation complexity, but modern advances in automated ECG analysis have revived scientific interest in these parameters.

FREQUENCY-DOMAIN ANALYSIS OF REPOLARIZATION PHASE ECG PARAMETERS

Frequency is a fundamental characteristic of oscillatory processes ubiquitous in biological systems. Physiological homeostasis is maintained through numerous feedback loops, whose operation is accompanied by characteristic oscillations in the parameters under their control. Consequently, alterations in the frequency characteristics of biosignals can reflect disturbances in homeostatic regulation. Periodicity in regulatory influences, as manifested in the heart's electrical activity, can be investigated using frequency-domain analysis of ECG and HRV signals. In addition, intrinsic oscillatory patterns of cardiac electrical processes, including impulse conduction, excitation, and myocardial repolarization, are of considerable interest.

Some frequency-domain indices are already established risk markers (e.g., frequency domain parameters of HRV), whereas others remain under investigation for clinical applicability.

Periodic repolarization dynamics (PRD)

In 2014, Rizas et al. proposed a novel risk stratification method for post-myocardial infarction (MI) patients, grounded in three key premises:

- The influence of sympathetic overactivity on myocardial repolarization process.
- Proven role of sympathetic stimulation in the pathogenesis of life-threatening arrhythmias.
- Experimentally proven pattern of sympathetic nerve activity manifesting as low-frequency «bursts».

The authors hypothesized that sympathetic modulation of repolarization should manifest as low-frequency periodic oscillations of the T-wave axis, termed PRD. PRD assessment was based on 20-minute high-resolution ECG recordings. A time series of angles between the electrical axes of successive T waves - reflecting instantaneous instability of the repolarization vector - was computed, followed by frequency transform to quantify low-frequency (<0.1 Hz) spectral power (Fig. 3).

Potential confounders were systematically excluded. Possible relationship between PRD and HRV was ruled out experimentally via fixed-rate atrial pacing in volunteers, which abolished HRV while leaving PRD unaffected. The effect of spontaneous respiration was excluded in an animal model (anesthetized pigs) using fixed-rate mechanical ventilation, which preserved PRD. The link between PRD and sympathetic activity was further supported by observations of PRD elevation during tilt-table testing and exercise, and PRD reduction following β-adrenergic blockade. In the ART study cohort, PRD demonstrated prognostic value for 5-year mortality. A threshold of 5,75°² (upper quartile) was associated with a nearly threefold increase in all-cause and cardiovascular mortality risk after adjustment for clinical history and cardiovascular risk factors. PRD was also evaluated alongside T-wave alternans (TWA) in the FINCAVAS study, showing independent predictive value for cardiovascular mortality, including among patients without detected TWA. Combined use of PRD and TWA improved prediction of 6-year all-cause mortality

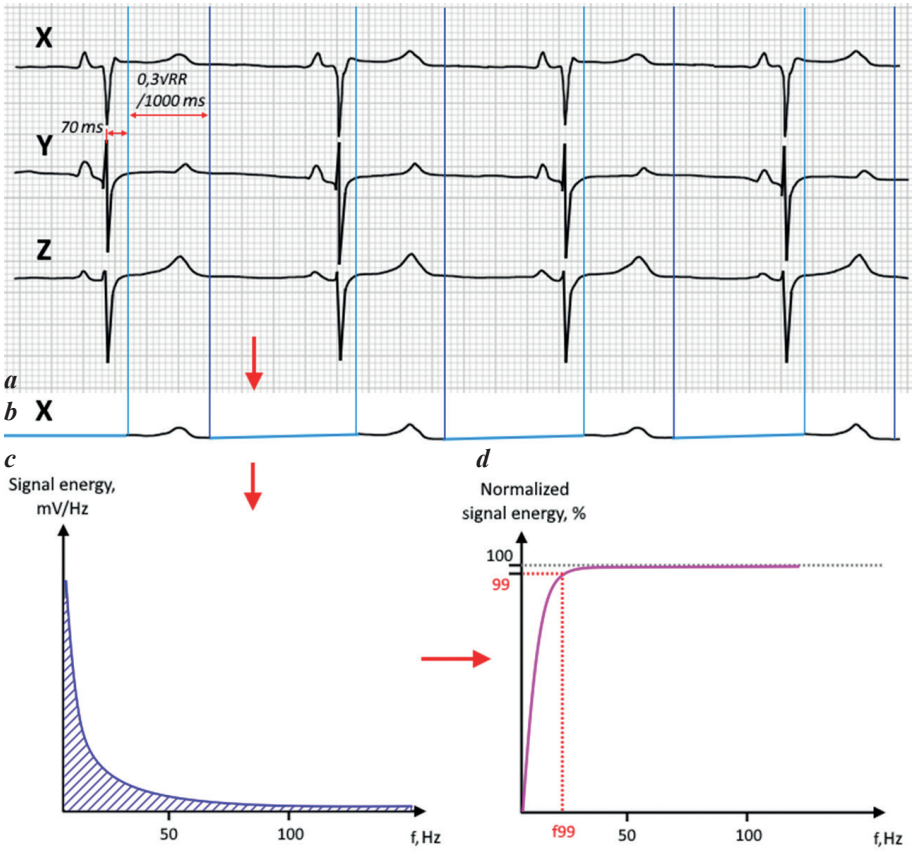

Fig. 4. f99 calculation: a - ECG in orthogonal leads and borders of «repolarization window», b - repolarization signal (ECG with QRS complexes and P waves removed and replaced by zeros), c - repolarization signal energy spectrum, d - normalized signal energy curve (0 to 100%). F99 is defined as frequency where normalized signal energy reaches 99%.

[13]. It is worth noting that the pilot study did not directly evaluate mortality from fatal VA.

Rizas et al. (2017) conducted the first dedicated investigation of PRD as an SCD risk marker in the MADIT-II cohort. Of 854 patients, 506 received ICDs and 348 received medical therapy. Given that in CHF elevated sympathetic tone is associated with both arrhythmic death and pump failure death (non-sudden cardiac death, non-SCD), the study endpoints included all-cause mortality, SCD and non-SCD. Over a median follow-up of 20,4 months, 53 SCD cases occurred. After adjustment for clinical history, cardiovascular risk factors, therapy, QRS width and LVEF, PRD was a significant predictor of SCD across the entire cohort. Among medically treated patients, PRD predicted SCD, whereas in ICD recipients, it predicted both appropriate ICD therapy and non-SCD. The authors noted the potential utility of PRD for identifying post-MI patients with reduced LVEF who may benefit from prophylactic ICD implantation. Study limitations included variability in ECG acquisition methods, exclusion of atrial fibrillation patients, changes in patient management protocols since MADIT-II, and a relatively small sample size [14].

Palacios et al. (2021) obtained further data on the prognostic role of PRD in the MUSIC cohort of CHF patients. Endpoints included SCD and non-SCD. Over the follow-up period, there were 53 SCD and 53 non-SCD events. PRD thresholds were established at 1,33°² for SCD and 1,31°² for non-SCD. SCD cases were significantly more common in patients with elevated PRD, whereas no significant difference in non-SCD cases was found between elevated and normal PRD groups. After adjusting for demographics, clinical history, laboratory parameters, HRV, HRT, TWA and Holter monitor findings (non-sustained VT and frequent PVCs), elevated PRD remained an independent predictor of a nearly twofold higher SCD risk. The combination of elevated PRD with abnormal turbulence slope or TWA further increased SCD risk two- to threefold.

In the discussion, the authors emphasized PRD's reliability for differentiating high- and low-risk patients, its prognostic relevance for both SCD and pump failure death, and its potential for combination with other MEI markers. Notably, HRV parameters showed no clinically significant prognostic value in this cohort, and overall among traditional risk factors, the most influential were CHF functional class and LVEF <35% [15].

Fragmentation of repolarization (f99 index)

In 2013, Burattini and Giuliani proposed an alternative approach to analyzing the frequency structure of repolarization. A comparative study of T-wave frequency content in healthy individuals and post-MI patients revealed significant differences. In the latter group, an increased number of harmonics was observed in the 10-35 Hz range, which the authors interpreted as reflecting fragmentation of the repolarization process - the appearance of additional electrical oscillations. This can be compared to the high-frequency notching and slurring in the QRS complex caused by depolarization heterogeneity in structurally abnormal myocardium, visible as QRS fragmentation on standard ECG or detectable via spectral analysis [17]. Given the intrinsic coupling between depolarization and repolarization, the similarity of these abnormal patterns supports the proposed hypothesis.

On this theoretical basis, Giuliani et al. (2014) introduced the f99 index, defined as the frequency (in Hz) at which the normalized T-wave spectral energy reaches 99% (Fig. 4). Their study included 108 post-MI patients and 47 clinically healthy controls (mean age 45 ± 15 years, 82% male). On average, f99 values were higher in post-MI patients. The best sensitivity and specificity for prior MI detection were achieved in leads I (threshold 15 Hz; sensitivity 80%, specificity 77%) and aVL (threshold 17,8 Hz; sensitivity 84%, specificity 74%), with the lowest performance in leads III and aVF. Averaging f99 across precordial leads yielded better results (sensitivity 81%, specificity 74%) than averaging across all 12 leads (sensitivity 69%, specificity 74%). The authors noted that f99 was robust to random fluctuations in T-wave end detection, independent of heart rate, and unaffected by spatial dispersion of repolarization, making the index promising for evaluating repolarization abnormality [18]. However, the pilot study did not examine f99 specifically as an arrhythmic risk marker.

Giuliani et al. later evaluated f99's prognostic value for life-threatening VA using the Leiden University database of 170 CHF patients (LVEF <35%) with ICDs. Over four years of follow-up from ICD implantation, patients underwent exercise testing with ECG recording. Based

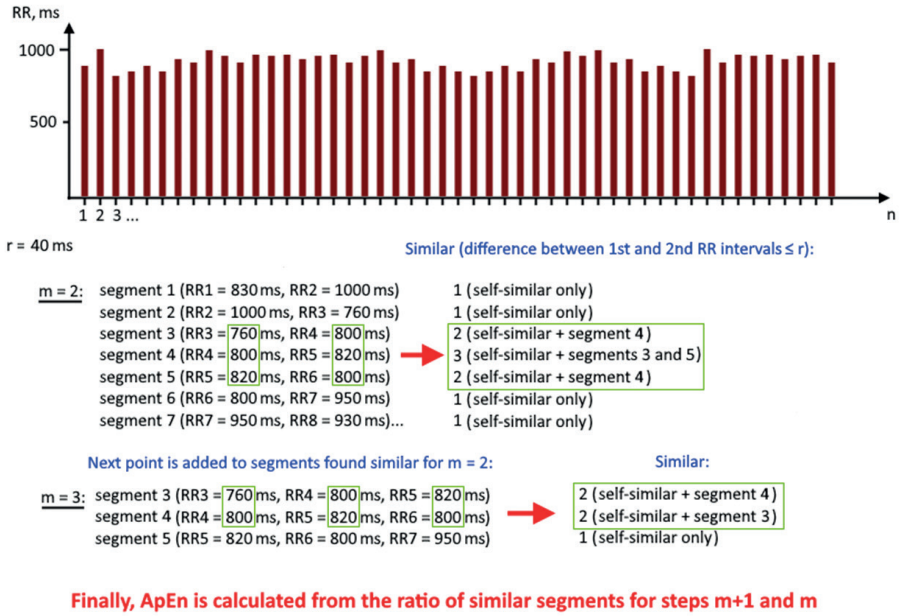

Fig. 5. Calculation of approximate entropy (ApEn) for HRV time series. If pairs of neighboring RR intervals (m = 2) are similar and adding next RR interval (m = 3) gives similar triplets, ApEn is low (system behavior is predictable); conversely, if increasing segment length (m = 2 → m = 3) drastically reduces the number of similar RR segments, ApEn is high and system behavior is more chaotic.

on whether ICD therapy occurred during follow-up, patients were classified into ICD-positive and ICD-negative groups, which were similar in clinical characteristics but differed in LVEF (31% ± 12% in ICD-positive vs. 39% ± 13% in ICD-negative). f99 was calculated from the first minute of exercise ECG using the previously described method. Maximum f99 values (maxF99) were computed for 6 precordial, 12 standard, and 3 orthogonal leads, and classification performance was assessed via ROC analysis. The highest AUC (0,68), comparable to that of LVEF (0,70) in this study, was obtained for orthogonal leads. Cross-correlation analysis showed independence between maxF99 and LVEF. The authors highlighted f99's reproducibility, robustness to spatial repolarization dispersion, and prognostic value comparable to LVEF - an established risk stratification marker [19].

Frequency-domain ECG markers emphasize the importance of a deep physiological understanding for work in electrophysiology. The approaches discussed - both the hypothesis linking PRD to burst-like sympathetic activity and the concept of repolarization fragmentation reflected in the spectral characteristics of the T wave - require investigators not only to possess comprehensive knowledge of cardiovascular regulation, myocardial electrophysiology and mechanisms of arrhythmogenesis, but also to engage in interdisciplinary collaboration with specialists in medical informatics and biosignal analysis.

NONLINEAR ANALYSIS OF ECG PARAMETERS

Among nonlinear indices derived from ECG and HRV signals and studied as MEI markers, particular interest lies in those reflecting chaoticity and fractality - properties directly linked both to the structure and function of the cardiac conduction system and myocardium, and to the autonomic regulation of the CV system.

A key quantitative measure of chaoticity, estimable from finite-length datasets, is entropy. In practice, several entropy measures are employed, differing in calculation methods and interpretative focus, including Shannon entropy (ShanEn), approximate entropy (ApEn), sample entropy (SampEn), fuzzy entropy (FuEn), Rényi entropy (RenEn), multiscale entropy (MSE), permutation entropy (PE), multiscale permutation entropy (MPE), and others.

For assessing fractal properties of a time series, the Hurst exponent is widely used, calculated using methods such as rescaled range (R/S) analysis, detrended fluctuation analysis (DFA), or frequency-domain approaches. For biomedical signals - which are typically nonstationary and noisy - DFA is a preferred method, as it removes the influence of local trends. Limitations of DFA include the assumption of monofractality (self-similarity at a single scaling factor) and the requirement for relatively long data series (several hundred points). For shorter segments, frequency-domain methods or DFA with modified detrending can be applied. Moreover, multiscale entropy methods (MSE and related) are also capable of incorporating the fractal properties of the analyzed signals.

Entropy and fractal properties of HRV

The pioneering application of entropy estimation in electrocardiology is attributed to S. Pincus, developer of the ApEn method [20] (Fig. 5), who described its use in cardiovascular disease diagnostics [21]; J. Richman and J. Moorman, who developed the improved SampEn method [22]; and A. Goldberger, M. Costa, and C.-K. Peng, who created the MSE method [23].

Concurrently, the concept of the fractal nature of CV system activity was being established. T. Musha and M. Kobayashi first described the HRV signal spectrum characteristic of fractal systems - the so-called pink noise [24]. A. Goldberger et al. identified the relationship between conduction system architecture and fractal spectral properties of the depolarization process (Fig. 6) [25]. C.-K. Peng and A. Goldberger developed DFA as a key tool for fractal analysis (Fig. 7) [26].

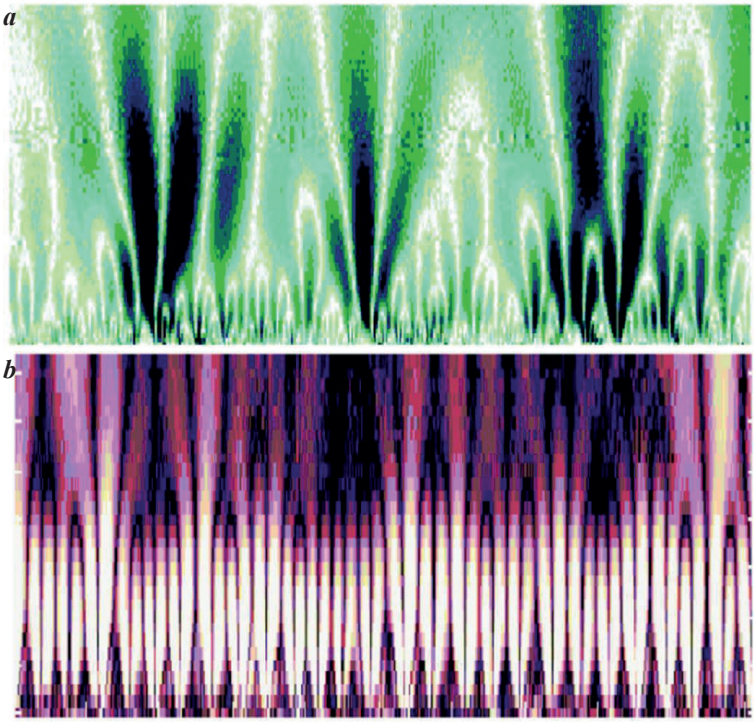

Fig. 6. a - fractal (self-similar) patterns in a spectrum obtained by wavelet analysis of RR time series of a healthy person. b - loss of fractality, increased rigidity and periodicity in a patient with obstructive sleep apnea. Adapted from [44].

Studies of nonlinear HRV analysis in the context of SCD can be broadly categorized into those addressing long-term risk stratification (identifying high-risk patients in specific cohorts, e.g., post-MI) and those addressing short-term prediction (anticipating life-threatening VA episodes before their onset). These two settings differ substantially in the temporal dynamics of nonlinear indices.

Long-term prognostic studies date back to the 1990s-2000s. In an early study by Voss et al. (1996; n = 26 post-MI patients, 16 with prior life-threatening VA or SCD), entropy indices were lower in the high-risk group, with predictive accuracy around 75%. In the DIAMOND-MI cohort study by Huikuri et al. (2000; 446 post-MI patients with LVEF <35%, mean follow-up 685 days, 75 SCD events), a reduced short-term fractal scaling exponent α_1

< 0,75, reflecting short-range RR interval correlation, was a significant SCD risk predictor (hazard ratio (HR) 2,5 in univariate analysis and 1,4 after clinical adjustment), outperforming established HRV measures (SDNN, LF, HF) [27]. Similarly, in a prospective study by Mäkikallio et al. (2001; random sample of 325 subjects > 65 years from a social insurance registry, 10-year follow-up, 29 SCD events), α_1 < 1,0 was the strongest predictor (HR 4,3 after adjustment; AUC 0,75), surpassing SDNN [28].

More recent studies include Rohila and Sharma (2020; 240 random 5-minute Holter segments from 20 SCD patients in the SDDB database), which showed significantly lower values of five entropy measures (SampEn, PEn, etc.) and α_1 DFA in the SCD group. Using these in a random forest classifier yielded an accuracy of 91,67% [29].

Yan et al. (2023; 22 Holter recordings from SCD patients in SDDB and AHADB databases) found reduced HRV SampEn to be a significant, though less powerful, SCD risk marker (AUC 0,66) compared to conventional HRV parameters (SDNN, RMSSD, LF) [30].

A large prospective study by Hernesniemi et al. (2024; 2794 1-minute ECGs from the FINCAVAS cohort, median follow-up 8,3 years, 83 SCD events) demonstrated that DFA with nonlinear detrending identified a significant correlation between reduced fractal HRV properties (lower α_1) and increased SCD risk (HR 2,4 per 1 SD), whereas differences in conventional HRV parameters were not significant. This study stands out for its large sample size and for proposing a spectral HRV analysis method applicable to ultrashort (1-minute) recordings, potentially enabling use in wearable devices [31].

Across long-term studies, reduced entropy and fractal measures in high-risk SCD patients is a notably consistent finding. Limitations include small and clinically heterogeneous samples in most reports. Future research should explore combined models incorporating both fractal and entropy measures in well-characterized cohorts, to facilitate validation, synthesis, and translation into clinical practice.

The first systematic studies on short-term SCD prediction using nonlinear HRV analysis date to the 2010s. A notable series by Ebrahimzadeh et al. (2014-2019), using the MIT-BIH database (35-40 Holter recordings with VF, 18 control sinus rhythm recordings), developed and refined prediction methods combining established linear HRV measures (time- and frequency-domain) with novel nonlinear indices (Poincaré plot cloud width and length, α DFA) and machine learning models (multilayer perceptron, support vector machines, k-nearest neighbors, mixture of experts). These approaches achieved VF prediction up to 13 minutes before onset [32-34]. Interestingly, α_1 DFA was significantly higher before VF onset (1,12 vs. 0,83 in controls), in contrast to findings in long-term SCD risk studies. In an early work [32], reported sensitivity was 83,75% but specificity only 0,159%, likely due to calculation error or classifier overfitting for sensitivity at the expense of specificity; later works did not replicate this issue.

Shi et al. (2020), also using MIT-BIH data (20 VF recordings, 18 controls), applied ensemble empirical mode decomposition (EEMD) to HRV data. Classification based on entropy measures and k-nearest neighbors achieved higher predictive accuracy in the first 2-minute interval before VF (94,7%) than a model using only linear parameters (86,8%), and the combined model reached 96,1%. The best-performing entropy measures were FuEn and improved MPE. Significant parameter changes were detectable up to 14 minutes before VF onset. The EEMD method's adaptability and noise robustness make it promising for wearable device applications [35].

Yang et al. (2023) reported a major advance in early SCD detection. They introduced a novel nonlinear multiscale index, Sv, derived from Poincaré plots. Using MIT-BIH data (20 VF Holter recordings, 18 without VA), a combined model incorporating Sv, ShanEn, and SDNN with an SVM classifier achieved 91,22% predictive accu-

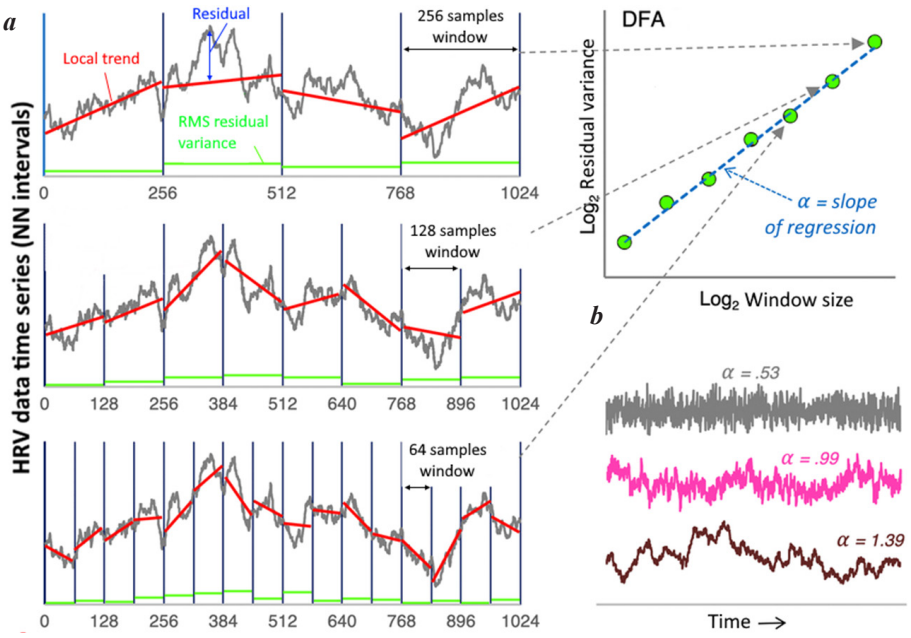

Fig. 7. Detrended fluctuation analysis (DFA) method. a - algorithm for DFA calculation: calculation of root-mean-square (RMS) residual variance (deviation from local trend) at various time scales, plot of residual variance against time scale and the regression approximating the variance-scale relation. Slope of regression line reflects the strength of self-similarity at various time scales (fractality). b - examples of signals with various level of self-similarity: low α signifies prevalence of small-scale oscillations and lack of longer-range patterns (chaotic behavior), α close to 1 reflects a balanced relation between amplitude and scale of oscillations (fractal-like behavior), high α demonstrates prevalence of long-range patterns over small-scale variation (rigid behavior, long-term «memory»: of the signal). Adapted from [45].

racy 60-70 minutes before SCD - a fivefold improvement in lead time compared to prior studies [36].

These short-term prediction studies benefit from the standardization inherent to public ECG databases but are limited by small sample sizes (35-40 recordings). Such methods may be particularly useful in ECG monitoring devices for high cardiovascular risk patients. Future directions include evaluating EEMD and combined DFA/Sv models on ECG recordings of varying quality and duration, and in diverse clinical populations, to define practical applicability.

Entropy and fractal properties of repolarization

An original approach to nonlinear ECG analysis was proposed by DeMazumder et al. (2016) [37]. The authors hypothesized that the degree of repeatability in ventricular repolarization patterns, assessed via QT interval variability, reflects the functional state of the body's regulatory systems. They introduced the repolarization entropy index (proprietary term EntropyXQT), an enhanced version of SampEn designed to assess the complexity and repeatability of ventricular repolarization patterns. This index is derived from QT interval variability analysis, thereby capturing embedded periodic oscillations in interval duration. Due to its calculation method, EntropyXQT can be considered a «hybrid» index, reflecting both complexity and fractality (scale invariance) of cardiac dynamics.

The prognostic value of EntropyXQT for life-threatening VA was assessed in the PROSe-ICD study [38]. The primary endpoint was the first appropriate ICD therapy delivery for VT or VF, the secondary endpoint was a composite of the primary and all-cause mortality. Over a mean follow-up of 45 ± 24 months, 134 patients reached the primary endpoint and 300 reached the secondary endpoint (166 deaths without prior ICD therapy). EntropyXQT's predictive value was evaluated in two models: the Seattle Heart Failure Model (SHFM) [39] and a baseline model incorporating clinical and laboratory variables plus established ECG measures, including HRV, QRS duration, late potentials, and repolarization indices (QTc, QT/RR, QTVi). High EntropyXQT values (fifth quintile) were independently associated with more than a threefold increased risk of ICD intervention, even after adjustment for 30 additional parameters. The prognostic value of EntropyXQT was independent of other repolarization indices, including QTVi. Adding EntropyXQT to the baseline model improved net reclassification by 31-36%, and adding it to the SHFM improved reclassification by 40%. The authors noted EntropyXQT's potential utility for primary prevention of SCD, its robustness to noise, its ease of calculation from short ECG recordings, and its consistency with prior research on entropy measures of cardiac activity for predicting pathological states [40, 41].

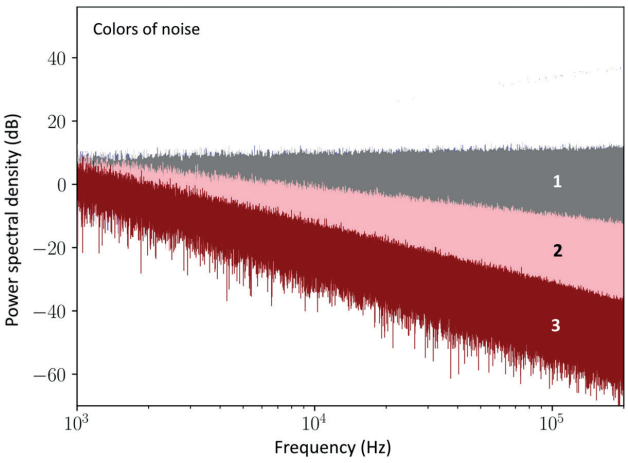

Fig. 8. Colors of noise. 1 - white noise characteristic of random processes with no autocorrelation. 2 - pink "fractal" 1/f noise characteristic of normally functioning systems containing multiple hierarchical levels of control and balanced autocorrelation. 3 - Brownian ("brown" or "red") noise characteristic of systems with strong dependence on past states and strong autocorrelation. Adapted from [46].

A noteworthy contribution comes from M. Murugappan et al. (2020), who focused on nonlinear analysis of the R-Tend segment for short-term SCD prediction, using the MIT-BIH database (18 Holter recordings with VF, 18 controls without VA). For each of the five consecutive 1-minute segments preceding VF onset, they calculated ApEn, SampEn, the largest Lyapunov exponent and the Hurst exponent - thus incorporating both entropy and fractal measures. Classification was performed using subtractive fuzzy clustering, neuro-fuzzy clustering and SVM. The best results were obtained with SVM: on the fifth minute before VF onset, predictive accuracy reached 100% for SampEn, 98,68% for ApEn, 97,37% for the largest Lyapunov exponent, and 94,74% for the Hurst exponent. The remarkably high accuracy for ApEn and SampEn contrasts with their more modest performance in HRV-based short-term SCD prediction. A major strength of the study is the novelty of analyzing the R-Tend segment, while its main limitation is the small sample size dictated by the MIT-BIH SCD database [42].

Of particular interest is the dynamic behavior of nonlinear HRV indices in long-term risk versus immediate pre-SCD states. While some entropy measures decrease over the long term, others exhibit a sharp rise immediately before fatal VA onset. Notably, for repolarization entropy, such a paradox was not observed. Clinically, these patterns may reflect two complementary pathological processes:

Chronic phase (entropy decrease): loss of the «healthy chaos» in heart rhythm characteristic of effective autonomic regulation [43], consistent with the depletion of adaptive reserves seen in CHF patients or those with prior MI.

Acute phase (entropy increase in HRV and repolarization): manifestation of critical MEI and increasing electrical heterogeneity, creating a substrate for fatal arrhythmias - consistent with the theory of «critical slowing down» in complex systems approaching a transition state.

Importantly, this acute-phase rise was most prominent for multiscale and adaptive measures (e.g., IMPE, FuEn) of HRV, whereas traditional single-scale measures (ApEn, SampEn) of HRV were less informative. For repolarization entropy, ApEn and SampEn also rose significantly, likely reflecting disorganization of ventricular electrical processes rather than changes in autonomic modulation.

A similar biphasic pattern was observed for fractal characteristics:

- Optimal regulation (α DFA ≈ 1,0): represents balanced vagal-sympathetic interaction and nested regulatory loops of the CV system, producing a "pink noise" spectrum.

• Long-term risk (α → 0,5; high EntropyXQT due to loss of self-similar oscillations): indicates disintegration of regulatory mechanisms, loss of correlations, and a random response pattern ("white noise" spectrum).
• Immediate SCD threat (α >1,5): may reflect sympathetic hyperactivation with dominance of low-frequency oscillations, increased «memory» and rigidity of the system, locking it onto a trajectory toward pathological state («brown noise» spectrum) (Fig. 8).

CONCLUSION

Modern approaches to the risk stratification of sudden cardiac death and life-threatening ventricular arrhythmias extend beyond traditional ECG markers, offering novel methods for assessing myocardial electrical instability. The groups of novel markers reviewed here reflect different aspects of arrhythmogenesis.

The key advantage of GEH vector parameters lies in their ability to quantify the spatiotemporal heterogeneity of depolarization and repolarization, which is particularly important in patients with both ischemic and non-ischemic cardiomyopathies. Interpretation of these markers requires careful consideration of the underlying myocardial pathology, given the differences in prognostic significance across conditions.

The distinctive value of frequency-domain MEI markers stems from their capacity to reflect disturbances in autonomic regulation and electrical heterogeneity of repolarization - both of which are critical components of arrhythmogenesis in post-MI and heart failure patients. Clinical implementation of frequency-based markers requires standardization of ECG acquisition and analysis protocols.

Nonlinear MEI markers - encompassing entropy and fractal properties of HRV and specific ECG components - represent a novel conceptual framework for understanding arrhythmogenesis, framing it as a multi-level collapse of the cardiovascular system's adaptive potential, a breakdown in the balance between chaos and order, and a simplification of regulatory mechanisms, where excessive rigidity of control (sympathetic hyperactivation) coexists with micro-level electrical fragmentation. This perspective is new and potentially highly promising, but it demands multidisciplinary collaboration between cardiologists, electrophysiologists, physicists, mathematicians and computer science specialists.

The challenges pertaining to research of novel MEI markers are typical for any rapidly evolving field in the process of evidence accumulation and synthesis: considerable heterogeneity of study populations, lack of standardized acquisition protocols for the studied indices, and, in many cases, contradictory results. These issues are likely to be temporary and should be resolved as the field progresses toward integrating findings and developing practical clinical applications.

Promising directions include exploring combined marker models from different groups using machine learning for long-term arrhythmic risk stratification, as well as identifying short-term SCD predictors in high cardiovascular risk populations - particularly through long-term monitoring, wearable medical electronics, and on-demand ECG analysis.

In summary, novel ECG MEI markers do not replace but rather complement traditional approaches, providing a deeper understanding of arrhythmogenesis pathophysiology and forming a basis for more flexible SCD prevention strategies. Future research will likely focus on validating these indices in large prospective cohorts and developing standardized algorithms for their practical clinical use.

REFERENCES

1. Stepanov DA, Tatarinova AA. ECG-based risk stratification of sudden cardiac death and life-threatening ventricular arrhythmias. *Journal of Arrhythmology*. 2024;31(1): 77-91. (In Russ.). https://doi.org/10.35336/VA-1213.
2. Nonlinear Biomedical Signal Processing / ed. by Metin Akay. Vol. 2. Dynamic Analysis and Modelling. New York: IEEE; 2001.
3. Nemirko AP, Manilo LA, Kalinichenko AN. Mathematical analysis of biomedical signals and data. Moscow 2017. (In Russ.) ISBN 978-5-9221-1720-3.
4. Wilson FN, Macleod AG, Barker PS, et al. The determination and the significance of the areas of the ventricular deflections of the electrocardiogram. *Am Heart J.* 1934;10: 46-61.
5. Tereshchenko LG, Cheng A, Fetics BJ, et al. Ventricular arrhythmia is predicted by sum absolute QRST integral but not by QRS width. *J Electrocardiol.* 2010;43(6): 548-52. https://doi.org/10.1016/j.jelectrocard.2010.07.013.
6. Tereshchenko LG, Cheng A, Fetics BJ, et al. A new electrocardiogram marker to identify patients at low risk for ventricular tachyarrhythmias: sum magnitude of the absolute QRST integral. *J Electrocardiol.* 2011;44: 208-16. https://doi.org/10.1016/j.jelectrocard.2010.08.012.
7. Tereshchenko LG, McNitt S, Han L, et al. ECG marker of adverse electrical remodeling post-myocardial infarction predicts outcomes in MADIT II study. *PLoS One*. 2012;7(12): e51812. https://doi.org/10.1371/journal.pone.0051812.
8. Oehler A, Feldman T, Henrikson CA, et al. QRS-T angle: a review. *Ann Noninvasive Electrocardiol.* 2014;19: 534-42. https://doi.org/10.1111/anec.12206.
9. Perez-Alday EA, Bender A, German D, et al. Dynamic predictive aCCC Curacy of electrocardiographic biomarkers of sudden cardiac death within a survival framework: The Atherosclerosis Risk in Communities (ARIC) study. *BMC Cardiovasc Disord*. 2019;19(1): 255. https://doi.org/10.1186/s12872-019-1234-9.
10. Waks JW, Sitlani CM, Soliman EZ, et al. Global Electric Heterogeneity risk score for prediction of sudden cardiac death in the general population: the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) Studies. *Circulation*. 2016;133(23): 2222-34. https://doi.org/10.1161/CIRCULATIONAHA.116.021306.
11. Waks JW, Hamilton C, Das S, et al. Improving sudden cardiac death risk stratification by evaluating electrocardiographic measures of global electrical heterogeneity and clinical outcomes among patients with implantable cardioverter-defibrillators: rationale and design for a retrospective, multicenter, cohort study. *J Interv Card Electrophysiol*. 2018;52(1): 77-89. https://doi.org/10.1007/

s10840-018-0342-2.
12. Waks JW, Haq KT, Tompkins C, et al. Competing risks in patients with primary prevention implantable cardioverter-defibrillators: Global Electrical Heterogeneity and Clinical Outcomes study. *Heart Rhythm*. 2021;18(6): 977-86. https://doi.org/10.1016/j.hrthm.2021.03.006.
13. Rizas KD, Nieminen T, Barthel P et al. Sympathetic activity-associated periodic repolarization dynamics predict mortality following myocardial infarction. *J Clin Invest*. 2014;124(4): 1770-80. https://doi.org/10.1172/JCI70085.
14. Rizas KD, McNitt S, Hamm W, et al. Prediction of sudden and non-sudden cardiac death in post-infarction patients with reduced left ventricular ejection fraction by periodic repolarization dynamics: MADIT-II substudy. *Eur Heart J*. 2017;38(27): 2110-8. https://doi.org/10.1093/eurheartj/ehx161.
15. Palacios S, Cygankiewicz I, Bayés de Luna A, et al. Periodic repolarization dynamics as predictor of risk for sudden cardiac death in chronic heart failure patients. *Sci Rep*. 2021;11(1): 20546. https://doi.org/10.1038/s41598-021-99861-1.
16. Burattini L, Giuliani C. T-wave frequency content evaluation in healthy subjects and patients affected by myocardial infarction. In: Signal Processing: New Research (ed. Naik GR). NY 2013: 79-93.
17. Langner PH, Jr., Geselowitz DB, Mansure FT, et al. High-frequency components in the electrocardiograms of normal subjects and of patients with coronary heart disease. *Am Heart J*. 1961;62(6): 746-55. https://doi.org/10.1016/0002-8703(61)90661-5.
18. Giuliani C, Agostinelli A, Fioretti S, et al. Abnormal repolarization in the acute myocardial infarction patients: a frequency-based characterization. *Open Biomed Eng J*. 2014;8: 42-51. https://doi.org/10.2174/1874120701408010042.
19. Giuliani C, Swenne CA, Man S, et al. Predictive power of f99 repolarization index for the oCCC Currence of ventricular arrhythmias. *Ann Noninvasive Electrocardiol*. 2016;21(2): 152-60. https://doi.org/10.1111/anec.12274.
20. Pincus SM. Approximate entropy as a measure of system complexity. *Proc Natl Acad Sci U S A*. 1991;88(6): 2297-301. https://doi.org/10.1073/pnas.88.6.2297.
21. Pincus SM. Approximate entropy in cardiology. *Herzschr Elektrophys*. 2000;11: 139-50. https://doi.org/10.1007/s003990070033.
22. Richman JS., Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol*. 2000;278(6): 2039-49. https://doi.org/10.1152/ajpheart.2000.278.6.H2039.
23. Costa M, Goldberger AL, Peng CK. Multiscale entropy analysis of complex physiologic time series. *Phys Rev Lett*. 2002;89(6): 068102. https://doi.org/10.1103/PhysRevLett.89.068102.
24. Kobayashi M, Musha T. 1/f fluctuation of heartbeat period. *IEEE Trans Biomed Eng*. 1982;29(6): 456-7. https://doi.org/10.1109/TBME.1982.324972.
25. Goldberger AL. Fractal electrodynamics of the heartbeat. *Ann N Y Acad Sci*. 1990;591: 402-9. https://doi.org/10.1111/j.1749-6632.1990.tb15104.x.
26. Peng CK, Havlin S, Stanley HE, et al. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos*. 1995;5(1): 82-7. https://doi.org/10.1063/1.166141.
27. Huikuri HV, Mäkikallio TH, Peng CK, et al. Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. *Circulation*. 2000;101(1): 47-53. https://doi.org/10.1161/01.cir.101.1.47.
28. Mäkikallio TH, Huikuri HV, Mäkikallio A, et al. Prediction of sudden cardiac death by fractal analysis of heart rate variability in elderly subjects. *J Am Coll Cardiol*. 2001;37(5): 1395-402. https://doi.org/10.1016/s0735-1097(01)01171-8.
29. Rohila A, Sharma A. Detection of sudden cardiac death by a comparative study of heart rate variability in normal and abnormal heart conditions. *J Appl Biomed*. 2020;40(3): 1-15. https://doi.org/10.1016/j.bbe.2020.06.003.
30. Yan SP, Song X, Wei L, et al. Performance of heart rate adjusted heart rate variability for risk stratification of sudden cardiac death. *BMC Cardiovasc Disord*. 2023;23(1): 144. https://doi.org/10.1186/s12872-023-03184-0.
31. Hernesniemi JA, Pukkila T, Molkkari M, et al. Prediction of sudden cardiac death with ultra-short-term heart rate fluctuations. *JACCC C Clin Electrophysiol*. 2024;10(9): 2010-20. https://doi.org/10.1016/j.jacep.2024.04.018.
32. Ebrahimzadeh E, Pooyan M, Bijar A. A novel approach to predict sudden cardiac death (SCD) using nonlinear and time-frequency analyses from HRV signals. *PLoS One*. 2014;9(2): e81896. https://doi.org/10.1371/journal.pone.0081896
33. Ebrahimzadeh E, Fayaz F, Ahmadi F, et al. Linear and nonlinear analyses for detection of sudden cardiac death (SCD) using ECG and HRV signals. *Trends Res*. 2018;1: 1-8. https://doi.org/10.15761/tr.1000105.
34. Ebrahimzadeh E, Foroutan A, Shams M, et al. An optimal strategy for prediction of sudden cardiacdeath through a pioneering feature-selection approach from HRV signal. *Comput Methods Programs Biomed*. 2019;169: 19-36. https://doi.org/10.1016/j.cmpb.2018.12.001.
35. Shi M, He H, Geng W, et al. Early detection of sudden cardiac death by using ensemble empirical mode decomposition-based entropy and classical linear features from heart rate variability signals. *Front Physiol*. 2020;11: 118. https://doi.org/10.3389/fphys.2020.00118.
36. Yang J, Sun Z, Zhu W, et al. Intelligent prediction of sudden cardiac death based on multi-domain feature fusion of heart rate variability signals. *EURASIP J Adv Signal Process*. 2023;32: 1-15. https://doi.org/10.1186/s13634-023-00992-6.
37. DeMazumder D, Limpitikul WB, Dorante M, et al. Entropy of cardiac repolarization predicts ventricular arrhythmias and mortality in patients receiving an implantable cardioverter-defibrillator for primary prevention of sudden death. *Europace*. 2016;18(12): 1818-28. https://doi.org/10.1093/europace/euv399.
38. Cheng A, Dalal D, Butcher B, et al. Prospective Observational Study of Implantable Cardioverter-Defibrillators in primary prevention of sudden cardiac death: study design and cohort description. *J Am Heart Assoc*. 2013;2(1): e000083. https://doi.org/10.1161/JAHA.112.000083.
39. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation*. 2006;113: 1424-33. https://doi.org/10.1161/

CIRCULATIONAHA.105.584102.
40. DeMazumder D, Lake DE, Cheng A, et al. Dynamic analysis of cardiac rhythms for discriminating atrial fibrillation from lethal ventricular arrhythmias. *Circ Arrhythm Electrophysiol*. 2013;6: 555-61. https://doi.org/10.1161/CIRCEP.113.000034.
41. Perkiomaki JS, Couderc JP, Daubert JP, et al. Temporal complexity of repolarization and mortality in patients with implantable cardioverter defibrillators. *Pacing Clin Electrophysiol*. 2003;26: 1931-6. https://doi.org/10.1046/j.1460-9592.2003.00298.x.
42. Murugappan M, Murugesan L, Jerritta S, et al. Sudden cardiac arrest (SCA) prediction using ECG morphological features. *Arab J Sci Eng*. 2020;46(2): 947-61. https://doi.org/10.1007/s13369-020-04765-3.
43. Buchman TG. Nonlinear dynamics, complex systems, and the pathobiology of critical illness. *Curr Opin Crit Care*. 2004;10(5): 378-82. https://doi.org/10.1097/01.CCCCx.0000139369.65817.b6.
44. Ivanov PCh, Rosenblum MG, Peng CK, et al. Scaling and universality in heart rate variability distributions. *Physica A*. 1998;249: 587-93. https://doi.org/10.1016/s0378-4371(97)00522-0.
45. Rigoli LM, Lorenz T, Coey C, et al. Co-actors exhibit similarity in their structure of behavioural variation that remains stable across range of naturalistic activities. *Sci Rep.* 2020;10(1): 6308. https://doi.org/10.1038/s41598-020-63056-x.
46. The Colors of Noise. Wikimedia Commons, 2015. ACCC Cessed 2025-08-02. Available from https://commons.wikimedia.org/wiki/File:The_Colors_of_Noise.png.