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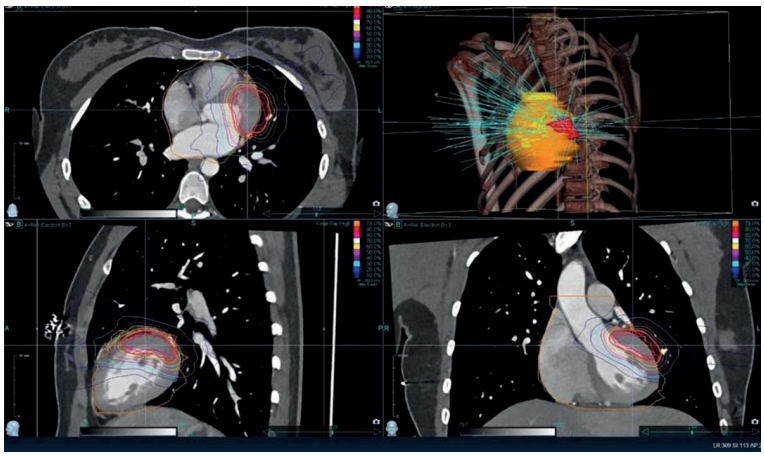

Figure from the article by A.V.Mazurok, V.A.Vaskovsky, N.A.Antipina, and A.Sh.Revishvili

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PREDICTORS OF SINUS RHYTHM RESTORATION DURING RADIOFREQUENCY ABLATION IN PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION

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Aim. To identify predictors of sinus rhythm restoration during radiofrequency ablation (RFA) in patients with persistent atrial fibrillation (AF).

Methods. The study included 51 patients with persistent AF who underwent primary RFA. All patients underwent left atrial (LA) voltage mapping. The percentage of low-voltage areas (LVA%) was calculated, with a low-voltage threshold 0.5 mV. After pulmonary vein isolation (PVI), if AF persist, posterior wall isolation and mitral isthmus ablation were performed. In cases of persistent AF, LA electrophysiological mapping was performed using a multielectrode catheter to identify areas of fractionated signals and local re-entry, followed by ablation of these areas. If AF transformed into atrial flutter, activation mapping was performed to verify the arrhythmia mechanism and ablate the critical isthmus. If the AF rhythm persisted, electrical cardioversion was performed.

Results. Sinus rhythm was restored during RFA in 29 patients (56.8%) and by electrical cardioversion in 22 patients (43.2%). Statistically significant differences between rhythm restoration types were found in AF duration (p=0.013; AUC=0.705) and LA appendage flow velocity (p=0.021; AUC=0.697). Patients who achieved rhythm restoration at the PVI stage had significantly smaller LA volume (p=0.004; AUC=0.796) and LVA% (p=0.002; AUC=0.792). In the group of patients in whom AF was eliminated by direct restoration to sinus rhythm during RFA, LVA% was significantly lower (p=0.039; AUC=0.738) compared with those in whom AF was eliminated via transformation into atrial flutter.

Conclusions. AF duration and LA appendage flow velocity are predictors of rhythm restoration during RFA. Among patients who achieved sinus rhythm restoration during ablation, those who converted at the PVI stage had smaller LA volume and LVA%. An LVA% greater than 28.5% was identified as a predictor of AF transformation into atypical atrial flutter during RFA of persistent AF.

Key words: atrial fibrillation; radiofrequency ablation; left atrial low voltage; sinus rhythm restoration

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Atrial fibrillation (AF) is the most common cardiac arrhythmia, significantly impairing patients' quality of life and increasing the risk of thromboembolic complications. Radiofrequency ablation (RFA) remains the leading interventional treatment for AF. However, the efficacy of the standard pulmonary vein isolation (PVI) procedure, especially in persistent AF (PersAF), remains unsatisfactory [1].

According to current data, the success rate of PVI alone in PersAF is 5070% after a single procedure, which is significantly lower than in paroxysmal AF [2]. This is due to the multifactorial nature of PersAF, where arrhythmia triggers may be located not only in the pulmonary vein ostia but also in other atrial regions. In the study by Y. Hung (2017), up to 50% of AF triggers were found outside the pulmonary veins [3].

Consequently, extended ablation strategies have been developed in clinical practice, including additional linear ablations in the left atrium (LA), ablation of complex fractionated signals, and modulation of parasympathetic elements in the LA [4, 5].

Studies have shown that extended strategies improve the efficacy of PersAF treatment compared with PVI alone [6, 7]. Several studies have demonstrated that restoration of sinus rhythm (SR) during RFA is associated with better longterm outcomes and may serve as an important prognostic factor for procedural efficacy in PersAF [810].

SR restoration during RFA for PersAF depends on the electrical and structural characteristics of the atria. For example, Matsuo et al. showed that a longer AF cycle length on the surface ECG and smaller LA size were associated with a higher likelihood of arrhythmia termination

during the procedure [11]. Similar findings were obtained in other studies - a longer baseline cycle length measured directly in the LA and smaller LA volume were independent predictors of successful rhythm restoration [9, 12, 13].

In recent years, special attention has been paid to the role of left atrial lowvoltage areas (LVA) and their impact on the efficacy of catheter ablation in PersAF. It has been shown that a smaller LVA percentage is associated with a higher probability of SR restoration during the procedure. In the study by S. Honarbakhsh et al. (2022), an LVA percentage <30% predicted successful arrhythmia termination with high sensitivity and specificity, although in that study the LVA threshold was 0.2 mV rather than the commonly used 0.5 mV [14].

Thus, the role of clinical factors (duration of history, comorbidities) and LVA percentage in predicting SR restoration remains insufficiently studied. The aim of this study was to identify predictors of SR restoration during ablation in RFA for patients with PersAF.

MATERIAL AND METHODS

The study included 51 patients with PersAF referred for firsttime RFA. Mean patient age was 67.10±9.49 years, 37 men (72%). In all patients, arrhythmia was clinically significant, manifesting as constant or transient palpitations and/or reduced exercise tolerance. AF was documented on electrocardiogram and Holter monitoring in all patients.

Inclusion criteria were: patients with PersAF referred for RFA who signed informed consent. Exclusion criteria were: age under 18 years, prior AF ablation, any prior cardiac surgery.

For each patient, the total arrhythmia history duration, persistent duration (PD), and the duration of arrhythmia history at the onset of persistence were determined. The total arrhythmia history was 50.38±10.00 months, with PD 17.03±3.76 months, and the duration before persistence onset was 32.5±8.21 months.

All patients underwent transoesophageal echocardiography within 24 hours before the procedure to exclude thrombi in the LA appendage and cavity, during which LA appendage emptying velocity was measured.

LA voltage maps were constructed using the CARTO 3 navigation mapping system (Biosense Webster, USA). Mapping was performed with a PentaRay multielectrode catheter (Biosense Webster, USA) using the "tissue proximity" function, with point distance from the atrial anatomical model ≤5 mm, using the Confidense module with the following parameters: catheter position stability 6 mm, electroanatomical point density 1 mm. All voltage maps consisted of at least 2000 points, with a mean of 2128±104 points. After mapping, voltage maps were analysed, LVA areas were identified, and the percentage of LVA was calculated.

Areas with bipolar signal amplitude >0.5 mV were defined as normalvoltage areas; areas with amplitude <0.5 mV were classified as LVA. The LVA percentage (LVA%) was calculated for each map. LVA assessment was performed only in the LA. Right atrial mapping was not performed, as its functional significance in PersAF remains uncertain and routine right atrial mapping is not included in standard recommendations (EHRA/HRS/APHRS/LAHRS Consensus 2024) [15].

The procedure was performed under general anaesthesia. RFA was performed using a ThermoCool Smart Touch irrigated ablation catheter with contactforce sensing (Biosense Webster, USA). After LA voltage mapping and PVI, if AF persisted, LA posterior wall isolation, mitral isthmus ablation, and, if AF still persisted, electrophysiological mapping of the LA with the multielectrode catheter was performed to identify areas of fractionated signals and conduction dispersion, followed by ablation of these areas. Areas of fractionated potentials and conduction dispersion were manually annotated based on local electrograms. When AF rhythm transformed into atrial flutter (AFL), activation mapping of the LA was performed to verify the arrhythmia mechanism and ablate the critical isthmus. If AF rhythm persisted, SR was achieved by electrical cardioversion. There was no randomisation in the study; the decision to perform electrical cardioversion did not depend on the patient's clinical profile and was the final standard step after all ablation stages were exhausted. The decision was made jointly by the operating surgeon and electrophysiologist.

After SR restoration, the presence of PVI was assessed by stimulation from a Lasso catheter sequentially placed in the pulmonary veins, confirming conduction block. Stimulation mapping was used to verify linear LA ablations; if block was absent, additional applications were delivered until conduction block was achieved. LA posterior wall block was verified by bipolar pacing from the distal pair of the SmartTouch

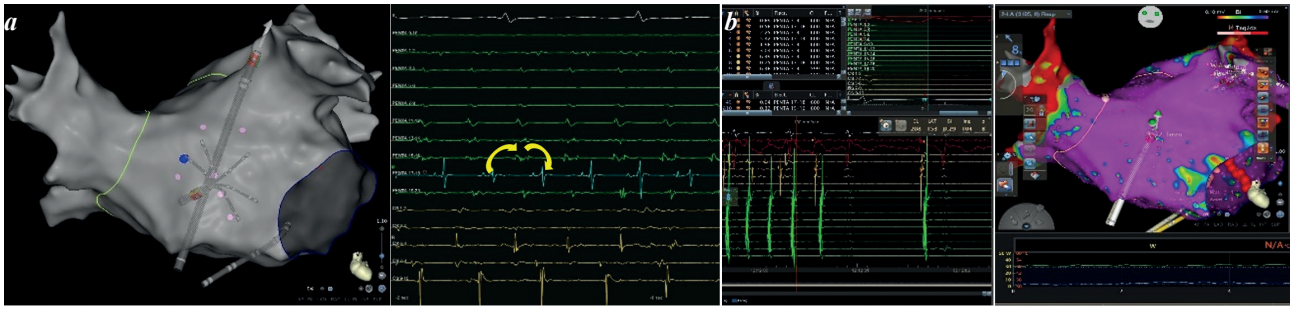

Fig. 1. Restoration of sinus rhythm: a - LA mapping with a PentaRay multielectrode catheter; the catheter is positioned at the anterior LA wall (CS - coronary sinus; CS12 - distal pair of electrodes, CS910 - proximal pair; on PentaRay electrodes 1516 and 1718, localised reentry is indicated by arrows); b - ablation at the anterior LA wall (on the LA voltage map, purple - voltage >0.5 mV, red - voltage <0.1 mV, green and orange - voltage 0.10.5 mV; ablation electrode at the anterior LA wall; the arrow indicates the direction of contact force; the PentaRay multielectrode catheter is positioned in the LA appendage).

Table 1.

Characteristics of patient groups depending on the mechanism and stage of the procedure at which sinus rhythm restoration occurred

Parameter	RFA	ECV	$P_{1,2}$	PVI	LAbl	Focal	P_{3-5}	LAbl+Focal	$P_{3,6}$	Direct SR	Via AFL	$P_{7,8}$
	1	2		3	4	5		6		7	8	
Age, years	72.0 (63.0-76.0)	65.0 (60.0-70.75)	0.055	63.0 (62.0-65.0)	72.0 (62.0-77.0)	74.0 (70.0-76.0)	0.145	74.0 (63.75-77.0)	0.073	65.0 (62.0-73.50)	75.5 (66.7-76.7)	0.097
Male sex, n (%)	22 (75.8)	15 (68.2)	0.752	4 (80)	9 (81.8)	9 (69.2)	0.751	18 (75)	1.00	12 (80)	10 (71.4)	0.682
Arrhythmia history duration, months	28.0 (11.0-84.0)	51.50 (11.25-84.0)	0.594	96.0 (12.0-96.0)	30.0 (12.50-78.0)	13.0 (6.0-36.0)	0.451	21.0 (10.75-54.0)	0.506	14.0 (5.0-96.0)	32.0 (11.2-47.5)	0.793
Persistent duration, months	4.50 (3.75-12.0)	13.0 (5.0-45.0)	0.013	3.0 (2.0-6.75)	6.0 (4.0-12.50)	5.0 (4.0-12.0)	0.529	5.50 (4.0-12.0)	0.320	4.0 (3.0-10.50)	8.0 (4.0-12.0)	0.246
Diabetes mellitus, n	12	7	0.566	2	3	7	0.419	10	1.00	6	6	1.00
CA, n	12	7	0.566	1	5	6	0.566	11	0.370	4	8	0.139
GFR, mL/min/1.73 m^2	62.91±16.70	65.05±15.20	0.650	78.90±18.82	65.73±14.20	65.46±15.36	0.077	65.58±14.52	0.057	57.80 (51.30-75.0)	64.1 (52.0-76.1)	1.00
BMI, kg/m^2	28.50±5.49	30.70±4.24	0.125	30.34±5.23	26.71±4.07	29.30±6.51	0.380	26.0 (24.3-30.6)	0.341	28.74±5.67	28.24±5.49	0.812
IVS thickness, mm	11.0 (10.0-12.0)	11.0 (10.0-13.0)	0.696	10.0 (9.0-12.0)	11.0 (9.50-12.50)	11.0 (10.0-12.0)	0.731	11.0 (10-12)	0.465	11 (9-12.5)	11 (10-12)	0.791
LA AP diameter, cm	4.0(4.0-5.0)	5.0 (4.0-5.0)	0.487	4.0±1	4.0±0	4.0±1	0.253	4.0±1	0.099	4.0±1	4.0±1	0.729
LAA EV, cm/s	48 (35-58)	34 (28-47)	0.021	61±27	42±14	50±19	0.188	46±17	0.114	53±21	43±17	0.184
LA volume by map, mL	165±46	189±41	0.066	128±42	176±31	171±53	0.126	169 (137-200)	0.040	150 (117-197)	168 (138-192)	0.275
LVA, %	34.27±21.88	37.48±18.66	0.583	15.10±9.69	36.58±24.11	39.68±20.28	0.089	38.26±21.68	0.002	26.25±20.94	42.86±20.13	0.039

Note: RFA - radiofrequency ablation; ECV - electrical cardioversion; PVI - pulmonary vein isolation; LAbl - linear ablations; Focal - focal activity ablation; AFL - atrial flutter; CA - coronary atherosclerosis; GFR - glomerular filtration rate; BMI - body mass index; IVS - interventricular septum; LA - left atrium; AP - anteroposterior; LAA EV - left atrial appendage emptying velocity; LVA - lowvoltage area.

ablation catheter (Biosense Webster, USA), positioned between the superior and inferior PVI lines. Catheter-tissue contact was monitored by contact force. Absence of atrial capture and no responses to pacing confirmed LA posterior wall block. Mitral isthmus block was assessed by pacing from the LA appendage and analysing the activation sequence on the coronary sinus catheter. Conduction block across the mitral isthmus was confirmed when activation proceeded from the proximal to the distal pair of the decapolar coronary sinus electrode. Fig. 1 illustrates SR restoration during ablation of focal activity in the anterior LA wall.

The following definitions were used: "AF elimination" - SR restoration achieved directly during RFA without electrical cardioversion; "mechanism of AF elimination" - termination of AF at various ablation stages (PVI, linear ablations, localised substrate ablation); "type of AF elimination" - the pattern of arrhythmia transition (direct SR restoration or AF transformation into AFL).

Patients were divided into the following groups: Group 1 - SR restored during RFA; Group 2 - SR restored by electrical cardioversion. Group 1 was further subdivided by mechanism of AF elimination: during PVI, during linear ablation, or during focal activity ablation. Group 1 was also divided into two subgroups by type of AF elimination: direct SR restoration and transformation into AFL.

Statistical analysis

Statistical analysis was performed using StatTech v. 4.8.11 (Stattech LLC, Russia). Quantitative variables were assessed for normality using the Shapiro-Wilk test. Normally distributed variables are presented as mean (M) and standard deviation (SD), with 95% confidence intervals (95% CI). Nonnormally distributed variables are presented as median (Me) and interquartile range (Q1-Q3). Categorical variables are presented as absolute numbers and percentages. Comparison of two groups for normally distributed variables with equal variances was performed using Student's ttest. Nonnormally distributed variables were compared using the Mann-Whitney Utest. Comparison of percentages in 2×2 contingency tables was performed using Fisher's exact test (if expected frequency <10). Odds ratios with 95% CI were calculated. The strength of association between categorical variables was assessed using Cramér's V, interpreted according to Rea & Parker (2014). Differences were considered significant at $p<0.05$.

ROC curve analysis was used to evaluate discriminative ability. The cutoff point was determined by the maximum Youden index. Discriminative ability was assessed by the area under the ROC curve (AUC), classified according to J.N. Mandrekar (2010): AUC 0.50.6 - poor, 0.60.7 - weak, 0.70.8 - satisfactory, 0.80.9 - good, >0.9 - excellent [16].

RESULTS

SR was restored during RFA in 29 patients (56.8%) and by electrical cardioversion in 22 patients (43.2%). Statistically significant differences between Group 1 and Group 2 were found in PD of AF (p=0.013) and LA appendage emptying velocity (p=0.021). No differences between groups were found for the other parameters. Results of the comparative analysis for all parameters are shown in Table 1. ROC curves for PD and LA appendage emptying velocity are shown in Fig. 2.

PD was a statistically significant predictor of rhythm restoration with satisfactory discriminative ability (AUC=0.705; 95% CI 0.5570.854, p=0.013). The optimal cutoff value for PD was 24 months. Rhythm restoration by electrical cardioversion was predicted at PD values ≥ this threshold. Sensitivity and specificity of the model were 45.5% and 92.9%, respectively.

LA appendage emptying velocity was a statistically significant predictor of rhythm restoration, but discriminative ability was weak (AUC=0.697; 95% CI 0.5470.846, p=0.021). The optimal cutoff for LA appendage emptying velocity was 48 cm/s. Restoration by electrical cardioversion was predicted at values below this threshold. Sensitivity and specificity were 85.7% and 61.5%, respectively.

In further analysis of subgroups within Group 1, the following results were obtained. According to the mechanism of AF elimination, Group 1 was divided into: AF elimination achieved at the PVI stage (n=5), during linear ablation (n=11), during ablation of focal activity areas (n=13). No differences were found between subgroups with different elimination mechanisms for all parameters. Results are shown in Table 1.

In further analysis, the subgroups with SR restoration during linear ablation and focal activity ablation were combined into one. They were compared with the subgroup in which rhythm restoration occurred during PVI. The PVI subgroup had significantly smaller LA volume (p=0.004) and LVA% (p=0.002). Results are shown in Table 1. ROC curves for LVA% and LA volume are shown in Fig. 3.

LVA% was a statistically significant predictor of AF elimination during PVI with satisfactory discriminative ability (AUC=0.792; 95% CI 0.6030.980, p=0.043). The optimal cutoff for LVA% was 28.5%. Rhythm restoration during PVI was predicted at LVA% below this threshold.

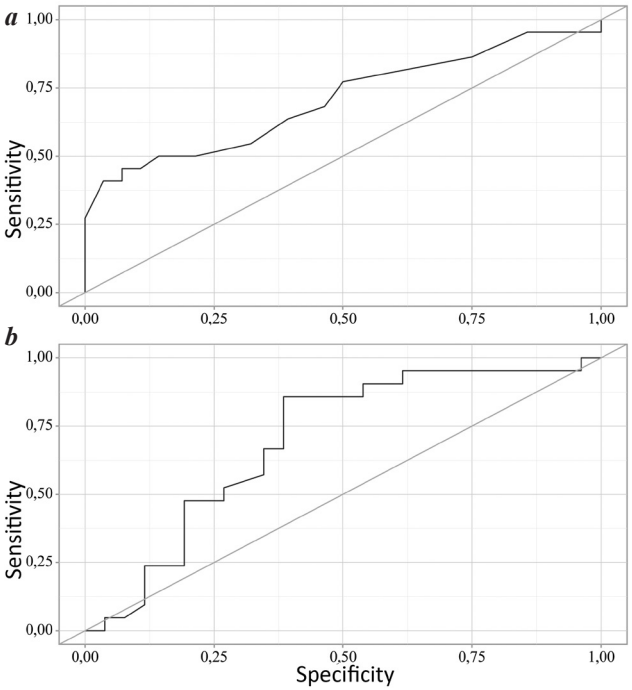

Fig. 2. ROC curves showing the discriminative ability of persistent duration (a) and LA appendage emptying velocity (b) for predicting rhythm restoration.

Sensitivity and specificity were 100.0% and 66.7%, respectively.

LA volume was a statistically significant predictor of AF elimination during PVI with satisfactory discriminative ability (AUC=0.796; 95% CI 0.6100.982, p=0.040). The optimal cutoff for LA volume was 114 mL. Rhythm restoration during PVI was predicted at LA volume below this threshold. Sensitivity and specificity were 60.0% and 100.0%, respectively.

According to the type of AF elimination, Group 1 was divided into: direct SR restoration (n=15) and transformation into AFL (n=14). The direct SR restoration subgroup had significantly lower LVA% (p=0.039). No differences in other parameters were found. Results are shown in Table 1. The ROC curve for LVA% is shown in Fig. 4.

LVA% was a statistically significant predictor of the type of AF elimination with transformation into AFL, with satisfactory discriminative ability (AUC=0.738; 95% CI 0.5530.923, p=0.029). The optimal cutoff for LVA% was 28.5%. Transformation into AFL was predicted at LVA% ≥ this threshold. Sensitivity and specificity were 78.6% and 66.7%, respectively.

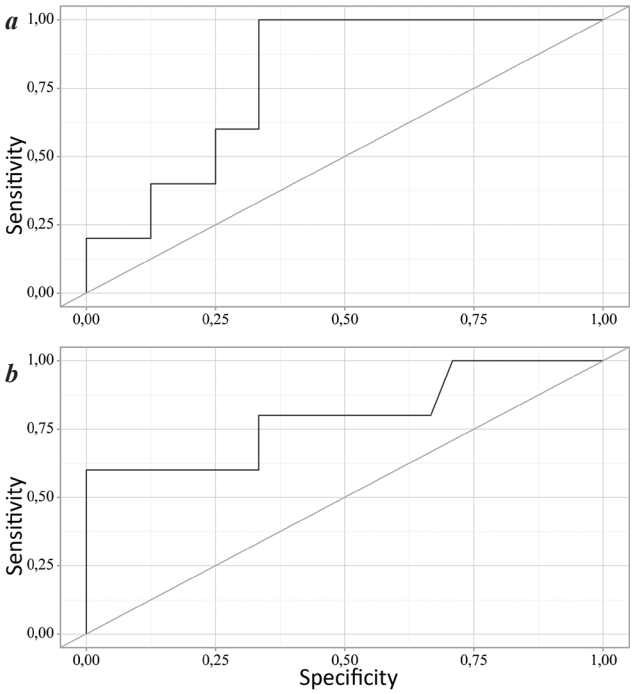

Fig. 3. ROC curves showing the discriminative ability of LVA% (a) and LA volume (b) for predicting the mechanism of AF elimination.

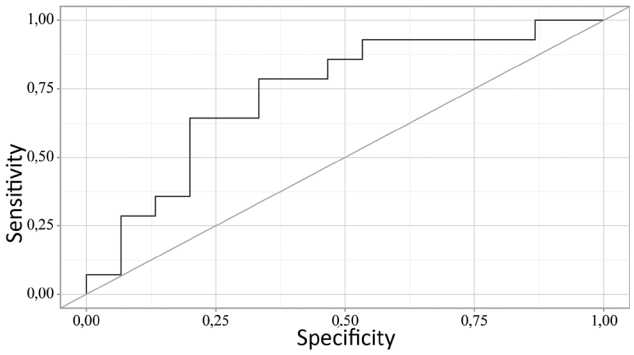

Fig. 4. ROC curve showing the discriminative ability of LVA% for predicting the type of AF elimination.

DISCUSSION

Our study showed that the probability of SR restoration during RFA in PersAF patients is associated with PD and LA appendage emptying velocity. Previous studies on this issue most frequently reported associations between LA size and AF cycle length (measured on surface ECG or during endocardial mapping) with rhythm restoration during RFA. For instance, S. Matsuo et al. (2009) demonstrated that shorter PD, smaller LA size, and longer AF cycle length on surface ECG were independent predictors of arrhythmia termination during the procedure [11]. Similar findings were reported by E.K. Heist et al. (2012), showing that AF cycle length and atrial size determined the likelihood of SR restoration during RFA [9]. S. Ammar et al. (2014) found that AF cycle length in the LA appendage within 155200 ms was associated with the highest probability of SR restoration and favourable clinical outcome [12]. Also, in the work by A.V. Chapurnykh et al. (2018), a longer cycle length on the coronary sinus catheter (210 ms) was a predictor of the presence of focal activity foci and, consequently, rhythm restoration during ablation [13].

In our study, we did not find an association between LA dimensions (either AP diameter or LA volume calculated from mapping data) and SR restoration. However, patients in whom rhythm restoration occurred at the PVI stage had significantly smaller LA volume. This may indicate that patients with larger LA volume have more widespread nonpulmonaryvein AF triggers requiring more extensive ablation.

PD proved to be a significant predictor of rhythm restoration in our study. This result agrees with studies showing that longer arrhythmia duration reduces the likelihood of AF elimination during RFA [8, 9, 11]. An interesting observation is that the cutoff PD predicting more likely rhythm restoration during ablation was 24 months. These data suggest that in patients with longstanding PersAF, a more aggressive surgical strategy should be adopted, as even in patients with PD of 24 months, SR restoration during RFA is highly probable.

Our study also revealed an association between LA appendage emptying velocity and the likelihood of SR restoration during RFA: lower values were associated with the need for electrical cardioversion, while higher values were more often associated with rhythm restoration during ablation. There are many publications indicating that reduced LA appendage emptying velocity correlates not only with thrombus formation risk but is also an important predictor of arrhythmia persistence and reflects atrial remodelling processes. Studies by D. Fatkin et al. (1994) showed that LA appendage emptying velocity <20 cm/s reflects pronounced mechanical and electrical atrial remodelling and is associated with highly persistent AF [17]. A metaanalysis by P. Chen et al. (2022) demonstrated that reduced LA appendage emptying velocity is associated with increased AF recurrence risk [18]. N. Isobe et al. (2005) emphasised that LA appendage emptying velocity was the best predictor of SR maintenance after cryoballoon AF ablation [19]. Other studies found that higher LA appendage emptying velocity was significantly higher in patients with successful electrical cardioversion [20].

Similar data on the clinical significance of LA appendage functional status were obtained in the work of V.V. Vlodyanovsky et al. (2019), who analysed acute changes in intraatrial haemodynamics after electrical and pharmacological cardioversion in PersAF patients [21]. Collectively, these data confirm that LA appendage emptying velocity characterises not only thrombus risk but also atrial functional status, which may be relevant to the likelihood of SR restoration. We did not encounter references indicating that LA appendage emptying velocity could predict SR restoration during RFA for PersAF. However, it is important to note that the discriminative ability of LA appendage emptying velocity remains weak. In our view, this indicates that this parameter is an important but not the sole factor influencing arrhythmia termination.

In recent years, assessment of LVA of LA has gained particular importance. In our study, no differences in LVA% were found between patients with SR restoration during RFA and those requiring electrical cardioversion. A crucial factor influencing study results is the choice of LVA threshold. The threshold value currently remains a subject of debate. In our work, we adopted the threshold of <0.5 mV as the most widely used in clinical studies and reflected in the EHRA/HRS/APHRS/LAHRS Expert Consensus Statement (2024) [15].

The relationship between LVA of LA and AF termination during RFA has been the subject of many studies. A. Jadidi et al. (2020) demonstrated that areas of arrhythmia termination during ablation correlated with LVA [22]. However, another study by the same group noted that the mean voltage in areas where arrhythmia terminated was 0.49±0.39 mV, which may often correspond to conventional normal voltage (>0.5 mV). In an earlier study by the same group (2016), 80% of rhythm restoration sites during ablation were located in LVA and 20% in adjacent areas [23].

A. Schade et al. (2016) showed that 30% of mapped arrhythmogenic areas were not associated with LVA and not related to pulmonary veins [24]. In the work by S. Honarbakhsh et al. (2024), which investigated the relationship between focal and rotor activity and LVA, rotor activity was associated with LVA, while focal activity was not [25]. In the previously mentioned study by the same group, an LVA percentage <30% was an independent predictor of SR restoration during ablation [14]. However, that study defined LVA as areas with signal amplitude <0.2 mV, whereas we used a threshold of 0.5 mV. Also, that study included patients with PD ≤24 months, while in our work 13 patients had longer PD.

Thus, as shown in many works, nonpulmonaryvein AF triggers are not always associated with LVA. This is consistent with our finding of no association between LVA% and rhythm restoration during RFA. At the same time, a lower LVA% was associated with rhythm restoration during PVI and direct SR restoration, whereas higher LVA% was more often associated with AF transformation into AFL.

In the study by A. Jadidi et al. (2016), in patients with LVA% <10%, only PVI or PVI plus additional ablations were performed, and efficacy was comparable in both groups [22]. This observation agrees with our data that patients with lower LVA% achieve SR restoration at the PVI stage and do not require additional ablation. We did not find studies examining the association between LVA extent and the type of AF termination during RFA. However, in the study by K. Sonoda et al. (2024), an association was shown between LVA extent and induction of macroreentry after PVI. In a multivariate model, only LVA area was associated with recurrence of macroreentry [26]. These data support our findings regarding the association between LVA and AFL. This observation is likely explained by the fact that LVA create conduction slowing, which may serve as a substrate for macroreentry. At the same time, our data indicate that in patients with longstanding persistence and a higher LVA%, SR restoration during ablation is still achievable.

Study limitations

It is important to note that the sample size limits the statistical power of the analysis, which may have affected the identification of independent associations. The results reflect the experience of a single centre and procedures performed under a unified protocol, limiting external validity. The study design did not include analysis of longterm freedom from arrhythmia, suggesting the need for continuation of the study.

CONCLUSION

1. Persistent duration <24 months and LA appendage emptying velocity >48 cm/s are predictors of SR restoration during RFA in patients with PersAF.
2. LVA% of LA does not correlate with SR restoration during RFA at the overall cohort level.
3. Among patients with SR restoration during RFA, rhythm restoration at the PVI stage was associated with less extensive LVA and smaller LA volume compared with patients in whom SR was restored at later ablation stages.
4. LVA% of LA >28.5% was a predictor of rhythm transformation into atypical atrial flutter during RFA for PersAF.

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CORRELATION BETWEEN PULMONARY VEIN ISOLATION EFFICACY AND MYOCARDIAL MORPHOLOGICAL CHANGES

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Aim. To investigate the correlation between the efficacy of pulmonary vein ostial isolation and morphological changes in the myocardium.

Methods. The study included 118 patients with paroxysmal or persistent atrial fibrillation (AF) and no significant structural heart disease. All patients underwent primary cryoballoon isolation of the pulmonary vein ostia with simultaneous implantation of a loop ECG recorder (Medtronic Reveal XT) and myocardial biopsy of the interatrial septum (IAS) and the interventricular septum (IVS). Tissue samples were obtained before cryoballoon ablation (CBA). Patients were followed for one year with regular visits at 3, 6, and 12 months. If AF recurred, patients underwent a repeat electrophysiological study to assess the durability of pulmonary vein isolation. In cases of recovered pulmonary vein conduction, reisolation was performed, followed by another year of followup using the same visit schedule. Consequently, two patient groups were formed: those without AF recurrence (after one or two procedures) and those with recurrence (after two catheter isolation attempts).

Results. Owing to an insufficient number of representative IAS biopsy samples (the biopsy material mainly consisted of the fibrous portion of the IAS), the analysis of the relationship between IAS morphological changes and nonpulmonaryveindependent AF recurrence could not be performed. In IVS biopsy samples, the most common morphological findings were myocardial hypertrophy, loss of myocardial crossstriation, endocardial thickening and lipomatosis, and cardiomyocyte dystrophy.

Conclusion. In all AF patients without severe organic heart disease, various morphological changes of the IVS myocardium were identified, including fibrosis, lipomatosis, and dystrophy. Histological changes in myocardial biopsies from AF patients, such as cardiomyocyte degeneration and endocardial thickening, are important components of atrial remodelling that contribute to arrhythmia initiation, maintenance, and progression - consistent with the concept of atrial cardiomyopathy (atrial myopathy) regardless of its origin. A deeper understanding of these cellular and molecular changes may inform the development of novel targeted strategies for AF prevention and treatment. No clear predictors of a specific electrophysiological type of AF recurrence (pulmonaryveindependent vs. nonpulmonaryveindependent) after radiofrequency ablation were identified, which may reflect common underlying mechanisms and warrants further investigation.

Key words: interatrial septum biopsy; atrial fibrillation; myocardial biopsy; loop ECG recorder; pulmonary vein isolation

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Atrial fibrillation (AF) has long remained the most common cardiac arrhythmia [1]. In most cases, the pathogenesis of AF is related to the electrical activity of the pulmonary vein (PV) sleeves; however, in many patients, recurrent AF episodes may be associated with the presence or emergence of ectopic foci outside the PVs [2]. Currently, there are no clear predictors of nonPVrelated AF, and therefore it cannot be predicted, prevented, or adequately managed with appropriate therapy for the respective patients.

The search for and development of new theories of arrhythmogenesis continues. One of the actively discussed theories is the role of the inflammatory process as a trigger and substrate for AF maintenance. One of the earliest works linking inflammatory myocardial changes and AF was published in 1991. In 14 patients with no thyroid dys-

function, an anteroposterior left atrium (LA) dimension <40 mm, no coronary pathology, and no other chronic diseases, with AF refractory to antiarrhythmic therapy, myocardial biopsy was performed. In more than half of the patients, ventricular myocardial fibrosis and/or cardiomyocyte necrosis was found, active myocarditis in three, and changes consistent with cardiomyopathy in three [3].

This line of research was continued, and in 2010, the results of a study of biopsy material from the interatrial septum (IAS) in patients with idiopathic AF refractory to antiarrhythmic therapy were published. Myocardial changes were detected in 100% of patients, including signs of active myocarditis in 66%. Moreover, in patients with successful immunosuppressive therapy for myocarditis, sustained remission of AF was achieved, suggesting a crucial role of the inflammatory process in the genesis of atrial tachyarrhythmias, particularly AF [4]. It is also important to compare the criteria for active myocarditis in biopsies from the IAS and the interventricular septum (IVS): their concordance has been proven, allowing reliance on IVS biopsy data, which is more commonly performed in clinical practice.

Confirmation of the impact of myocardial inflammation on arrhythmias was also obtained by our compatriots in 2015. An association between heart rate variability in rats with autoimmune myocarditis was demonstrated, with a decrease in parasympathetic and an increase in sympathetic influence during a cold stress test [5].

Since 2012, catheter treatment has been the mainstay of therapy for AF refractory to pharmacological management (class IA recommendation), and pulmonary vein isolation is the primary method to achieve efficacy [6, 7].

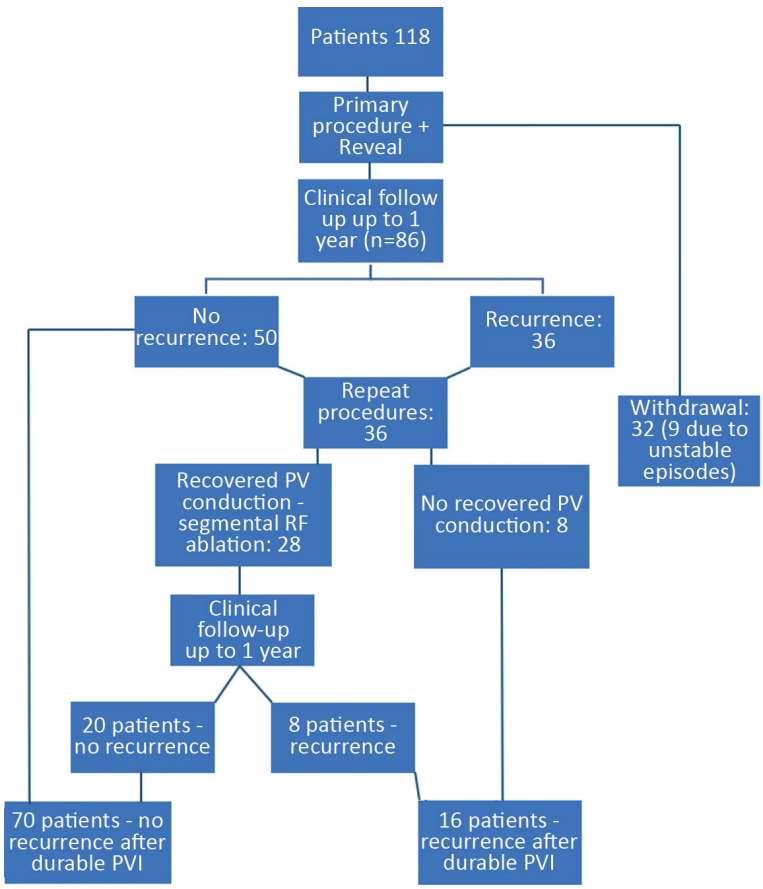

Fig. 1. Graphical representation of the study design.

However, according to a 2009 systematic metaanalysis including 31 studies, the success rate of the initial radiofrequency ablation (RFA) procedure is 57%, and the success rate of repeat procedures is 71% in patients without any antiarrhythmic therapy (AAT) [8].

In our study, we divide AF variants into two categories: (1) AF predominantly arising from the PV ostia ("PVdependent" AF) and (2) AF predominantly developing from sources outside the PVs ("nonPVdependent" AF). Hypothetically, achieving durable electrical isolation of the PVs by catheter ablation (in our study, cryoballoon ablation) in patients with the first category should result in complete freedom from arrhythmia. In contrast, patients in the second category would experience recurrences. This division is logically applicable but somewhat arbitrary, as AF may be triggered by several sources simultaneously, and PV isolation may have a partial effect (e.g., recurrence of episodes with reduced frequency and duration). Within this framework, we make another assumption: after repeat PV isolation, the likelihood of AF recurrence associated with PV activity is negligible. This distinction has practical value - dividing patients into those who can be treated with PV isolation and those who require extended ablation, since PV isolation is currently the goldstandard, universally accepted treatment for nonvalvular AF.

The aim of this study is to investigate the correlation between the efficacy of isolated PV ostial isolation and morphological changes in the myocardium.

MATERIAL AND METHODS

This is a prospective, singlecentre study. Patient enrolment was performed consecutively from 2017 to 2021, with a total of 118 patients included. All patients signed written informed consent before enrolment. The protocol was approved by the local ethics committee and complied with the Helsinki Declaration. The main objective of the study was to identify "PVdependent" and "nonPVdependent" AF groups and compare the results of endomyocardial biopsy (EMB). Any morphological changes in either the IAS or the IVS were considered equally relevant. The primary efficacy endpoint was AF recurrence within one year after one or two catheter procedures (outside the "blanking period", which lasts 3 months after the intervention). To achieve this goal, the following study design was planned.

Study design

The study included patients >18 years of age with paroxysmal or persistent AF, EHRA symptom class 2b4, who signed informed consent and underwent cryoballoon ablation of the pulmonary vein ostia (CBA PVI) with simultaneous implantation of a loop ECG recorder and EMB. Exclusion criteria included: decompensated comorbidities (hypertension, diabetes mellitus, unstable coronary artery disease, etc.), significant structural heart disease on echocardiography (LA >50 mm, intracardiac thrombosis, mitral regurgitation grade ≥3,

LVEF <40%, myocardial hypertrophy >14 mm), and withdrawal from the study at any stage.

Primary CBA PVI with simultaneous implantation of a loop ECG recorder (Medtronic Reveal XT) and biopsy of endocardium and myocardium from the IAS and IVS (tissue sampling was performed before CBA) was performed in 118 patients. However, 23 patients withdrew from the study voluntarily before the first followup visit, and 9 patients also withdrew because of unstable paroxysms lasting <30 seconds at the 6month followup visit. Consequently, the statistical analysis was performed on a cohort of 86 patients (53 men and 33 women) with paroxysmal (n=63) and persistent (n=23) AF, with a mean age of 56±9.9 years (Fig. 1). Detailed clinical characteristics are presented in Table 1.

Prospective followup

The first followup period lasted 12 months with regular visits at 3, 6, and 12 months. When sustained AF recurrences (symptomatic or asymptomatic after the blanking period - >3 months after the intervention) were detected by ECG, Holter monitoring, or the loop recorder, patients were referred for a repeat PV isolation procedure with assessment of PV activity and subsequent catheter treatment. In patients in whom the repeat electrophysiological study revealed nondurable PVI, segmental RFA of the PVs alone (reisolation) was performed; these patients then continued followup on the same visit schedule for an additional 12 months. If the repeat procedure showed no electrical activity in any PV, the patient was considered to have reached the endpoint, assigned to the "nonPVdependent" AF group, and could receive additional ablation outside the PVs as part of standard clinical practice. Based on the followup results, two groups were formed: patients with sustained remission after one or two procedures and patients with AF recurrence despite durable PVI or after repeat PVonly isolation.

The study was considered complete after 12 months of followup after the last catheter procedure, or upon AF recurrence with verification of PVI durability during a repeat procedure, or upon AF recurrence (after the blanking period) after the second intervention.

Study methods

Intraoperatively, patients underwent CBA of the PVs using a cryoconsole and Arctic Front Advance cryoballoon (Medtronic, USA), and implantation of a Reveal XT loop ECG recorder (Medtronic Reveal XT, USA). Postoperatively, no routine antiarrhythmic therapy was prescribed; betablockers were given to a few patients with symptomatic postoperative sinus tachycardia. Recurrence was defined as detected AF episodes lasting >2 minutes on the loop recorder, or >30 seconds on a 12lead ECG or Holter monitoring.

Table 1.

Clinical and demographic characteristics of the overall patient group

Parameter	Overall group (n=86)	PV dependent AF (n=70)	Non PV dependent AF (n=16)	p
Age, years	56 [48;62]	56 [47.75;62]	57 [51;67]	0.365
Age at arrhythmia onset, years	50 [42.5;59]	50 [43.75;59]	51 [40;58]	0.904
AF history duration, years	3 [1.5;6]	3 [1;5]	6 [3;9]	0.027
Body mass index, kg/m^2	30.1 [26.75;32.9]	29.8 [26.8;32.9]	30.7 [26.3;32.9]	0.894
Left atrial volume, mL	42 [39;46]	42 [39;45]	43 [41;49]	0.215
Left ventricular ejection fraction, %	62 [60;66]	62.5 [60;66]	61 [58;65]	0.146
Left ventricular end diastolic dimension, mm	51 [48;54]	51 [47;54.2]	51 [49;54]	1.000
CHA_2DS_2 VASc score	2 [1;3]	1.5 [1;3]	2 [2;2]	0.439
HAS BLED score	0 [0;2]	1 [0;2]	0 [0;1]	0.302
High sensitivity CRP	1.83 [0.95;4.00]	2.04 [1.01;4.24]	1.60 [0.785;3.140]	0.402
NT proBNP	272 [90.9;697.0]	191 [72.9;573]	719 [225;1235]	0.014
Hypertrophy (>14 mm), n (%)	9 (10.6)	4 (5.8%)	5 (31.3%)	0.010
Male sex, n (%)	53 (61.6)	46 (65.7%)	7 (43.8)	0.103
Persistent AF, n (%)	63 (73.3)	52 (74.3)	11 (68.8%)	0.652
Hypertension, n (%)	54 (62.8)	43 (61.4)	11 (68.8%)	0.585
Systemic diseases, n (%)	5 (5.8)	4 (5.7%)	1 (6.3%)	1.000
Obesity, n (%)	41 (47.7)	33 (47.1%)	8 (50%)	0.880
Coronary artery disease, n (%)	4 (4.7)	4 (5.7%)	0 (0)	1.000
Stroke, n (%)	4 (4.7)	3 (4.3%)	1 (6.3%)	0.568
Transient ischaemic attack, n (%)	3 (3.5)	2 (2.9%)	1 (6.3%)	0.465
Diabetes mellitus, n (%)	9 (10.5)	7 (10%)	2 (12.5%)	0.672
Impaired glucose tolerance, n (%)	4 (4.7)	4 (5.7%)	0 (0)	1.000

Note: PV - pulmonary veins; AF - atrial fibrillation; CRP - C reactive protein; NT proBNP - N terminal pro B type natriuretic peptide; p - significance of differences between PV dependent and non PV dependent AF groups.

EMB was performed in the catheterisation laboratory via femoral vein puncture using Cordis Biopsy Forceps 7F 104 cm. Under intracardiac echocardiography and fluoroscopic guidance (RAO 30°, LAO 40°), biopsy samples were obtained from the IAS (one site, aiming for the muscular portion of the septum) and the lower third of the IVS (two sites). Tissue was placed in buffered formalin, stained with haematoxylineosin and Van Gieson, and subjected to morphological examination. Biopsy data analysis included a description of individual morphological changes. Changes in the IAS and IVS were considered of equal value in this study.

The aim of this study was not to detect myocarditis or its activity, but merely to attempt to find a correlation between morphological changes and the arrhythmia focus localisation; therefore, immunohistochemical examination was not performed (to avoid unjustified cost increase).

Statistical analysis

Statistical analysis was performed using R v. 3.6.1. The ShapiroWilk test was used to check normality. Quantitative variables were expressed as mean ± standard deviation or median with interquartile range, and compared using Student's ttest or the MannWhitney Utest. Categorical variables were expressed as absolute and relative frequencies (percentages), and compared using Pearson's χ^2 test or Fisher's exact test. Univariate and multivariate regression analyses were used to identify predictors of AF recurrence in patients with durable PVI (i.e., predictors of "nonPVdependent" AF). Differences were considered significant at twosided $p<0.05$.

RESULTS

The study included 118 patients; however, after followup, 86 patients were included in the analysis for morphological predictors, of whom 70 had "PVdependent" AF and 16 had "nonPVdependent" AF. The remaining patients were excluded from the analysis due to incomplete followup (mostly due to refusal of a repeat procedure in the presence of clinically insignificant recurrences and, consequently, inability to assess PVI status). Differences in clinical parameters between the two groups are presented in Table 1. The AF recurrence rate, considering asymptomatic recurrences detected by the implantable subcutaneous loop recorder, was 58.1% after primary CBA PVI, and 71.4% after repeat PV isolation without additional ablation.

Table 2.

Frequency of individual morphological changes in interventricular septum biopsy samples

Parameter	PV dependent AF (n=70)	Non PV dependent AF (n=16)	p
Endocardial blood clots, n (%)	2 (2.86)	0 (0)	0.494
Endocardial thickening, n (%)	13 (18.6)	7 (43.75)	0.031
Endocardial sclerosis, n (%)	28 (40)	8 (50)	0.464
Lymphocytic infiltration of endocardium, n (%)	4 (5.7)	2 (12.5)	0.309
Eosinophils in endocardium, n (%)	2 (2.86)	0 (0)	1.000
Endocardial lipomatosis, n (%)	15 (21.4)	7 (43.75)	0.108
Endocardial hyalinosis, n (%)	0 (0)	1 (6.25)	0.186
Endocardial fibrosis, n (%)	0 (0)	0 (0)	-
Myocardial hypertrophy, n (%)	64 (91.4)	15 (93.75)	1.000
Loss of myocardial cross striation, n (%)	39 (55.7)	10 (62.5)	0.621
Contraction bands in myocardium, n (%)	28 (40)	4 (25)	0.263
Cardiomyocyte dystrophy, n (%)	45 (64.3)	3 (37.5)	<0.001
Necrosis / myolysis / apoptosis of cardiomyocytes, n (%)	12 (17.1)	1 (6.25)	0.446
Lipofuscin in cardiomyocytes, n (%)	20 (28.6)	7 (43.75)	0.238
Loss / lysis of cardiomyocyte nuclei, n (%)	21 (30)	5 (31.25)	1.000
Perinuclear cytolysis of cardiomyocytes, n (%)	12 (17.1)	0 (0)	0.111
Fatty degeneration of cardiomyocytes, n (%)	9 (12.9)	1 (6.25)	0.680
Karyopyknosis / karyorrhexis of cardiomyocytes, n (%)	1 (1.4)	0 (0)	1.000
Interstitial expansion, n (%)	6 (8.6)	2 (12.5)	0.639
Interstitial oedema, n (%)	7 (10)	1 (6.25)	1.000
Perimuscular interstitial sclerosis, n (%)	28 (40)	6 (37.5)	0.854
Perivascular interstitial sclerosis, n (%)	31 (44.3)	6 (37.5)	0.621
Focal interstitial sclerosis, n (%)	3 (4.3)	0 (0)	1.000
Interstitial infiltration with 10-13 cells, n (%)	3 (4.3)	1 (6.25)	0.568
Interstitial infiltration with >14 cells, n (%)	52 (74.3)	12 (75%)	1.000
Eosinophils in interstitium, n (%)	0 (0)	0 (0)	-

According to the study results, analysis of the relationship between IAS morphological changes and "nonPVdependent" AF recurrence was not performed because of an insufficient number of representative IAS biopsy samples (the biopsy material mainly consisted of the membranous portion of the IAS). In IVS biopsy samples, the most common morphological findings were myocardial hypertrophy, loss of myocardial crossstriation, endocardial thickening and lipomatosis, and cardiomyocyte dystrophy. Detailed frequencies of morphological criteria are presented in Table 2. Among the analyzed parameters, predictors of "nonPVdependent" AF were endocardial thickening (p=0.031) and cardiomyocyte dystrophy (p<0.001). Other morphological parameters did not demonstrate significant predictive value for AF recurrence in patients with durable PVI.

DISCUSSION

To increase the efficacy of catheter interventions based on previously obtained data on the relationship between myocardial changes and AF, a study of 54 patients with AF refractory to AAT who underwent CBA PVI was conducted at the National Medical Research Center for Therapy and Preventive Medicine. The results suggested that inflammation is one of the significant and potentially treatable causes of insufficient CBA efficacy in AF patients [9]. The present study is a continuation of that work [9]. Both studies (the initial and the current, with an expanded cohort) aimed to identify among morphological changes predictors of "PVdependent" AF. The previous analysis, including 54 patients, demonstrated a predictor role of interstitial oedema for "nonPVdependent" AF. After expanding the sample and reanalysis, the predictive value of interstitial oedema was not confirmed, while two other parameters showed prognostic significance - endocardial thickening (p=0.031) and cardiomyocyte dystrophy (p=0.001). Cardiomyocyte dystrophy itself is a nonspecific myocardial change encompassing many subtypes; it can develop through various mechanisms, reflecting cell and structural damage resulting from different factors, one of which is inflammation, leading to subsequent fibrosis and myocardial remodelling.

A comparison of catheter ablation outcomes for AF and EMB data was recently performed by our compatriots: only 13.4% of 67 patients with "idiopathic" AF had no histological changes; fibrosis was found in 38.8%, and Dallas criteria for myocarditis in 47.8% [10]. Followup of 9.3±3.7 months after ablation showed that the procedure's success directly depended on the myocardial changes - it was 88.9% in patients with intact myocardium (no early recurrences), 46.2% in patients with various degrees of fibrosis, and only 34.4% in patients with myocarditis. Previously, we also established a high (up to 75%) incidence of immuneinflammatory diseases (myocarditis, vasculitis) on right ventricular EMB in patients with "idiopathic" AF, increased efficacy of medical and interventional treatment as a result of immunosuppressive therapy for detected myocarditis, and partial loss of the effect over the longterm (up to 10 years or more) due to gradual therapy withdrawal and, probably, the development of irreversible atrial changes [11]. These data once again confirm that the goal of complete AF elimination is often unattainable because of the multicomponent pathogenesis and the dependence on the overall condition of the atria and their individual zones.

The morphological results obtained in this study primarily indicate that all AF patients without socalled severe organic heart disease have pronounced and diverse changes in ventricular myocardium. The mere presence of these changes (which can reasonably be assumed to also occur in the atria) is a factor that predisposes to AF recurrences after catheter ablation. To our knowledge, no study has attempted to correlate the type of morphological changes with a specific AF recurrence mechanism ("PVdependent" vs. "nonPVdependent"). This study also did not yield definitive results, possibly due to the low informative value of IAS biopsy samples. Most likely, the morphological changes leading to both pathological activation of the PV ostia and atrial myocardial substrate are not substantially different; the crucial factor is their presence and progression (the "extent" of involvement) - and the specific mechanism in an individual patient may be less important for understanding the nature of the process (though it remains important for choosing repeat intervention).

In addition to histological studies, recent electrophysiological evidence of the involvement of fibrosis and cardiomyocyte changes in AF substrate formation has emerged. In one recent study of 230 patients, EMB results (from the IAS under intracardiac echocardiography and fluoroscopy) were compared with electroanatomical multipolar mapping of the atria in AF patients. Histological factors associated with electroanatomical characteristics were fibrosis, stromal expansion (intercellular space), and loss of myofibrils and cardiomyocyte nuclear density (which are particular manifestations of cardiomyocyte dystrophy). The degree of fibrosis in biopsy samples significantly correlated with altered global LA voltage during mapping, and stromal changes were associated with the proportion of fractionated activity. Moreover, all these histological findings were related to the detection of areas with slow conduction [12]. Another study of EMB in patients with "lone" AF demonstrated significant histological changes in the atria, including vacuolar dystrophy, also a subtype of dystrophy [13].

Thus, cardiomyocyte dystrophy appears to be a common finding in patients with AF refractory to catheter treatment. This finding supports the hypothesis that the more extensive the myocardial damage outside the PVs, the less likely a therapeutic effect from PV ostial isolation. Detected endocardial thickening may also be viewed as a result of fibrosis due to an inflammatory process, analogous to the beststudied rheumatic endocarditis. Direct studies addressing the role of endocardial thickening in AF are lacking. However, endocardial thickening is often mentioned as a component of general "atrial remodelling" in AF and it is found in patients with the most treatmentresistant "idiopathic" AF [11].

In our study, the AF recurrence rate, accounting for asymptomatic episodes, was considerably higher than in previous reports: 58.1% after primary CBA PVI and 71.4% after repeat PV isolation. This is obviously due to the use of the implantable subcutaneous loop recorder, which allows detection of significantly more arrhythmia episodes compared with standard monitoring methods.

Study limitations

The main limitations include the small sample size and the lack of immunohistochemical analysis. On the other hand, this study was not designed to diagnose myocarditis, as many similar projects by colleagues have failed. The goal was to move one step closer to understanding the pathogenesis of AF sources outside the PVs. It should also be noted that the concept of AF sources outside the PV ostia is somewhat conditional, based on the absence of arrhythmia recurrences after one or two stages of PVonly isolation.

CONCLUSION

In all AF patients without severe organic heart disease, various morphological changes of the IVS myocardium were identified, including fibrosis, lipomatosis, and dystrophy. Histological changes in EMB from AF patients, such as cardiomyocyte degeneration and endocardial thickening, are important components of atrial remodelling that may be associated with arrhythmia initiation, maintenance, and progression - consistent with the theory of atrial cardiomyopathy (atrial myopathy) regardless of its origin. A deeper understanding of these cellular and molecular changes may inform the development of novel targeted strategies for AF prevention and treatment. No clear morphological predictors of a specific electrophysiological focus of arrhythmia in or outside the PVs were identified, likely due to the common mechanisms of atrial myopathy regardless of its location.

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COMBINED ANTIARRHYTHMIC THERAPY FOR REFRACTORY PAROXYSMAL ATRIAL FIBRILLATION: A MULTICENTER OBSERVATIONAL STUDY

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Aim. To evaluate the efficacy of the class IC antiarrhythmic drug flecainide in combination with an atrioventricular nodal slowing agent (metoprolol succinate or diltiazem) for the suppression of refractory to other antiarrhythmic medication atrial fibrillation (AF) in patients with symptomatic paroxysmal AF without significant structural heart disease, as well as to assess the incidence of adverse events associated with this therapy.

Material and Methods. This multicenter observational study enrolled patients aged 18-75 years with documented symptomatic (EHRA class ≥2a) paroxysmal AF and frequent episodes (≥2 per month). All patients received flecainide combined with either metoprolol succinate or diltiazem. The primary endpoint was a documented episode of AF within 3 months of therapy. Secondary endpoints included time to AF recurrence and treatment-related adverse events. Rhythm monitoring was performed using a portable device for self-recording of lead I electrocardiograms: daily during the first week, twice weekly during weeks 2-4, and additionally on an ad hoc basis when symptoms occurred. Quality of life was assessed using the EQ-5D questionnaire at baseline and at study completion.

Results. The study included 59 patients (57.6% female; mean age 63.5±9.9 years). The combination of flecainide with metoprolol succinate was prescribed to 93.2% (n=55) of patients, and flecainide with diltiazem to 6.8% (n=4). The primary endpoint was reached in 33.9% of patients (n=20). The majority of AF recurrences (85% of all events, n=17) occurred during the first month of follow-up. Adverse events were reported in 10.2% of cases (n=7).

Conclusion. In patients with paroxysmal AF refractory to other antiarrhythmic drugs (including prior ineffective catheter ablation in half of the study patients), a combination of flecainide with metoprolol or diltiazem demonstrated a recurrence-free rate of 66% over 3 months, with an acceptable safety profile. Combination therapy is associated with a significant improvement in quality of life. Single-lead remote ECG monitoring is useful for detecting arrhythmia recurrences but is insufficient for a comprehensive assessment of the safety of intraventricular conduction disturbances.

Key words: atrial fibrillation; combination antiarrhythmic therapy; antiarrhythmic drugs; flecainide; refractory atrial fibrillation; portable ECG recorder

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Atrial fibrillation (AF) is the most common tachyarrhythmia, characterized by rapid, disorganized electrical activity of the atria, resulting in ineffective atrial contraction. The natural history of AF is associated with numerous complications, including arrhythmiainduced cardiomyopathy with reduced left ventricular ejection fraction, chronic heart failure, increased risk of cardioembolic stroke, higher hospitalization rates, and premature death [1].

According to the 2024 European Society of Cardiology (ESC) guidelines for the management of patients with AF, an integrated ABC pathway is recommended, in which alongside effective anticoagulation (A) and optimization of cardiovascular and comorbidity management (C), equal emphasis is placed on effective symptom control (B) [1]. In the clinical guidelines approved in Russia in 2025, the management strategy for AF patients is described within the AFCARE framework, which also highlights the impor-

tance of reducing arrhythmiarelated symptoms (R - reduce symptoms by rate and rhythm control) [2]. This goal can be achieved through either rhythm control or rate control strategies. However, according to the EASTAF NET4 trial results, rhythm control therapy is associated with a better prognosis [3-6]. This has refocused attention on intensified rhythm control strategies, which include cardioversion, antiarrhythmic drug therapy, and catheter ablation, alongside anticoagulation and comprehensive cardiovascular risk factor management.

The available class IC antiarrhythmic agents for patients without structural heart disease or heart failure were limited to three main drugs: propafenone, lappaconitine hydrobromide, and ethacizine in the Russian Federation until 2024 [7]. Following the registration of flecainide, there is a growing need to thoroughly evaluate the efficacy of class IC antiarrhythmic therapy in symptomatic paroxysmal AF [8]. Importantly, both the 2024 ESC guidelines and the 2025 Russian guidelines recommend the use of flecainide for AF treatment in combination with a betablocker to prevent the complication of 1:1 conducted atrial flutter [2].

In patients with a history of ineffective therapy with class IC antiarrhythmic agents, recurrence of arrhythmia is more likely even with a new regimen from this class. When AF episodes persist despite the use of at least two antiarrhythmic drugs at optimal therapeutic doses, the condition is considered refractory AF. It is hypothesized that the combination of flecainide with betablockers or calcium channel blockers for continuous prophylaxis of AF recurrences may be advantageous when the effect of other antiarrhythmic therapy is incomplete, with frequent AF episodes persisting. In such cases, the ventricular rate during AF recurrences can be modulated by suppressing atrioventricular (AV) conduction with diltiazem or metoprolol succinate.

The safety of the combination of metoprolol succinate and flecainide has been previously studied and confirmed [9]. Among nondihydropyridine calcium channel blockers, studies have confirmed the absence of drugdrug interactions and the safety of coadministering verapamil and flecainide; however, no such studies exist for flecainide and diltiazem [10]. Unlike verapamil, whose combination with flecainide has been associated with documented cases of cardiogenic shock, asystole and death, diltiazem has a more favorable safety profile for rate control in AF due to its less pronounced negative inotropic effect and lower risk of haemodynamic complications [11]. The present study aims to investigate the feasibility of coadministering flecainide and diltiazem and to assess potential adverse events associated with this antiarrhythmic regimen. This therapeutic strategy may offer advantages in reducing the number of symptomatic arrhythmic episodes, thereby improving patients' quality of life.

The aim of this study is to evaluate the clinical efficacy of flecainide, a class IC antiarrhythmic drug, in combination with an AVnodal slowing agent for the prevention of AF recurrences in patients with symptomatic paroxysmal AF without significant structural heart disease and to analyze the incidence of adverse events associated with this therapy.

MATERIALS AND METHODS

Study design

This was an observational, multicenter study. Patients were enrolled at three medical institutions from October 2024 to March 2026 according to the following criteria: (1) age 18-75 years; (2) documented paroxysmal AF; (3) at least two symptomatic AF episodes during the month prior to enrolment, with a minimum duration of 30 seconds, confirmed by any available method; (4) patients with refractory AF and failure of prior antiarrhythmic therapy or catheterbased treatment, for whom one of the combination regimens of flecainide with either the slow calcium channel blocker diltiazem or the betablocker metoprolol succinate was prescribed; (5) EHRA symptom class ≥2a; (6) signed informed consent.

Patients with structural myocardial pathology (left ventricular hypertrophy ≥14 mm, chronic heart failure NYHA class III-IV, left ventricular ejection fraction <40%), documented coronary artery disease, conduction disturbances (second or thirddegree AV block or sinoatrial block without an implanted pacemaker, complete bundle branch block, or distal intraventricular conduction disturbances with QRS ≥120 ms) were excluded, as were patients who had suffered a stroke or transient ischaemic attack within the previous 3 months, those on chronic therapy with other antiarrhythmic drugs, and those with <30 days since amiodarone discontinuation.

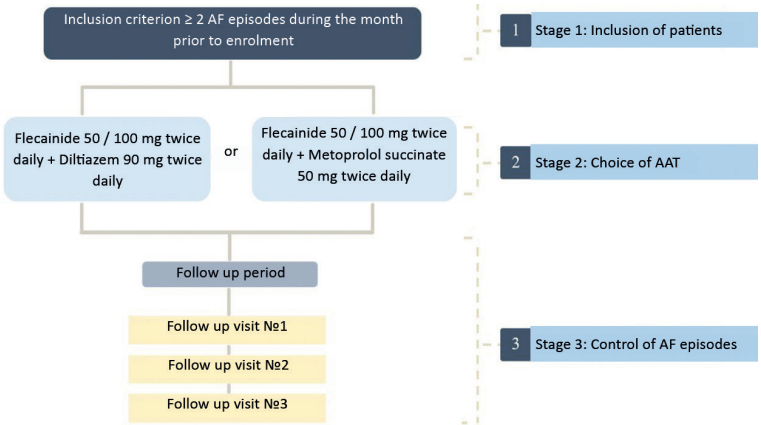

Fig. 1. Research design: AAT - antiarrhythmic therapy; AF - atrial fibrillation.

The study protocol was approved by the Independent Interdisciplinary Committee for Ethical Review of Clinical Research (Protocol No. 18 dated 11 October 2024). Local ethics committee approvals were obtained where required by institutional regulations. All patients provided written informed consent to participate. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study endpoints

The primary endpoint was a documented AF episode within 3 months of taking the first dose of the combination therapy. Secondary endpoints included time to AF recurrence, AF episode lasting >7 days, electrical cardioversion performed within 3 months of study

therapy, and adverse events related to flecainide in either combination, including sustained ventricular tachycardia.

Research design

Patients for whom the attending physician prescribed flecainide in combination with one of the AVnodal slowing agents (metoprolol succinate or diltiazem) were provided with a portable device for selfrecording and transmission of lead I electrocardiography (ECG) (singlechannel audio cardiac rhythm indicator "IKRZ1" («Serdechko», Bioss, Russia). Before initiating therapy and 2-4 hours after the first dose of flecainide (50 mg), an ECG was recorded on an outpatient basis and reviewed by the attending cardiologist. In the absence of recorded adverse effects, patients continued the prescribed combination under the control of selfrecorded ECGs using the portable recorder (Fig. 1). If necessary, the attending physician titrated the doses of each antiarrhythmic drug to improve the prevention of AF recurrences. In such cases, the flecainide dose was increased by 50 mg/day every 5 days under daily selfrecorded ECG monitoring; titration was stopped if any adverse event occurred. The maximum permitted daily dose of flecainide in the study was 300 mg/day, in accordance with the prescribing information. The doses of metoprolol succinate and diltiazem were titrated to achieve a resting heart rate of 50-65 bpm.

During the first week of followup, ECG recordings of 30second duration were performed daily at the same time and transmitted to a central email address for evaluation by the study coordinator and the attending physician. During weeks 2-4, selfrecorded ECGs were performed twice weekly on any two nonconsecutive days. To improve adherence, each patient received a reminder card with predetermined dates for ECG recordings at enrolment. If no ECG was received at the central email address on the scheduled dates, the attending physician or study coordinator reminded the patient by telephone. Unscheduled ECG recordings and transmissions were not restricted and were performed whenever symptoms suggestive of AF occurred.

Monthly inperson visits were scheduled for evaluation of therapy efficacy and potential adverse effects. The duration of patient participation was 3 months. At enrolment and at study completion (reaching endpoint, exclusion criteria, or 3month followup), each patient completed the EQ5D qualityoflife questionnaire. Patients were asked to rate their health status on a scale from 0 to 100, where 100 represented the best imaginable health state.

Statistical analysis

Statistical analysis was performed using Microsoft Excel (Microsoft, USA) and Jamovi (Computer Software, Version 2.6.44). This was a purely observational study; statistical calculations were based on all enrolled patients who received one of the combination regimens. Descriptive statistics are presented as mean ± standard deviation. For normally distributed data, differences between means were assessed using Student's ttest. Paired ttests were used for dependent samples. Differences were considered statistically significant at $p<0.05$.

RESULTS

A total of 59 patients with paroxysmal AF were enrolled. Patient clinical characteristics are presented in Table 1. 34 (57.6%) patients were female, with a mean age of 63.5±10.0 years. The most common comorbidity was arterial hypertension, present in 55 (93.2%) patients, for which 47 (79.7%) received ACE inhibitors or angiotensin II receptor blockers, and 23 (39.9%) received diuretics. The majority of patients were overweight (n=25, 42.4%) or obese (n=30, 50.9%).

Echocardiography showed preserved left ventricular ejection fraction in all patients, with no significant left ventricular hypertrophy or valvular heart disease. The mean left atrial volume index was 31.0±19.8 mL/m² (Table 2).

The mean duration of paroxysmal AF history was 4.5±4.6 years. All patients had frequent, symptomatic episodes - 5.5±5.0 episodes per month prior to enrolment - with no response to other class IC, II, or III antiarrhythmic

Table 1.

Clinical characteristics of the study patients (n=59)

Parameter	Value
Male sex, n (%)	25 (42.4)
Age, years	63.5±9.96
Arterial hypertension, n (%)	55 (93.2)
Stroke/TIA in history, n (%)	2 (3.4)
Type 2 diabetes mellitus, n (%)	8 (13.6)
Documented atherosclerosis, n (%)	14 (23.7)
ACE inhibitors/ARBs, n (%)	47 (79.7)
Diuretic therapy, n (%)	23 (39)
Anticoagulant therapy, n (%)	57 (96.6)
BMI, kg/m²	30.8±4.9
BMI <25 kg/m², n (%)	4 (6.8)
BMI 25-30 kg/m², n (%)	25 (42.4)
BMI ≥30 kg/m², n (%)	30 (50.9)
AF history duration, years	4.5±4.6
Number of AF episodes*, n	5.5±5.0
Prior cardioversion, n (%)	33 (55.9)
Pharmacological cardioversion, %	78
Prior catheter ablation for AF, n (%)	31 (52.5)

Note: here and further * - during the month prior to enrolment; TIA - transient ischemic attack; ACE - angiotensin converting enzyme; ARB - angiotensin II receptor blocker; BMI - body mass index; AF - atrial fibrillation.

Table 2.

Echocardiographic parameters of patients

Parameter	Value
LV ejection fraction (Simpson), %	60.8±6.7
Left atrial diameter, mm	41.1±0.5
Left atrial volume index, mL/m²	31±19.8
IVS / LV posterior wall thickness, mm	10.6±1.6
LV end diastolic volume, mL	112±29.6
LV end systolic volume, mL	50±16.7
Mitral regurgitation < grade 1, %	100

Note: LV - left ventricle; IVS - interventricular septum.

drugs. More than half of the patients had a history of cardioversion for rhythm restoration (n=33, 55.9%), predominantly pharmacological (78% of cases). Catheter ablation of pulmonary veins had been previously performed in 31 patients (52.54%). It was known that after surgical treatment, these patients experienced recurrence of frequent, symptomatic AF paroxysms with no clinical benefit from class IC (propafenone, lappaconitine hydrobromide), class II (metoprolol succinate, bisoprolol), class III (d,lsotalol), or class IV (verapamil) agents. Before initiating study therapy, a 12lead ECG showed no conduction disturbances. The combination of flecainide and diltiazem was prescribed to 4 patients (6.8%), and flecainide with metoprolol succinate to 55 patients (93.2%).

Arrhythmia recurrences

All enrolled patients fully complied with the study-approved selfrecorded ECG protocol until reaching an endpoint or completing the observation period. In the event of AF recurrence while on a suboptimal flecainide dose, dose titration was performed. If AF recurred at the optimal dose, the patient reached the study endpoint.

At baseline, all patients were in sinus rhythm on a 12lead ECG. At the ECG performed 4 hours after the first 50mg flecainide dose, two patients had AF episodes with a mean ventricular rate of 123-150 bpm, which resolved within 24 hours.

During the first week, daily selfrecorded ECGs revealed AF episodes in 13 patients (22%). In addition, two patients had episodes of supraventricular tachycardia (AF with transition to atrial flutter at a ventricular rate of 127 bpm (Fig. 2) and atrial tachycardia, respectively), which resolved spontaneously (Table 3).

By the first scheduled visit (1 month), AF paroxysms were documented in 17 patients (28.8%), including one case of persistent AF in which attempts at termination with the “pillinthepocket” flecainide strategy and pharmacological cardioversion (amiodarone) were unsuccessful. At the second visit, the number of patients with documented AF episodes during the study reached 20 (33.9%). By the third visit, this number had not changed, and no new episodes of supraventricular tachyarrhythmia were recorded.

At the end of the study, the maximum flecainide dose achieved was 200 mg/day in 29 patients. According to the KaplanMeier curve, the median time to AF recurrence during the 90day followup was not reached (Fig. 3).

The group of patients with AF recurrence on combination therapy consisted of 14 (70%) women and 6 men, with a mean age of 62.4±10.0 years. Arterial hypertension was present in 19 (95%) patients. All patients were overweight or obese, with a mean body mass index (BMI) of 32.6±5.6 kg/m². Echocardiographic left atrial diameter was 40.3±0.5 mm. The mean duration of AF history was 4.4±4.9 years, and 13 (65%) patients had previously undergone catheter pulmonary vein isolation. Comparison of clinical characteristics between patients with and without AF recurrence on therapy revealed no statistically significant correlation. The combination of flecainide and diltiazem was prescribed to 3 (15%) patients, and flecainide with metoprolol succinate to 17 (85%) patients (Table 4).

Among the 31 patients who had undergone prior catheter pulmonary vein isolation, 13 (41.9%) experienced AF recurrence on combination antiarrhythmic therapy. This subgroup included 3 males (23.1%) and 10 females (76.9%), with a mean age of 58.8±10.2 years. All patients in this subgroup were overweight or obese, with a mean BMI of 33.0±6.4 kg/m²; 12 (92.3%) also had arterial hypertension. Mean left atrial diameter was 42.3±4.3 mm. The mean duration of AF history was 4.8±4.1 years. Prior to enrolment, these patients had 6.2±3.9 AF episodes per month, and 6 (46.2%) were not on chronic antiarrhythmic therapy due to its ineffectiveness. Among the 28 patients (47.46%) who had not undergone catheter ablation, AF recurrences were observed in 7 patients (25%).

Comparison of patients with (n=31, 52.54%) and without (n=28, 47.46%) prior catheter intervention revealed no statistically significant differences in age (p=0.469), BMI (p=0.506), AF history duration (p=0.996), or left atrial diameter (p=0.072) by Student’s ttest. KaplanMeier analysis

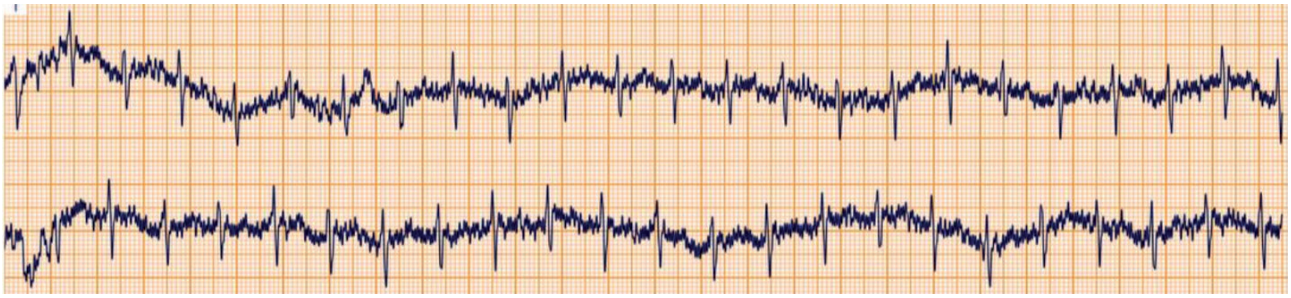

Fig. 2. Self recorded ECG by the patient using a portable recorder (single channel audio cardiac rhythm indicator “IKRZ 1” Serdechko, Bioss, Moscow, Russia) at 25 mm/s, 10 mm/mV, lead I. Episode of regular supraventricular tachycardia with a ventricular rate of 127 bpm.

Table 3.

Efficacy of antiarrhythmic therapy during the first week of follow up by portable ECG recorder

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
AF recurrence, n (%)	4 (6.8)	5 (8.5)	9 (15.5)	10 (17)	12 (20.4)	12 (20.3)	13 (22)
SVT*, n (%)	1 (1.7)	2 (3.4)	2 (3.4)	2 (3.4)	2 (3.4)	2 (3.4)	2 (3.4)
Sinus rhythm, n (%)	54 (91.5)	52 (88.2)	48 (81.4)	47 (79.7)	45 (76.3)	45 (76.3)	44 (74.6)

Note: *SVT - supraventricular tachycardia (atrial flutter, atrial tachycardia).

of time to AF recurrence also showed no statistically significant difference between the groups (p=0.167) (Fig. 4).

Adverse events with combination antiarrhythmic therapy

Adverse events related to combination antiarrhythmic therapy were recorded in 7 patients (10.2%). In one patient (1.7%), flecainide at the starting dose (50 mg twice daily) caused severe dizziness, requiring drug discontinuation.

Among atrial arrhythmias, one patient had episodes of atrial tachycardia recorded by the portable ECG device, and another had frequent symptomatic premature atrial contractions - single (4,505 per day) and paired (2,102 per day) on 24hour Holter monitoring. In one patient, increasing the flecainide dose to 200 mg/day was associated with frequent monomorphic premature ventricular contractions, clinically manifested as palpitations (Fig. 5). Dose reduction eliminated the ventricular ectopy; however, the therapy lost its efficacy in preventing AF recurrences.

Two patients developed intraventricular conduction disturbances. Both were receiving flecainide 100 mg/day and metoprolol succinate. At the first monthly visit, a 12lead ECG showed complete right bundle branch block with QRS >160 ms in one patient. Retrospective review of previously transmitted singlelead ECGs did not reveal these changes due to the limitation of the leadIonly recording. Flecainide was discontinued, metoprolol succinate was continued, and intraventricular conduction normalized (QRS 120 ms). In the second patient, the portable recorder detected AF with QRS widening to 160 ms, confirmed by 12lead ECG. After sinus rhythm restoration, QRS narrowed to 80 ms; however, since the patient had reached the primary endpoint, they discontinued study participation.

Quality of life assessment

According to the EQ5D questionnaire, the mean score at enrolment was 59.6±20.0, which improved to 72.8±14.8 at the final assessment (p=0.00002).

DISCUSSION

This multicenter observational study is the first in Russian clinical practice to evaluate the efficacy and safety of combination therapy with flecainide (class IC) plus metoprolol succinate (class II) or diltiazem (class IV) in patients with paroxysmal AF. A key feature of the patient cohort is that all patients had documented failure of prior antiarrhythmic monotherapy (class IC, II, III drugs), and 52.5% had previously undergone unsuccessful catheter ablation for AF. Thus, the study was conducted in a group with severe, refractory AF.

Efficacy of combination therapy in the refractory group

Despite the unfavorable baseline prognosis, combination therapy with flecainide plus metoprolol or diltiazem resulted in freedom from AF recurrence in 66.1% of patients during 3 months of followup. This is comparable to the efficacy of flecainide monotherapy in the general paroxysmal AF population (approximately 70% according to Clementy et al., 1992), but importantly, our results were obtained in a group with proven failure of other antiarrhythmic agents and, in many cases, invasive treatment [12]. We therefore suggest that combination therapy can "restore" the antiarrhythmic response in a substantial proportion of patients previously considered resistant.

Most documented recurrences (85%, 17 of 20) occurred during the first week of therapy. This may indicate that the initial flecainide dose (50 mg twice daily) was insufficient for some patients and that earlier dose escalation might have been required to achieve a therapeutic effect. Theoretically, more aggressive uptitration in the first few days (up to 100 mg twice daily) might reduce the rate of

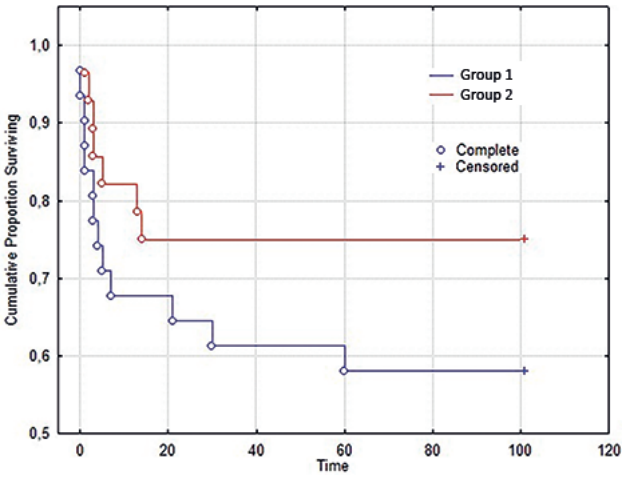

Fig. 3. Kaplan-Meier curves estimating time (days) to AF recurrence. Group 1 - patients with prior catheter pulmonary vein isolation; Group 2 - patients without prior catheter ablation for AF.

Table 4.

Clinical characteristics of patients with AF recurrence on combination antiarrhythmic therapy (n=20)

Parameter	Value
Male sex, n (%)	6 (30)
Age, years	62.4±10.0
BMI, kg/m^2	32.6±5.6
Arterial hypertension, n (%)	19 (95)
Stroke/TIA in history, n (%)	1 (5)
Type 2 diabetes mellitus, n (%)	3 (15)
Documented atherosclerosis, n (%)	4 (20)
ACE inhibitors/ARBs, n (%)	18 (90)
Diuretic therapy, n (%)	10 (50)
Flecainide + diltiazem, n (%)	3 (15)
Flecainide + metoprolol succinate, n (%)	17 (85)
AF history duration, years	4.4±4.9
Number of AF episodes*	5.1±3.8
Prior cardioversion, n (%)	2 (10)
Pharmacological cardioversion, %	100
Prior catheter ablation for AF, n (%)	13 (65)
LV ejection fraction (Simpson), %	58.8±4.6
Left atrial diameter, mm	40.3±0.5
IVS / LV posterior wall thickness, mm	10.3±1.6
LV end diastolic volume, mL	110.0±31.8
LV end systolic volume, mL	48.1±17.9

early recurrences. Alternatively, these early recurrences may reflect true resistance to class IC therapy that is not overcome even by combination.

In the study by Capucci et al. (2016), the combination of flecainide and metoprolol in persistent AF reduced recurrences by 40% compared with monotherapy [9]. Our study lacked a control group, precluding a direct comparison with monotherapy. Nevertheless, it can be stated that in the population with paroxysmal refractory AF, the combination demonstrates efficacy close to that seen in less severe groups.

Owing to the small number of patients receiving diltiazem with flecainide (n=4), no statistically significant conclusions can be drawn. One of the four patients remained recurrencefree, but these data are illustrative only. Further studies with larger samples are needed to evaluate the efficacy of the flecainide-diltiazem combination specifically.

Safety

The adverse event rate (10.2%) is comparable to that of flecainide monotherapy and does not exceed expectations [12]. No lifethreatening arrhythmias were recorded: no ventricular tachycardia, ventricular fibrillation, or 1:1 conducted atrial flutter. The latter is particularly important, as the risk of rapid AV conduction during atrial flutter is a major concern when prescribing class IC drugs [13-16]. Concomitant use of metoprolol or diltiazem likely effectively prevents this complication even in a highrisk group.

Two patients developed complete right bundle branch block with QRS ≥160 ms. In one, the changes were not detected by routine singlelead ECG (portable recorder). This highlights a critical limitation of remote monitoring: singlelead devices can be used to detect AF recurrences and monitor heart rate but cannot replace 12lead ECG for safety assessment of intraventricular conduction. Therefore, all patients receiving flecainide (and other class IC drugs) should have a full 12lead ECG at each followup visit and whenever changes appear on portable recordings.

One patient developed dosedependent premature ventricular contractions that resolved after flecainide dose reduction. This is a known proarrhythmic effect of class IC agents requiring individual dose titration [13].

Impact on quality of life

Significant improvement in EQ5D scores (from 59.6 to 72.8; p=0.00002) indicates the clinical relevance of therapy, even though onethird of patients experienced recurrences. The improvement in quality of life is likely related both to the reduced frequency of paroxysms and to decreased symptom severity, as some recurrences were asymptomatic and detected only on scheduled ECG recordings.

Comparison with previous study results in the context of refractory AF

Data on the use of the flecainide-diltiazem combination in refractory paroxysmal AF are lacking in the available literature. Our study is the first to demonstrate the feasibility and safety of this combination in a Russian population.

Conversely, the flecainide-metoprolol combination has been studied more extensively. In addition to the work by Capucci et al., there are data on its safety and efficacy in AF patients after ablation [9]. Our study complements these findings by showing that even in patients with prior failed ablation (52.5% of our cohort), the combination retains efficacy.

The EHRA-ESC consensus (2025) recommends combination class IC and class III therapy to create a "pseudoamiodarone" effect [17]. Our work expands this option by demonstrating that the combination of class IC with class II/IV agents also has an acceptable safety profile and may be used in patients without structural pathology, especially when monotherapy is ineffective.

Study limitations

Several limitations should be considered when interpreting the results. First, the observational, nonrandomized design and the absence of a control group (placebo or monotherapy) do not allow causal inference. However, in a population with proven refractoriness to prior therapy and catheter ablation, placebo use would be unethical.

Quality of life assessed with the EQ5D was obtained in an openlabel observational study without blinding or a control group, which does not exclude the possibility of a placebo effect.

Owing to the extreme imbalance between groups (only 4 patients received diltiazem), no conclusions can be drawn regarding the efficacy of the flecainide-diltiazem combination; a separate study is required.

The short followup period (3 months) precludes assessment of longterm efficacy, safety, and the effect of the combination on AF progression.

Despite unrestricted availability of selfrecorded ECGs during the study, unscheduled recordings were performed only when symptoms suggestive of AF occurred. Therefore, the presence of asymptomatic AF episodes not recorded on ECG cannot be excluded.

An important technical limitation is the use of a singlelead portable ECG recorder, which does not allow assessment of the QRS complex in all leads or detection of right bundle branch block; this is particularly critical for class IC drugs.

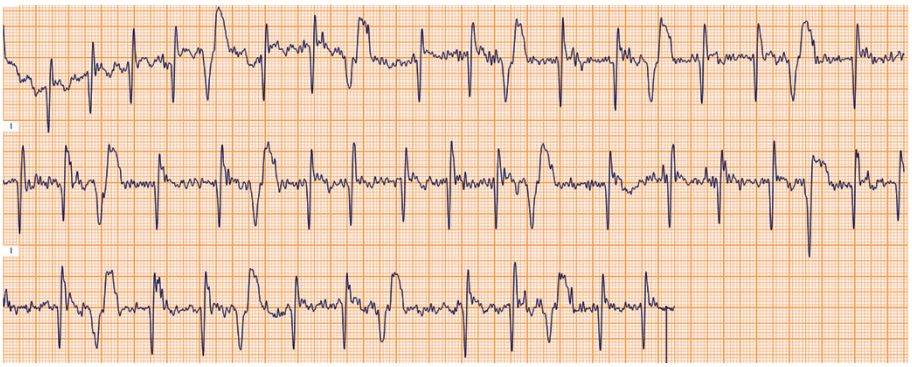

Fig. 4. Self recorded ECG by the patient using a portable recorder at 25 mm/s, 10 mm/mV, lead I. Regular rhythm at 98 bpm with a single premature ventricular contraction..

CONCLUSION

In this observational study of patients with paroxysmal AF refractory to other antiarrhyth-

mic drugs (and with prior failed catheter ablation in half of the subjects), the combination of flecainide with metoprolol or diltiazem demonstrated freedom from recurrence in 66% of patients over 3 months. The safety profile was acceptable, with an adverse event rate of 10.2% and no life-threatening arrhythmias. Therapy was associated with significant improvement in quality of life. Singlelead remote ECG monitoring is useful for detecting AF recurrences but is insufficient for comprehensive assessment of the safety of intraventricular conduction disturbances.

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https://doi.org/10.35336/VA-1620

RISK OF VENTRICULAR ARRHYTHMIAS AND RELAPSE OF SYSTOLIC DYSFUNCTION IN PATIENTS WITH HEART FAILURE WITH IMPROVED LEFT VENTRICULAR EJECTION FRACTION: RESULTS OF LONG-TERM FOLLOW-UP

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Aim. To assess the long-term risk of life-threatening ventricular arrhythmias and recurrent systolic dysfunction in patients with chronic heart failure (CHF) and improved left ventricular ejection fraction (LVEF) following implantation of implantable cardioverter-defibrillators (ICD) or cardiac resynchronization therapy defibrillators (CRT-D) for primary prevention of sudden cardiac death (SCD), and to identify factors associated with these outcomes.

Methods. The study represents a continuation of the analysis of a previously described single-center retrospective cohort of patients with CHF and improved LVEF who had undergone ICD or CRT-D implantation for primary prevention of SCD. The study included 87 patients: 34 with ICDs and 53 with CRT-D. In contrast to the previously published work, which focused on survival, inappropriate electrical therapy, and complications related to implanted devices, the primary endpoint of the present study was the development of sustained ventricular arrhythmia terminated by ICD/CRT-D therapy (arrhythmic composite endpoint - ACE), while the secondary endpoint was relapse to an LVEF ≤35%.

Results. Duration follow-up after study inclusion was 5.2±2.8 years, and the total duration after device implantation was 8.3 ± 3.6 years. ACE was observed in 7.1% (n=6) of patients, and in 4.8% of those with persistently improved LVEF. Recurrent reduction in LVEF to ≤35% occurred in 24.4% (n=20) of patients and was associated with higher all-cause mortality (35.0% vs. 5.0%), presence of atrial fibrillation, more pronounced baseline left ventricular remodeling.

Conclusion. While a significantly reduced risk of life-threatening arrhythmias is observed upon improvement in LVEF, a certain risk of recurrent progression of systolic dysfunction persists. Despite the retrospective design and limited sample size, these results underscore the need for an individualized management approach for this patient category and provide a basis for planning further prospective studies in this field.

Key words: chronic heart failure; heart failure with improved ejection fraction; left ventricular reverse remodeling; implantable cardioverter-defibrillator; cardiac resynchronization therapy; primary prevention of sudden cardiac death; ventricular arrhythmias; appropriate device therapy; relapse in systolic dysfunction

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The prevalence of chronic heart failure (CHF) continues to rise steadily, representing one of the central challenges in modern cardiology [1]. Despite therapeutic advances, overall mortality among CHF patients remains high, reaching 6% in the general population and 12% among patients with clinically overt disease [2]. A significant proportion of deaths is attributable to sudden cardiac death (SCD), the main mechanism of which is lifethreatening ventricular arrhythmias (VAs) [3]. The key method for primary prevention of SCD in patients with left ventricular (LV) systolic dysfunction, alongside optimal medical therapy, is implantation of an implantable cardioverterdefibrillator (ICD) or a cardiac resynchronisation therapy defibrillator (CRTD) [3, 4]. However, as shown by the results of the Russian registry study PRIORITETCHF, the uptake of this preventive measure remains unsatisfactorily low: only 8.9% of patients had an ICD and 3.1% had a CRTD among CHF patients with reduced LV ejection fraction (LVEF) enrolled in the study [5]. This underscores the need for the most accurate selection of patients who will derive the greatest benefit from an expensive invasive procedure that carries a risk of complications.

At the same time, advances in CHF treatment over recent decades have led to a significant proportion of patients developing cardiac reverse remodelling with improvement in myocardial contractile function [6-9]. This has led to the recognition of a distinct clinical phenotype - heart failure with improved LVEF (HFimpEF) - which occurs in 10-40% of patients with initially reduced LVEF [10-13]. According to current Russian clinical guidelines, this category includes patients with a history of LVEF ≤40% who, on repeat assessment, show an absolute improvement in LVEF of ≥10% and a value of ≥40% [2].

The prognosis for HFimpEF patients is more favourable than for those with persistently reduced LVEF, including lower allcause and cardiovascular mortality and a reduced risk of SCD [14-16]. In particular, reverse remodelling is associated with a reduced risk of VAs. In the MADITCRT trial, a 10% reduction in LV endsystolic volume correlated with a 21% reduction in the risk of VAs or death [17]. A posthoc analysis of the DAPAHF trial demonstrated that every 5% increase in LVEF was associated with a 14% reduction in the risk of SCD [18]. Modern drugs such as angiotensin receptorneprilysin inhibitors (ARNIs) and sodiumglucose cotransporter 2 inhibitors (SGLT2is) contribute substantially to the reduction of arrhythmic risk, both through reverse remodelling mechanisms and via direct molecular effects [19-22].

Table 1.

Descriptive statistics of medical therapy in the study cohort

Parameter	Visit 1	Visit 2	Visit 3
No RAASi, n (%)	19 (21,8)	8 (9,2)	29 (33,3)
ACEi, n (%)	46 (52,9)	36 (41,4)	17 (19,5)
ARNI, n (%)	4 (4,6)	21 (24,1)	30 (34,5)
ARB, n (%)	18 (20,7)	22 (25,2)	11 (12,7)
Proportion of target dose RAASi, %	25 [12,5; 50]	50 [20; 67]	50 [25; 100]
BB, n (%)	76 (87,4)	87 (100)	58 (66,7)
Proportion of target dose BB, %	37,5 [25; 50]	62,5 [50; 100]	50 [25; 81,3]
MRA, n (%)	66 (75,9)	71 (81,6)	48 (55,2)
Proportion of target dose MRA, %	100 [100; 100]	100 [100; 100]	100 [50; 100]
SGLT2i, n (%)	1 (1,1)	10 (11,5)	21 (24,1)
Diuretics, n (%)	67 (77,0)	59 (67,8)	50 (57,5)
Statins, n (%)	45 (51,7)	48 (55,2)	47 (54,0)
Antiplatelets, n (%)	50 (57,5)	31 (35,6)	23 (26,4)
Anticoagulants, n (%)	24 (27,5)	31 (35,6)	35 (40,2)
Amiodarone, n (%)	14 (16,1)	7 (8,0)	4 (4,6)
Digoxin, n (%)	4 (4,6)	0 (0,0)	1 (1,1)
DHP CCB, n (%)	4 (4,6)	3 (3,4)	4 (4,6)

Note: RAASi - renin angiotensin aldosterone system inhibitors; ACEi - angiotensin converting enzyme inhibitors; ARNI - angiotensin receptor neprilysin inhibitors; ARB - angiotensin II receptor blockers; BB - beta blockers; MRA - mineralocorticoid receptor antagonists; SGLT2i - sodium glucose cotransporter 2 inhibitors; DHP CCB - dihydropyridine calcium channel blockers.

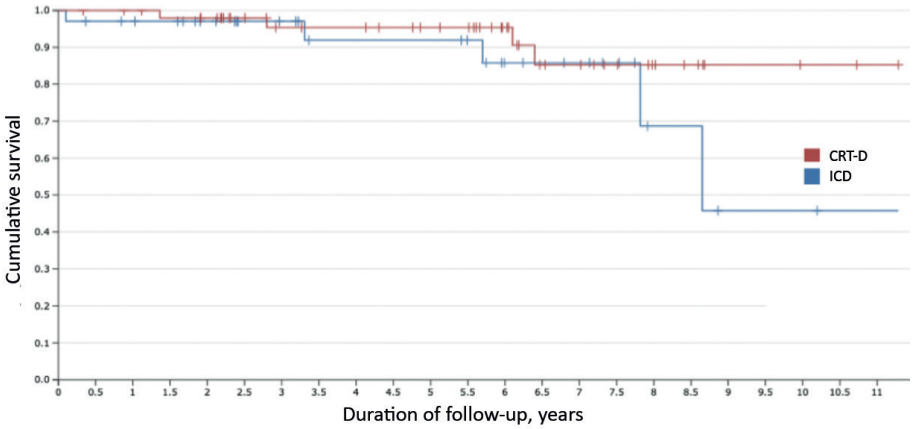

Fig. 1. Survival free from sustained ventricular arrhythmia terminated by ICD/CRTD therapy in CHF patients with improved LVEF. Here and below: VA - ventricular arrhythmia; ICD - implantable cardioverterdefibrillator; CRTD - cardiac resynchronisation therapy defibrillator; LVEF - left ventricular ejection fraction; CHF - chronic heart failure.

Consequently, clinicians face difficult questions: what is the subsequent risk of SCD in patients who have experienced improvement in systolic function after ICD/CRTD implantation and thus have moved outside the standard indications for primary prevention of SCD? How justified is the continuation of such prevention, especially in the context of planned device replacement, which carries a risk of complications [23-25]? Current guidelines and recommendations emphasise the need for reassessment of indications for SCD prevention before ICD/CRTD replacement, but do not provide clear management algorithms [2, 4, 26].

Existing data on the prognosis of HFimpEF patients with implanted devices are heterogeneous and often contradictory. One of the most recent publications on this topic is a large 2024 metaanalysis including 41 studies, which showed that in HFimpEF the risk of arrhythmic events (a composite of sustained VAs, appropriate ICD therapy, and SCD) was 57% lower than in patients with persistent LVEF ≤35%, but still amounted to 5.1% over a mean followup of 3.5 years [27]. However, most published studies used relatively lenient criteria for defining LVEF improvement (LVEF >35%) and the patient populations belonged to an earlier era when modern drug classes (ARNIs, SGLT2is) were unavailable or not widely used [27-29]. Moreover, it is important to note that patients with LV reverse remodelling constitute a heterogeneous group; in some of them this phenomenon is not durable, and at some point, a negative remodelling may recur. According to the literature, a relapse of LVEF reduction is registered even among patients who con-

tinue to receive guidelinedirected medical therapy for CHF, with the incidence of this outcome ranging from 28% to 80% depending on the study group and design [13, 30-32]. However, factors allowing risk stratification within the HFimpEF group itself, as well as the relationship between arrhythmic outcomes and longterm systolic function dynamics, remain poorly understood.

Of particular interest is the comparison of outcomes between patients with ICDs and CRTDs after LVEF improvement, because the effect of cardiac resynchronisation therapy (CRT) on the incidence of VAs is controversial: on one hand, earlier data showed that LV pacing could increase transmural dispersion of repolarisation and provoke arrhythmias; on the other, CRT in the presence of LV reverse remodelling is associated with a reduced incidence of VAs, and LVEF improvement is more durable compared with patients having an ICD [33-37]. Thus, there is an obvious need for studies that, in the setting of contemporary medical therapy and using agreed criteria for HFimpEF, would evaluate longterm arrhythmic and clinical outcomes and identify predictors of adverse events in patients who have already undergone ICD or CRTD implantation for primary prevention of SCD. Obtaining such data is critical for substantiating personalised decisions about the need for device replacement in this patient category.

We have previously published the results of an analysis of survival, inappropriate ICD/CRTD therapy, complications related to implanted devices, and reinterventions in a singlecentre retrospective cohort of CHF patients with improved LVEF who had received an ICD/CRTD for primary prevention of SCD [38]. The present work extends the previously published data by assessing the incidence of appropriate ICD/CRTD therapy and recurrent decline of LVEF to ≤35%.

The aim of this study was to evaluate the longterm risk of lifethreatening VAs terminated by appropriate ICD/CRTD therapy, and relapse of systolic dysfunction in CHF patients with improved LVEF, and to identify factors associated with these outcomes.

MATERIAL AND METHODS

This was a singlecentre, nonrandomised, retrospective cohort study. To enroll patients, we analysed 2,954 electronic medical records of patients for whom an indication for ICD or CRTD implantation at the Almazov National Medical Research Centre (a referral for hightech medical care was opened) between 2016 and 2022 was established. From these, 87 patients with an ICD or CRTD who met the inclusion and exclusion criteria were selected.

Inclusion criteria were: age >18 years, CHF NYHA functional class II-III with initial LVEF ≤35%, and documented at the time of enrolment an increase in LVEF to ≥40% with an absolute increase of ≥10% on repeat transthoracic echocardiography (TTE) performed no earlier than 3 months after ICD/CRTD implantation. The exclusion criterion was the presence of an indication for secondary prevention of SCD at enrolment.

The primary endpoint was an arrhythmic composite endpoint (ACE): development of sustained VA (ventricular tachycardia, ventricular fibrillation) terminated by ICD/CRTD therapy. The secondary endpoint was a relapse of LVEF reduction to ≤35% as a marker of increased SCD risk in accordance with current clinical guidelines and CHF management protocols.

The patient evaluation plan included standard clinical and laboratory assessment (history, physical examination, ECG, Holter ECG monitoring, clinical and biochemical blood tests), TTE data, ICD/CRTD programming protocols, and information on medical therapy. LVEF was determined by the Simpson method. Target doses of CHF

Table 2.

Factors associated with the arrhythmic composite endpoint

Parameter	Appropriate ICD/CRT D therapy		P
	No	Yes	
Number of HF hospitalisations	1 [1; 2]	2 [1; 2]	0.046
TR ≥ grade 2 (visit 1), n (%)	29 (37.1%)	5 (83.3%)	0.001
Stroke, n (%)	4 (8.5%)	3 (60.0%)	0.014
LV end systolic dimension (visit 1), mm	58.0 [50.0; 63.0]	66.0 [65.5; 68.5]	0.034
Proportion of target BB dose (visit 3), %	68.7 [50.0; 100.0]	25.0 [25.0; 25.0]	<0.001
Non sinus rhythm (visit 3), n (%)	30 (38.5%)	5 (83.3%)	0.048

Note: HF - heart failure; TR - tricuspid regurgitation; LV - left ventricle; BB - beta blockers.

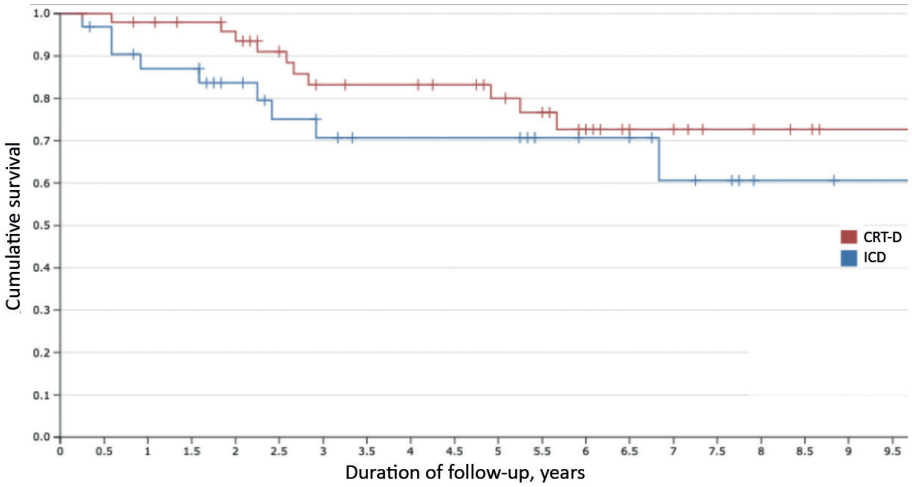

Fig. 2. Survival free from recurrent LVEF decline to ≤35% in CHF patients with improved LVEF.

diseasemodifying therapy were defined according to the 2024 clinical guidelines "Chronic Heart Failure"; for earlier patient visits, therapy was reassessed retrospectively.

Given the retrospective design, to standardise the analysis and presentation, the data were structured around three key visits.

Visit 1 - screening stage: hospitalisation for ICD/CRTD implantation, CHF with reduced LVEF.

Visit 2 - inclusion stage: the visit at which LVEF improvement according to the inclusion criteria was first recorded. To identify this visit, a retrospective analysis of all available TTE reports for each patient was performed. The minimum time interval between ICD/CRTD implantation and visit 2 was at least 3 months.

Visit 3 - control stage: the most recent inperson visit at which TTE and device interrogation were performed.

Outcome registration was carried out as follows:

- for assessment of arrhythmic outcomes, all ICD/CRTD interrogation reports during followup were analysed;
- for identification of LVEF decline (secondary endpoint), all TTE reports during followup were analysed.

Data on fatal outcomes were collected by telephone contact with the patient's relatives if information was not available in the medical information system of the centre.

Statistical analysis

Statistical analysis was performed using StatTech v. 4.11.0 (Stattech LLC, Russia). Normality of quantitative variables was assessed by the Shapiro-Wilk test (n<50) or Kolmogorov-Smirnov test (n≥50). For normally distributed data, values are presented as mean (M) and standard deviation (SD); for nonnormally distributed data - as median (Me) and interquartile range [Q1; Q3]. For relative values, 95% confidence intervals (95% CI) were calculated: for means using the standard formula, for proportions using the Clopper-Pearson method. Comparison of two groups by quantitative variables was performed using Student's ttest (for normal distribution) or the Mann-Whitney Utest (for nonnormal). Categorical data were compared using Pearson's χ^2 test (if expected frequency >10) or Fisher's exact test (if expected frequency ≤10). For multifield tables, Pearson's χ^2 test was used, and the strength of association was assessed by Cramér's V (Rea & Parker, 2014). Differences were considered statistically significant at p<0.05.

RESULTS

The study included 87 patients: 39.1% (n=34) with singlechamber/dualchamber ICDs, 60.9% (n=53) with CRTD. Detailed clinical and demographic characteristics of the cohort, including distribution by device type, CHF aetiology, comorbidities, and baseline echocardiographic parameters, were presented previously [38]. Given the potential impact of CHF diseasemodifying therapy on the risk of ventricular arrhythmias and the durability of LV reverse remodelling, we additionally assessed medication use at different stages of followup. At baseline (visit 1), reninangiotensinaldosterone system inhibitors (RAASi) were taken by 78.2% of patients, betablockers (BB) by 87.4% (though the median proportion of target dose was only 37.5%), mineralocorticoid receptor antagonists (MRA) by 75.9% (100% of target dose), and SGLT2is by only 1.1%, reflecting that most patients were enrolled when this class was not yet available for CHF. Diuretics were prescribed to 77% of patients. At the time of LVEF improvement registration, the prescription rates and doses of diseasemodifying therapy increased; however, at the control visit, a decline in prescription of RAASi, BB, and MRA was noted, along with an increase in SGLT2i use. At the control visit, a significantly higher prescription rate of MRA was recorded among ICD patients compared with CRTD patients (67.6% (n=23) vs. 47.2% (n=25), p=0.006); otherwise, no statistically significant differences in therapy were found between ICD and CRTD groups at any visit.

Table 3.

Factors associated with recurrent LVEF decline to ≤35%

Parameter	Recurrent LVEF decline to ≤35%		P
	No	Yes	
Atrial fibrillation, n (%)	29 (48,3%)	15 (75,0%)	0,043
Hypertension, n (%)	39 (66,1%)	18 (90,0%)	0,046
PCI, n (%)	12 (19,7%)	5 (23,8%)	0,03
CABG, n (%)	3 (4,9%)	1 (4,8%)	
PCI+CABG, n (%)	1 (1,6%)	4 (19,0%)	
Myocarditis, n (%)	18 (29,5%)	1 (4,8%)	0,033
Non specific intraventricular conduction disturbance on ECG (visit 1), n (%)	12 (38,7%)	8 (80,0%)	0,032
Lower limb oedema (visit 1), n (%)	7 (21,2%)	6 (66,7%)	0,016
MR ≥ grade 2 (visit 1), n (%)	24 (40,0%)	15 (75,0%)	<0,001
TR ≥ grade 2 (visit 1), n (%)	18 (30,0%)	10 (50,0%)	0,019
LV end systolic dimension (visit 1), mm	58,0 [50,0; 63,0]	66,0 [65,5; 68,5]	0,034
E/E' (visit 2)	8,09 [6,7; 9,2]	15,3 [11,0; 16,0]	0,021
TR ≥ grade 2 (visit 2), n (%)	2 (3,2%)	5 (25,0%)	0,003
Maximal LVEF after inclusion, %	50,0 [45,0; 59,0]	45,0 [41,5; 51,0]	0,011
All cause mortality, n (%)	3 (5,0%)	7 (35,0%)	0,002

Note: PCI - percutaneous coronary intervention; CABG - coronary artery bypass grafting; ECG - electrocardiogram; MR - mitral regurgitation; E/E' - ratio of early diastolic mitral inflow velocity to tissue Doppler early diastolic velocity at the mitral annulus; LVEF - left ventricular ejection fraction.

Despite LVEF improvement, nearly twothirds of patients continued diuretic therapy. In a realworld clinical practice setting, this may be interpreted either as a lack of timely drug withdrawal after improvement or as a persistent need for the drug due to ongoing congestive CHF (Table 1).

DISCUSSION

Appropriate ICD/CRTD therapy in HFimpEF patients

Outcomes were ascertainable for 84 of 87 patients. During 8.3±3.6 years of followup after ICD/CRTD implantation and 5.2±2.8 years after LVEF improvement registration, the ACE was reached in 7.1% (n=6) of the overall cohort: 9.7% among ICD recipients (n=3) and 5.8% among CRTD patients (n=3) (p>0.05). Survival free from sustained VA terminated by ICD therapy was 92.9% in the overall cohort (90.3% for ICD and 94.2% for CRTD); the KaplanMeier curve is shown in Fig. 1. In 4 patients, the ACE consisted of sustained VA requiring antitachycardia pacing; in 2, shock delivery. In 3 cases, the ACE occurred after a relapse of LVEF to ≤35%, when standard indications for primary SCD prevention according to clinical guidelines apply (15% of the patients in this subgroup). Therefore, only 3 cases of ACE occurred with LVEF >35% (37%, 46%, 51%), and the incidence of ACE among patients with persistently improved LVEF was 4.8%. In all cases, the therapy was antitachycardia pacing.

In the literature, the incidence of appropriate ICD therapy in improved LVEF ranges from 9.7% over 2.9 years to 19% over 3 years [28, 29]. More contemporary data come from the 2024 metaanalysis, which showed that improved LVEF was associated with a 57% relative risk reduction in arrhythmic events, with an absolute event rate in the improved LVEF group of 5.1% over 3.5 years [27]. The lower ACE rate in our study may be explained by several methodological differences from previous work. For example, in the study by Pillarisetti et al., the proportion of ischaemic aetiology was higher (72% vs. 43%), and the criteria for LVEF improvement were less stringent (LVEF >35% and increase >5% vs. ≥40% and ≥10% in our study) [28]. In the metaanalyses by Smer et al. and AlSadawi et al., improved LVEF was also defined as >35% on repeat TTE [27, 29]. Furthermore, in those studies patients received older therapies, whereas in ours up to a third of patients were taking contemporary drugs (ARNIs, SGLT2is), which are associated with reduced arrhythmic risk. It is worth noting that the design of those studies did not include analysis of arrhythmic events according to the subsequent dynamics of LV systolic function after improvement, which we have done here. Nevertheless, although our patient sample had a much longer followup (8.3±3.6 years after ICD/CRTD implantation) compared with literature data (3-3.5 years), the ACE rate was lower, which is of particular value given the more contemporary patient population included.

The ACE rate with persistently improved LVEF (4.8% over 8 years) is consistent with the position of clinical guidelines emphasising the need for reassessment of SCD prevention indications before routine ICD replacement and the lack of a need for routine device replacement when LVEF improvement is sustained [2, 4, 26]. However, the limitations of this study - its retrospective nature and relatively small sample size - should be taken into account, allowing only hypothesisgenerating statements that require confirmation in randomised clinical trials.

Factors associated with ACE included: history of stroke, tricuspid regurgitation (TR) ≥ grade 2 at inclusion, and larger LV endsystolic dimension on baseline TTE. An important finding was a significantly lower proportion of betablocker target dose at control (25.0% vs. 68.7%; p<0.001), and also a significantly higher prevalence of nonsinus rhythm at control (83.3% vs. 38.4%; p=0.048). Overall disease severity was reflected by a higher number of hospitalisations for heart failure decompensation in the appropriatetherapy group. Sex, age, duration of CHF history, length of followup after inclusion, and other parameters did not show significant associations (Table 2).

Recurrent LVEF decline to ≤35% in HFimpEF

Echocardiographic data at the control visit (visit 3) were available for 82 of 87 patients. In our study, 24.4% of patients experienced a recurrent LVEF decline to ≤35% (median time to event from inclusion 2.2 [1.3; 3.2] years), with no statistically significant difference between ICD (28.1%, n=9) and CRTD (22.0%, n=11) groups. Further details are shown in Fig. 2.

Patients with LVEF relapse had significantly higher rates of atrial fibrillation/flutter, arterial hypertension, and a history of combined revascularisations (PCI+CABG: 19.0% vs. 1.6%), reflecting the burden of cardiovascular comorbidity.

At baseline, they more often had lowerlimb oedema, mitral regurgitation and TR ≥ grade 2, and larger LV endsystolic dimension. At inclusion (visit 2), patients reaching the endpoint had significantly higher E/E' values and TR ≥ grade 2, indicating persistent diastolic dysfunction and incomplete rightheart reverse remodelling despite LV systolic recovery. The maximum LVEF achieved after inclusion was lower in those with subsequent relapse, and allcause mortality was significantly higher (35.0% vs. 5.0%; p=0.002). Sex, age, aetiology, and duration of CHF did not show significant associations with LVEF relapse, and no significant differences in medication therapy between groups were found at any stage (Table 3).

CONCLUSION

In CHF patients with improved LVEF who had previously undergone device implantation for primary SCD prevention, a risk of lifethreatening VAs persists, albeit substantially reduced - 4.8% over 8 years with sustained LVEF improvement. A relapse of systolic dysfunction was recorded in 24.4% of patients and was associated with more severe remodelling, biventricular CHF, and high mortality (35.0%).

Even when LVEF improvement is achieved, careful patient monitoring, continuation of optimal diseasemodifying therapy, and consideration of a range of clinical and instrumental predictors are required to stratify the risk of both arrhythmic events and systolic dysfunction relapse. Despite the retrospective design and limited sample size, the results underscore the need for an individualised approach to managing this patient category and provide a basis for planning further prospective studies in this direction.

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ASSOCIATION BETWEEN LEFT ATRIAL LOW-VOLTAGE AREAS AND OUTCOMES OF RADIOFREQUENCY ABLATION IN ATRIAL FIBRILLATION

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Aim. To evaluate the impact of the extent of left atrial (LA) low-voltage areas on the risk of atrial arrhythmia recurrence after radiofrequency ablation (RFA) in patients with atrial fibrillation (AF).

Methods. The study included 159 patients (mean age 65.36±9.33 years; 61.6% male) undergoing first-time RFA for AF (68.6% paroxysmal, 31.4% persistent). High-density LA voltage mapping was performed using a multielectrode catheter and CARTO 3 system. Areas with bipolar amplitude <0.5 mV were classified as low-voltage areas (LVA), and <0.1 mV as very low-voltage areas (vLVA). The percentage of LVA (LVA%) and vLVA% were calculated. The primary endpoint was recurrence of any atrial arrhythmia during 12-month follow-up. Kaplan-Meier survival analysis, Cox regression models, and ROC analysis were performed.

Results. Arrhythmia recurrence occurred in 40% of patients with persistent AF and 18.3% with paroxysmal AF. LVA% was significantly higher in patients with recurrence (40.40% vs. 4.80%; $p < 0.001$). In the Cox model, each 1% increase in LVA% was associated with a 3.6% higher recurrence risk (HR 1.036; $p < 0.001$). After adjustment for AF type and LA volume, LVA% remained an independent predictor (adjusted HR 1.034; $p < 0.001$). ROC analysis identified an optimal threshold of 22.4% (AUC=0.746). Patients with LVA% ≥22,4% had more than six-fold higher recurrence risk (adjusted HR 6.478; $p < 0.001$). LVA% measured during AF showed even stronger discrimination (AUC=0.786 for any arrhythmia; AUC=0.790 for atypical flutter/atrial tachycardia recurrence).

Conclusions. The extent of low-voltage substrate in the left atrium is a strong and independent predictor of arrhythmia recurrence after RFA. Thresholds of ≥22,4% (or ≥24,7% for mapping during atrial fibrillation) allow reliable risk stratification and may guide individualized ablation strategies.

Key words: atrial fibrillation; radiofrequency ablation; low-voltage areas; left atrium; arrhythmia recurrence; high density mapping

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Atrial fibrillation (AF) remains one of the most common sustained tachyarrhythmias and an important public health problem. According to epidemiological studies, over the past 20 years the prevalence of AF has increased by more than 30% and continues to rise, driven both by population ageing and the accumulation of cardiovascular risk factors [1-3]. Therefore, the search for methods to improve the effectiveness of treatment for this arrhythmia is a pressing issue in modern medicine.

Pulmonary vein isolation (PVI) is currently the first-line therapy for patients with both paroxysmal and persistent AF [3]. However, the problem of arrhythmia recurrence after ablation remains relevant. According to various metaanalyses, a single radiofrequency ablation (RFA) procedure provides longterm freedom from atrial arrhythmia in approximately 50% of patients, with lower rates in nonparoxysmal AF [4, 5]. These data underscore the need for more accurate risk stratification and individualisation of ablation strategies.

Structural atrial remodelling, particularly left atrial (LA) fibrosis, plays an important role in the development and maintenance of AF. The anatomical correlate of fibrosis is areas of myocardial thinning, disruption of muscle bundle continuity, and replacement with connective tissue, creating a heterogeneous conducting substrate and promoting the initiation and maintenance of reentry mechanisms and trigger activity [6]. These changes are reflected in local reduction of bipolar electrogram amplitude, and therefore lowvoltage areas (LVA) of the LA, identified by highdensity mapping, are considered a surrogate marker of LA fibrosis [6].

In recent years, substantial evidence has accumulated on the prognostic value LVA of LA for catheter ablation outcomes. In prospective studies by M. Masuda et al. and K. Vlachos et al., it was established that in patients with paroxysmal AF, the presence of LVA in the LA after PVI is associated with an increased risk of AF recurrence [7, 8]. Studies by T. Yamaguchi et al. showed that an ablation strategy targeting LVA improves outcomes of RFA for persistent AF compared with PVI alone, and that more extensive LVA is associated with worse prognosis [9, 10].

At the same time, despite a large body of evidence supporting the prognostic role LVA of LA, the results remain controversial. Several randomised trials have found that additional ablation of LVA did not improve RFA efficacy compared with PVI alone [11, 12]. Thus, the impact of LVA on RFA efficacy remains debatable.

The aim of this study was to evaluate the effect of the extent LVA of LA on the efficacy of RFA for AF.

MATERIAL AND METHODS

This was a singlecentre, prospective, nonrandomised cohort study. The study included 159 patients with paroxysmal (n=109, 68.6%) and persistent (n=50, 31.4%) AF referred for firsttime RFA. Mean age was 65.36±9.33 years, 98 men (61.6%) and 61 women. In all patients, arrhythmia was clinically significant, manifesting as sensations of constant or transient palpitations and/or reduced exercise tolerance. AF was documented on electrocardiography (ECG) and Holter monitoring in all patients. In 28 patients, typical atrial flutter was also recorded on ECG in addition to AF. In 18 patients, episodes of organised atrial tachyarrhythmia with cycle length up to 350 ms and atrial activity morphology different from typical flutter were noted, which were considered atypical flutter. No episodes of atrial tachycardia (AT) were recorded.

Inclusion criteria were: patients with AF referred for RFA who signed informed consent. Exclusion criteria were: age under 18 years, prior AF ablation, prior openheart cardiac surgery. Characteristics of patients with paroxysmal and persistent AF are presented in Table 1. The groups differed significantly in the prevalence of diabetes mellitus, left atrial appendage (LAA) emptying velocity, and left ventricular ejection fraction. No differences were found for other parameters.

All patients underwent transoesophageal echocardiography within 24 hours before the procedure to exclude thrombi in the LAA and LA cavity, during which LAA emptying velocity was measured.

On admission to the operating room, if the patient was in arrhythmia, rhythm restoration was not performed, and LA voltage mapping was performed during arrhythmia (n=72, 45.3% - 50 patients with persistent AF, 22 with paroxysmal). For patients in sinus rhythm (SR) on admission (n=87, 54.7%, all with paroxysmal AF), mapping was performed during

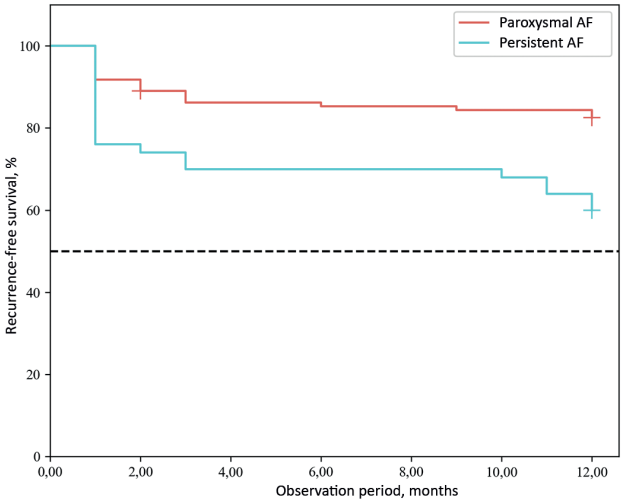

Fig. 1. Arrhythmiafree survival according to AF type.

Table 1.

Clinical and echocardiographic characteristics of patients

Parameter	Paroxysmal AF	Persistent AF	p
Age, years	64.56±9.18	67.10±9.49	0.111
Male sex, n (%)	62 (56.9%)	36 (72.0%)	0.069
Arrhythmia history duration, months	48.0 (21.0-110.0)	36.0 (11.0-84.0)	0.070
Diabetes mellitus, n (%)	13 (11.9%)	18 (36.0%)	<0.001
Coronary atherosclerosis, n (%)	32 (29.4%)	19 (38.0%)	0.278
GFR, mL/min/1.73 m²	63.5 (55.0-80.0)	61.8 (51.8-74.7)	0.261
BMI, kg/m²	29.3 (26.5-33.0)	29.3 (25.7-32.7)	0.521
CHA_2DS_2 VASc score	3 (2-3)	3 (2-4)	0.091
IVS thickness, mm	11.0 (10.0-12.0)	11.0 (10.0-13.0)	0.808
LA AP diameter, cm	4.0 (4-4)	4.0 (4-5)	0.07
LAA emptying velocity, cm/s	60.0 (47.0-68.0)	43.0 (29.0-52.0)	<0.001
LVEF, %	60 (58-63)	55 (50-60)	<0.001

Note: AF - atrial fibrillation; GFR - glomerular filtration rate; BMI - body mass index; IVS - interventricular septum; LA - left atrium; AP - anteroposterior; LAA - left atrial appendage; LVEF - left ventricular ejection fraction.

Table 2.

Risks of arrhythmia recurrence according to individual factors in multivariate Cox regression

Risk factor	Unadjusted model		Adjusted model	
	HR; 95% ДИ	p	HR; 95% ДИ	p
LVA%	1.036; 1.023-1.049	<0.001	1.034; 1.018-1.051	<0.001
Persistent AF	2.646; 1.412-4.961	0.002	0.904; 0.409-2.001	0.804
LA volume	1.012; 1.006-1.019	<0.001	1.003; 0.995-1.012	0.443

Note: HR - hazard ratio; CI - confidence interval; LVA% - percentage of low voltage areas; AF - atrial fibrillation; LA - left atrium.

atrial pacing from the proximal pair of electrodes of the diagnostic catheter in the coronary sinus at a cycle length of 600 ms. Voltage maps were constructed using the CARTO 3 navigation mapping system (Biosense Webster, USA). Mapping was performed using a PentaRay multielectrode catheter.

All voltage maps consisted of at least 1500 points, with a mean number of points of 1748±254. Areas with bipolar signal amplitude >0.5 mV were defined as normal-voltage areas, areas with amplitude <0.5 mV as LVA, and areas with amplitude <0.1 mV as very lowvoltage areas (vLVA). After mapping, voltage maps were analysed, and the percentage of LVA (LVA%) and vLVA (vLVA%) was calculated. The mapping and LVA% calculation methodology is described in detail in our previous work [13].

The thresholds described above were chosen based on numerous previous studies. A threshold of 0.5 mV for low voltage was proposed in several studies [14-16]. Currently, this threshold is the most widely used in the literature. Moreover, it is reflected in the 2024 EHRA/HRS/APHRS/LAHRS Expert Consensus Statement [17]. In the study by Y. Lin (2014), voltage <0.1 mV was defined as "dense scar" [18].

In persistent AF, after PVI, if arrhythmia persisted, additional ablation was performed (linear ablation, substrate ablation) with verification of conduction block. If RFA failed to restore SR, electrical cardioversion was used.

In paroxysmal AF, after achieving PVI, induction of atrial tachyarrhythmias was performed using a burst pacing protocol. If sustained arrhythmia was induced, electrophysiological mapping of the LA was performed to verify the tachycardia mechanism, followed by ablation. If arrhythmia persisted after ablation, electrical cardioversion was performed; for linear ablations, conduction block was verified after SR restoration. For patients with documented typical atrial flutter, cavotricuspid isthmus ablation was performed with bidirectional block verification.

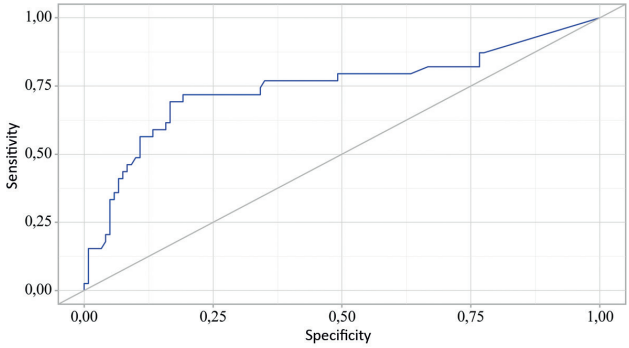

Fig. 2. ROC curve showing the discriminative ability of LVA% for predicting recurrence of any arrhythmia.

The followup period was 12 months. Recurrence was defined as any atrial arrhythmia lasting >30 seconds documented on ECG or Holter monitoring. ECG assessment with verification of arrhythmia type (AF, flutter, AT) was performed. No blanking period was applied; the 12month followup period commenced immediately after the RFA procedure.

Antiarrhythmic drugs other than betablockers were discontinued 5 days before the procedure; amiodarone was discontinued at least 3 weeks before. After the procedure, no antiarrhythmic therapy other than betablockers was prescribed, except in cases of recurrence, which was considered an endpoint.

The primary endpoint was recurrence of any atrial arrhythmia. Secondary endpoints were recurrence of AF and recurrence of left atrial organised arrhythmias (atypical flutter and AT). We analysed the association of LVA% and vLVA% with recurrence of any arrhythmia, as well as with recurrence of AF and leftsided organised arrhythmias (atypical flutter and AT).

Statistical analysis

Statistical analysis was performed using StatTech v. 4.10.3 (Stattech LLC, Russia). Quantitative variables were assessed for normality using the Kolmogorov-Smirnov test. Normally distributed variables are presented as mean (M) and standard deviation (SD), with 95% confidence intervals (95% CI). Nonnormally distributed variables are presented as median (Me) and interquartile range (Q1-Q3).

Categorical variables are presented as absolute numbers and percentages. Comparison of two groups for normally distributed variables with equal variances was performed using Student's ttest. Nonnormally distributed variables were compared using the Mann-Whitney Utest.

Comparison of percentages in 2×2 contingency tables was performed using Pearson's χ^2 test (if expected frequency >10) or Fisher›s exact test (if expected frequency ≤10). Odds ratios with 95% CI were calculated. ROC curve analysis was used to evaluate discriminative ability. The cutoff point was determined by the maximum Youden index. Freedom from arrhythmia was estimated using Kaplan-Meier analysis. Cox regression was used to analyse arrhythmiafree survival. Hazard ratios (HR) with 95% CI were calculated, and statistical significance of each predictor was assessed. Differences were considered significant at p<0.05.

Table 3.

Risks of arrhythmia recurrence according to individual factors in multivariate Cox regression

Risk factor	Unadjusted model		Adjusted model	
	HR; 95% ДИ	p	HR; 95% ДИ	p
LVA ≥22.4%	6.95; 3.45-13.98	<0.001	6.48; 2.87-14.63	<0.001
Persistent AF	1.01; 1.01-1.02	<0.001	1.0; 1.0-1.01	0.294
LA volume	2.65; 1.41-4.96	0.002	0.82; 0.38-1.77	0.621

Note: HR - hazard ratio; CI - confidence interval; LVA% - percentage of low voltage areas; AF - atrial fibrillation; LA - left atrium.

RESULTS

The median LVA% was 8.8%, and vLVA% was 0.0%. Mean LVA% and vLVA% were 18.13±21.20% and 1.74±3.95%, respectively. Median LVA% for paroxysmal AF was 2.1% (mean 9.76±15.88%), and for persistent AF 37.15% (mean 36.37±19.97%). Median vLVA% for paroxysmal AF was 0.0% (mean 1.03±3.66%), and for persistent AF 1.55% (mean 3.28±4.18%).

In patients with persistent AF, arrhythmia recurrences occurred in 20 patients (40%), AF recurrence in 8 (16%), atypical flutter in 8 (16%), AT in 3 (6%), and typical flutter in 1 (2%). In patients with paroxysmal AF, recurrences occurred in 20 patients (18.3%), AF recurrence in 13 (11.9%), atypical flutter in 7 (6.4%). Arrhythmiafree survival curves for paroxysmal and persistent AF are shown in Fig. 1. The difference in arrhythmiafree survival between paroxysmal and persistent AF, assessed by the logrank test, was statistically significant (p=0.003).

We analysed the association between LVA% and recurrence of any arrhythmia in the overall cohort. Patients with and without recurrence differed significantly in LVA%. In patients without recurrence, LVA% was 4.80 (1.00-17.52), while in those with recurrence it was 40.4 (11.65-53.55) (p<0.001). In univariate Cox regression, LVA% showed a statistically significant association with recurrence risk. Each additional 1% of LVA% was associated with a 3.6% increase in recurrence risk (HR 1.036; 95% CI 1.023-1.049; p<0.001).

After adjustment for clinically relevant covariates (AF type and LA volume), LVA% retained independent prognostic significance. Neither AF type nor LA volume showed statistically significant effects after adjustment for LVA%. The model indicated that a 10% increase in LVA% was associated with approximately a 40% increase in recurrence risk ($1.034^{10} \approx 1.40$). Results of the multivariate analysis are shown in Table 2.

ROC analysis for the discriminative ability of LVA% for any arrhythmia recurrence yielded the curve shown in Fig. 2. LVA% was a statistically significant predictor of recurrence (AUC=0.746; 95% CI 0.649-0.842; p<0.001). The cutoff value for LVA% was 22.4%. Sensitivity and specificity were 71.8% and 80.8%, respectively. Positive predictive value was 54.9%, negative predictive value 89.8%.

We additionally stratified patients by the ROCderived cutoff LVA% of 22.4%. Kaplan-Meier curves showed substantial divergence between groups (Fig. 3). Freedom from recurrence at the end of followup was 89.8% in the LVA% <22.4% group and 45.1% in the LVA% ≥22.4% group (p<0.001).

In univariate Cox regression, LVA% ≥22.4% was associated with a marked increase in recurrence risk: HR 6.946; 95% CI 3.45-13.98; p<0.001. This corresponds to nearly a sevenfold increase in recurrence risk in patients with extensive LVA substrate. In a multivariate model including LVA% ≥22.4% (main predictor), LA volume, and AF type, LVA% ≥22.4% remained independently significant: adjusted HR 6.48; 95% CI 2.87-14.63; p<0.001.

LA volume and AF type, significant in univariate analysis, lost association in the multivariate model (p=0.294 and p=0.621, respectively). This indicates that the extent LVA of LA is an independent predictor of recurrence risk. Results are shown in Table 3.

We also analysed the prognostic significance of LVA% and vLVA% for different thresholds (0.1 and 0.5 mV) and for different recurrence types. In patients with persistent AF, LVA% and vLVA% showed a statistically significant association with recurrence of any arrhythmia (LVA% p=0.003, AUC=0.752; vLVA% p=0.006, AUC=0.731) and with recurrence of atypical flutter and AT (LVA% p=0.004, AUC=0.783; vLVA% p=0.012, AUC=0.749). However, no significant association with AF recurrence alone was found (LVA% p=0.443; vLVA% p=0.418).

For paroxysmal AF, we analysed the association of LVA% and vLVA% with recurrence separately for mapping performed in SR and in AF. In patients with paroxysmal AF mapped in SR (n=87), LVA% and vLVA% showed no association with any arrhythmia recurrence (LVA% p=0.227; vLVA% p=0.065), nor with AF recurrence (LVA% p=0.068; vLVA% p=0.070) or with atypical flutter/AT (LVA% p=0.487; vLVA% p=0.299).

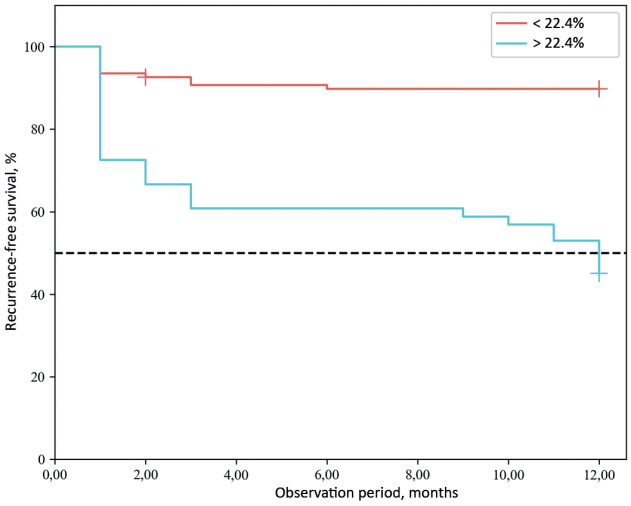

Fig. 3. Arrhythmiafree survival according to LVA% (<22.4% vs. ≥22.4%).

Table 4.

Results of correlation and ROC analysis according to mapping rhythm

	Mapping in SR		Mapping in AF	
	LVA%	vLVA%	LVA%	vLVA%
Recurrence of any ATA	p=0.227; AUC=0.596; 95% ДИ: 0.432-0.761	p=0.065; AUC=0.617; 95% ДИ: 0.454-0.781	p <0.001; AUC=0.786 95% ДИ: 0.666-0.906	p=0.002; AUC=0.723; 95% ДИ: 0.592-0.855
Recurrence of AF	p=0.068; AUC=0.673; 95% ДИ: 0.481-0.866	p=0.070; AUC=0.591; 95% ДИ: 0.415-0.756	p=0.105; AUC=0.661; 95% ДИ: 0.465-0.856	p=0.222; AUC=0.620; 95% ДИ: 0.422-0.819
Recurrence of AFl or AT	p=0.487; AUC=0.593; 95% ДИ: 0.351-0.835	p=0.299; AUC=0.590; 95% ДИ: 0.348-0.833	p=0.001; AUC=0.790; 95% ДИ: 0.636-0.945	p=0.009; AUC=0.733; 95% ДИ: 0.567-0.899

Note: SR - sinus rhythm; AF - atrial fibrillation; LVA% - percentage of low voltage areas; vLVA% - percentage of very low voltage areas; ATA - atrial tachyarrhythmia; AFl - atypical flutter; AT - atrial tachycardia.

In patients with paroxysmal AF mapped in AF (n=22), LVA% showed a statistically significant association with any arrhythmia recurrence (p=0.015, AUC=0.875). However, no correlation was found with AF recurrence (p=0.087) or with atypical flutter/AT (p=0.171). vLVA% did not show any association with any recurrence type (p=0.212 for any; p=0.299 for AF; p=0.526 for atypical flutter/AT).

In the combined group of patients with paroxysmal and persistent AF mapped in AF (n=72), LVA% and vLVA% showed significant associations with any arrhythmia recurrence (LVA% p<0.001, AUC=0.786; vLVA% p=0.002, AUC=0.723) and with atypical flutter/AT recurrence (LVA% p=0.001, AUC=0.790; vLVA% p=0.009, AUC=0.733), but not with AF recurrence (LVA% p=0.105; vLVA% p=0.222). Results are summarised in Table 4.

LVA% was a statistically significant predictor of recurrence of atypical atrial flutter and AT (AUC=0.790; 95% CI: 0.636-0.945; p=0.001). The optimal cutoff value for LVA% was 29.0%, with a sensitivity of 92.3% and a specificity of 53.4%. The positive predictive value was 30.8%, and the negative predictive value was 96.9%. The ROC curves demonstrating the discriminative ability of LVA% derived from mapping during AF for predicting recurrence of any arrhythmia, as well as of atypical flutter and atrial tachycardia, are shown in Fig. 4.

DISCUSSION

Our data show that the extent of LVA remains one of the most significant markers of arrhythmia recurrence risk after RFA. In our study, the cutoff of 22.4% derived from the overall cohort demonstrated strong discriminative ability: patients with LVA% ≥22.4% had a nearly sevenfold increased recurrence risk in univariate Cox analysis. After adjustment for LA volume and AF type, the effect remained independently significant (adjusted HR 6.48), highlighting the key role of electrical remodelling in AF recurrence pathogenesis. These findings agree with studies showing that LVA extent is the strongest predictor of arrhythmia recurrence. Several studies have demonstrated that LVA of LA extent is an independent predictor of recurrence after RFA [7, 19-21].

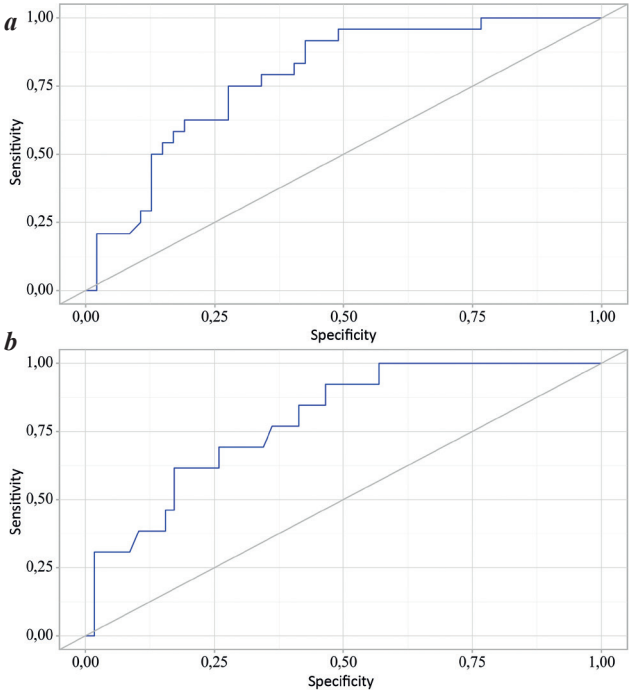

Fig. 4. ROC curves showing the discriminative ability of LVA% for predicting (a) recurrence of any arrhythmia and (b) recurrence of atypical atrial flutter and atrial tachycardia.

In the multivariate model including LVA% alongside clinically relevant covariates (AF type and LA volume), LVA% retained independent significance, while clinical AF type and LA volume lost association. This observation is consistent with the results of Georgi et al. (2024), who showed that it is LVA%, rather than LA volume, that independently predicts recurrence after ablation, although their analysis focused on repeat procedures [22]. A metaanalysis by W. Zhang et al., including 12 studies and over 1000 patients, also demonstrated that the presence of baseline LA LVA nearly triples the risk of AF recurrence after ablation, an effect that persisted across different followup durations [23].

Together with our data, this supports the view that LA LVA is a key predictor of recurrence of atrial arrhythmias after RFA for AF, whereas persistent AF and increased LA volume are likely correlated with recurrence only through their association with increased LVA%.

We found that the prognostic value of LVA depends on the rhythm during voltage mapping. In SR mapping, LVA% was not associated with recurrence, whereas during AF mapping, LVA% showed significant association with recurrence. This suggests that AFmapping better reflects the arrhythmogenic substrate than SR mapping.

Previous studies have repeatedly demonstrated substantial differences in voltage mapping results depending on the rhythm. In the multicentre study by Nairn et al. (2023), the spatial correlation of LVA between SR and AF was only moderate, and LVA areas defined during AF systematically exceeded those obtained in SR [24]. Lahuerta et al. (2022) showed that AFmapping reveals more LVA, and some areas with preserved voltage in SR show amplitude reduction during AF [25]. Mannion et al. (2023) found a histogram shift toward lower voltages during AF and weak correlation of amplitude characteristics between rhythms at the same anatomical points [26]. Based on these works, we believe it is important to evaluate voltage mapping results separately for SR and AF.

In addition to more extensive LVA during AF, several studies have shown that AFmapping reveals significantly more areas of fractionated and continuous activity compared with SR. Sághy et al. (2012) showed that fractionated potentials are much more pronounced during AF and may be completely absent in SR [16]. Huang et al. (2022) and Masuda et al. (2017) reached similar conclusions [27, 28].

Voltage mapping in AF, according to several authors, correlates better with LA fibrosis on cardiac MRI. Qureshi et al. (2019) showed that the correlation between LVA identified by endocardial mapping and MRI-

detected fibrosis significantly improves when mapping is performed during AF compared with SR [29]. Chen et al. (2019) compared three parameters in persistent AF patients: arrhythmogenic zones identified by high-density mapping during AF, LVA in SR, and MRI fibrosis [30]. They showed that LVA determined during AF demonstrated the strongest spatial correspondence with fibrosis, whereas SRbased voltage maps only partially overlapped with the morphological substrate. Furthermore, most arrhythmogenic LA areas (spatiotemporal dispersion and continuous activity) coincided with LVA identified during AF, not SR.

Given the absence of unified recommendations on LVA thresholds and their wide variability in the literature, it is important to compare our findings with existing studies that analyse different thresholds for substrate assessment. Some authors have proposed alternative thresholds for AF mapping, ranging from 0.24 to 0.35 mV, which may correspond to the 0.5 mV threshold in SR [25, 30, 31]. However, a standard LVA threshold for AF mapping has not been established. As noted by Nairn et al. (2023), even with alternative thresholds, the correspondence of LVA between SR and AF remains moderate [24].

In our study, we used two thresholds: 0.5 and 0.1 mV. The results for these two thresholds were very similar, indicating that the 0.5 mV threshold during AF mapping yields results comparable to alternative lower thresholds recommended by some authors. It is important to note the difference between the 0.1 and 0.5 mV thresholds in the analysis of paroxysmal AF patients mapped during AF, which may be explained by the small sample size (22 patients), as in larger cohorts (persistent AF and the combined AFmapped group) no differences were observed.

Many studies have confirmed the prognostic value of LA LVA for recurrence after RFA [8-11]. However, few studies have compared the prognostic value of LVA determined in different rhythms. In Lahuerta et al. (2022), each patient underwent both SR and AF mapping; AFderived LVA% correlated with recurrence, whereas SRderived LVA% did not. The authors noted insufficient statistical power (sample size 23 patients) [25].

Other contemporary studies have mainly compared mapping results in different rhythms by area and by correlation with structural substrate, showing that AFmapping reveals more pronounced functional abnormalities and correlates better with MRI fibrosis, but did not analyse longterm outcomes separately for each group [24, 29, 30]. In this context, our finding that LVA determined during AF is a significant predictor of recurrence, while SR mapping is not, represents a novel clinically meaningful observation, logically extending the advantages of AF mapping reported in the literature. However, these differences are based on analysis of different patient groups and do not imply direct comparison within the same patient; confirmation in further studies with paired mapping is needed.

An interesting finding was that LVA% was significantly associated with the risk of atypical flutter and AT recurrence, but not AF recurrence. This is pathophysiologically plausible. Postablation atypical flutters are typically macroreentry tachycardias whose circuits form around scar tissue, ablation lines, and LVA boundaries. The higher the LVA%, the higher the probability of stable reentry circuits and postablation atypical flutters. In contrast, AF recurrences may be driven not only by substrate burden but also by persistent triggers, which may be unrelated to LVA. Thus, our data suggest that LVA% primarily reflects the "scar" component of the atrial substrate, associated with organised macroreentry tachycardias, while AF recurrence involves additional mechanisms.

An important complement to our data is the identified threshold LVA% associated with any arrhythmia recurrence (24.7%) and atypical flutter/AT recurrence (29.0%). Similar thresholds have been reported. Zhang et al. (2025) concluded that LVA% ≥15% was associated with worse outcomes after ablation [32]. These observations highlight that quantitative assessment of LVA may have practical value for risk stratification of postoperative recurrences.

Our results have important clinical implications. We showed that LVA assessment performed during AF likely has greater prognostic value. This underscores the need to consider the heart rhythm when planning interventional strategy, and the potential benefit of performing highdensity mapping during arrhythmia.

Study limitations

One limitation is that the ablation strategy was not completely uniform: in addition to standard PVI, a significant proportion of patients received additional ablation, which may have influenced outcomes and the probability of different recurrence types.

It should be noted that comparisons of mapping results in different rhythms were performed between different patient groups, limiting interpretation and highlighting the need for further studies with paired mapping in the same patient.

The group of paroxysmal AF patients mapped during AF was relatively small (n=22), but the statistical patterns in this group, in the persistent AF group, and in the combined AFmapped group were similar.

It is important to note that vLVA (<0.1 mV) were not identified in all patients, and their low prevalence and small event numbers in subgroups limit the statistical power of analyses of vLVA prognostic significance.

Furthermore, our results reflect highdensity mapping performed with the CARTO 3 system using the PentaRay catheter. The LVA threshold of 0.5 mV may not be generalisable to other mapping platforms or alternative thresholds.

CONCLUSION

The percentage of left atrial lowvoltage areas is an independent predictor of atrial arrhythmia recurrence after RFA of AF.

A LVA of LA >22.4% was a predictor of recurrence of any arrhythmia.

Voltage mapping performed during AF demonstrated greater prognostic value for atrial arrhythmia recurrence compared with mapping in SR, a finding that requires confirmation in further studies.

The percentage of LVA of LA determined during AF mapping is a predictor of recurrence of atypical atrial flutter and AT, but not of AF.

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RADIOFREQUENCY ABLATION OF THE PULMONARY VEINS USING A SINGLE-CATHETER METHOD IS AS EFFECTIVE AS THE TRADITIONAL APPROACH IN THE TREATMENT OF PAROXYSMAL ATRIAL FIBRILLATION

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Aim. To conduct a comparative analysis of the efficacy and safety of radiofrequency ablation (RFA) of pulmonary vein (PV) in patients with paroxysmal atrial fibrillation (AF) using a single-catheter method (experimental group) versus the standard technique with a multipolar diagnostic Lasso catheter (Biosense Webster, Johnson & Johnson, USA) (control group).

Methods. A single-center prospective randomized study included 206 patients with paroxysmal AF, randomized into two groups: single-catheter (n=103) and control (n=103). All procedures utilized the CARTO 3 (Biosense Webster, Johnson & Johnson, USA) 3D electroanatomical mapping system, and PV isolation was performed according to the CLOSE protocol based on the ablation index. In the experimental group, only a navigated ablation catheter was used for mapping and ablation, with verification of conduction block (entrance and exit) via stimulation from the ablation electrode. The control group underwent the standard approach with a circular diagnostic Lasso catheter. The primary endpoint was the absence of atrial arrhythmias (AF/atrial flutter) after 12 months of follow-up.

Results. Procedure efficacy after a median follow-up of 400 days was 83.5% (86/103 patients) in the single-catheter group and 78.7% (81/103) in the control group. The difference between groups was not statistically significant (OR 1.298; 95% CI 0.649-2.595; p=0.354). Kaplan-Meier analysis also revealed no significant differences (log-rank test, p=0.405). The first-pass PV isolation rate was comparable between groups (94.2% vs. 93.2%, p=0.874). The total procedure time was statistically significantly shorter in the single-catheter group (65.3±20.0 min vs. 82.2±13.0 min, p=0.011), while fluoroscopy time and RFA duration did not differ significantly. Three periprocedural complications were recorded (1 in the experimental and 2 in the control group), all of them were managed successfully.

Conclusion. Radiofrequency ablation of pulmonary veins using a single-catheter method is not inferior in efficacy to the standard approach utilizing a circular Lasso catheter in patients with paroxysmal atrial fibrillation.

Key words: atrial fibrillation; paroxysmal form atrial fibrillation; radiofrequency ablation; single-catheter method; circular catheter

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After M. Haïssaguerre and colleagues demonstrated in 1998 the key role of trigger activity from the myocardial sleeves of the pulmonary veins (PVs) in initiating atrial fibrillation (AF), catheter ablation of the PV ostia became established as the standard interventional strategy for treating this arrhythmia [1, 2].

The classical radiofrequency ablation (RFA) technique involves a double transseptal puncture and the use of a circular diagnostic Lasso catheter for realtime monitoring of PV electrical isolation. In the early stages of its application, this technique achieved clinically acceptable efficacy outcomes [3].

However, with technological advances, including the introduction of catheters with contactforce sensing and lesiondepth assessment based on calculated indices (such as ablation index - AI, contact force index - CFI), ablation efficacy has significantly improved [4]. An important milestone was the introduction in 2017 of the CLOSE protocol (Ditschaever et al.), which allows PV isolation with the first series of applications in more than 95% of cases [5].

Consequently, the use of multipolar diagnostic catheters in primary PV isolation using modern RFA technologies is no longer considered mandatory. Although these catheters retain their clinical value in treating complex atrial tachyarrhythmias and in repeat procedures, their routine use during the first PV isolation procedure may be unnecessary [6]. Avoiding a double transseptal puncture may make the procedure technically simpler and reduce its cost [7].

A number of studies demonstrate high efficacy of the singlecatheter technique in RFA in patients with various

forms of AF [6, 8]. However, the question of whether the omission of multipolar diagnostic catheters may reduce the overall procedure efficacy remains debatable.

Aim - to conduct a comparative analysis of the efficacy of RFA of the PV ostia using two approaches: the single-catheter technique (experimental group) and the standard technique with a multipolar Lasso catheter (control group) in patients with paroxysmal AF.

MATERIAL AND METHODS

Study design: singlecentre, prospective, randomised controlled trial. Patient enrolment was conducted from January 2023 to February 2024. During this period, a total of 578 interventional AF procedures were performed. From these, 234 patients meeting the established criteria were selected for participation in the study. The work was carried out after approval from the local ethics committee (permission No. 115 dated 12.01.2023).

Inclusion and exclusion criteria

The study enrolled firstprocedure patients aged 40-75 years with symptomatic paroxysmal AF (paroxysm duration up to 7 days) who had documented inefficacy or intolerance to class IC or III antiarrhythmic drugs [9]. A mandatory requirement was the ability to undergo postoperative followup.

Exclusion criteria were: nonparoxysmal AF, combined AF and atrial flutter, haemodynamically significant valvular pathology (valvular stenosis or regurgitation > grade I), left atrial (LA) diameter >55 mm, and left ventricular ejection fraction <45%.

After signing informed consent, patients were randomised using a random number generator into two groups. In the experimental group (n=115), PV ostial isolation was performed using only an ablation catheter. In the control group (n=119), the procedure was performed with the additional use of a circular diagnostic Lasso catheter (Biosense Webster, Johnson & Johnson, USA). Due to the inability to undergo subsequent followup, 28 patients (12 and 16 from each group) were excluded from the analysis. Thus, data from 206 patients, equally divided between the groups, were available for efficacy assessment at the end of the study (Fig. 1). Baseline clinical and demographic parameters did not differ significantly between the groups (Table 1).

The procedural technique is described in detail in a previously published article [10]. Two different mapping techniques were used in the study. In the group of patients undergoing ablation with the singlecatheter technique, anatomical reconstruction of the LA was performed using the CARTO 3 threedimensional electroanatomical mapping system (Biosense Webster, Johnson & Johnson, USA). For this purpose, a navigational EZ Steer Nav SmartTouch ablation catheter (Biosense Webster, Johnson & Johnson, USA) was used. Access to the LA was achieved via a single transseptal puncture. In the second group, also after a single transseptal puncture, a 20pole navigational diagnostic Lasso catheter (Biosense Webster, Johnson & Johnson, USA) was used to construct the LA map. After mapping was completed, the Lasso catheter was exchanged for an ablation catheter, PV ostial isolation was performed, and the ablation catheter was again exchanged for the Lasso catheter to verify conduction block. Thus, in the first group, no instrument exchange was performed; in the second group, it was performed twice.

In patients who presented with AF either initially or intraoperatively, electrical cardioversion was performed after radiofrequency applications around the right and left

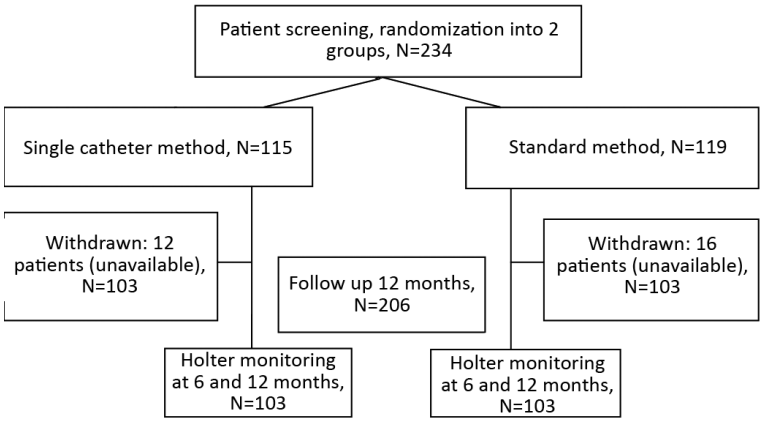

Fig. 1. Research design.

Table 1.

Baseline characteristics of the patient groups

	All patients (n=206)	Single catheter method (n=103)	Standard method (n=103)	p
Age, years	60.8±8.5	61.5±8.5	60.2±8.4	0.260
Male sex, n (%)	108 (52.4%)	48 (46.6%)	54 (52.4%)	0.406
Body mass index, kg/m²	29.6±4.1	29.4±3.7	29.8±4.5	0.419
Left ventricular ejection fraction, %	62.1±6.0	61.8±5.9	62.4±6.1	0.494
Left atrial volume, mL	70.3±16.2	70.2±15.3	70.3±17.2	0.942
Left atrial diameter, mm	39.9±3.7	39.9±3.7	39.8±3.6	0.791
Arrhythmia history duration, months	48 [24;72]	49 [23;70]	47 [24;73]	0.887
Diabetes mellitus, n (%)	25 (12.1)	12 (11.7)	13 (12.6)	0.832
Hypertension, n (%)	177 (85.9)	88 (85.4)	89 (86.4)	0.842
Coronary artery disease, n (%)	18 (8.7)	11 (10.7)	7 (6.8)	0.094

Note: p - significance of differences between single catheter and standard method groups.

PV ostia. Verification of PV electrical isolation was carried out after restoration of sinus rhythm.

In the first group, the criterion for achieving entrance block into the PV was the disappearance of spike electrical activity recorded on the ablation catheter electrograms. Exit block was confirmed by the absence of LA myocardial capture in response to stimulation from the ablation electrode (stimulation parameters: current 10 mA, pulse duration 1 ms). Stimulation was performed at eight equidistant points along the perimeter of the ablation line, provided that catheter-tissue contact force was at least 4 grams (Fig. 2, 3).

In the second group, a diagnostic 20pole navigational Lasso catheter, sequentially positioned at the ostium of each PV, was used to verify PV isolation. Entrance block was confirmed by the disappearance of PV spikes on the electrograms. Exit block was verified by stimulation from each pair of Lasso catheter electrodes using parameters identical to those in the first group. Exit block was defined as the absence of LA myocardial capture upon stimulation, or the presence of local LA myocardial captures without conduction to the atrium [10]. If PV isolation was not achieved after the first series of applications, additional RFA applications were delivered until complete electrical PV isolation was attained.

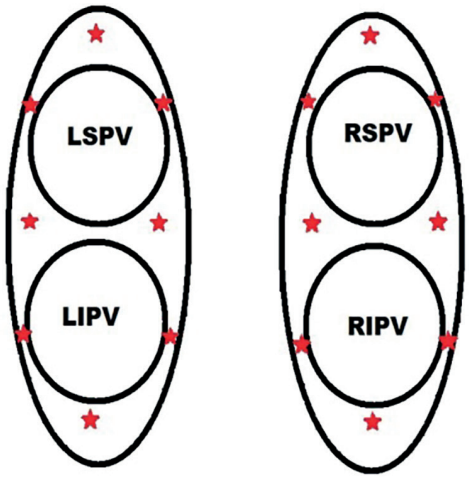

Fig. 2. Schematic representation of stimulation sites from the ablation electrode (marked with stars). RSPV - right superior pulmonary vein; RIPV - right inferior pulmonary vein; LSPV - left superior pulmonary vein; LIPV - left inferior pulmonary vein.

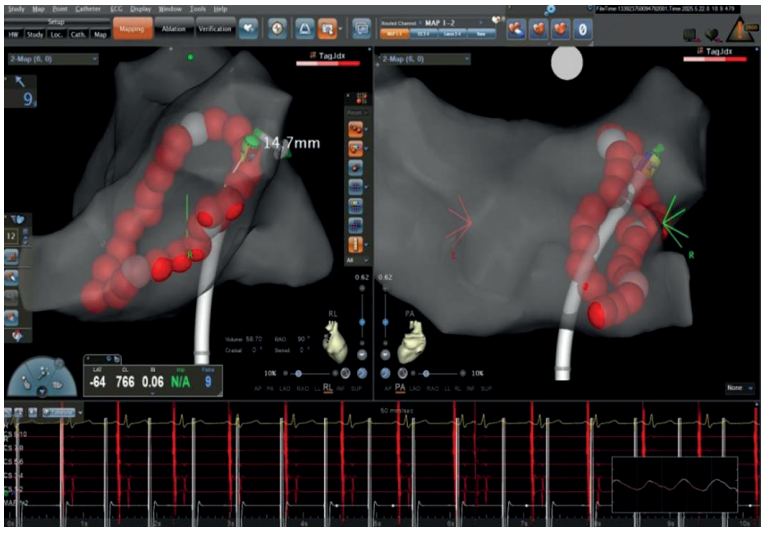

Fig. 3. Exit block verification from the right superior pulmonary vein using the ablation electrode positioned behind the ablation line. Stimulation is delivered from the distal pair of electrodes; absence of atrial myocardial capture indicates vein isolation.

Three complications were recorded during the study. In the first group, intraoperative haemopericardium developed and was successfully managed by pericardial drainage. In the second group, in the early postoperative period, hydropericardium with pericardial separation of up to 6 mm, which resolved with conservative therapy, and an arteriovenous fistula between the superficial femoral artery and common femoral vein located 20 mm from the common femoral artery bifurcation (as detected by computed tomography), which was also managed conservatively (by compression), were identified.

For 4 weeks after the RFA procedure, all patients continued antiarrhythmic therapy. The decision to discontinue it was made by the attending physician at the place of residence. Anticoagulant therapy was continued in all patients, regardless of the procedure's efficacy.

Postprocedural followup was organised using a combined scheme that included both inperson and remote visits. Local patients underwent scheduled inperson examinations at the outpatient department, which included clinical assessment and 24hour Holter ECG monitoring. For patients residing in remote regions, remote followup was used: at 6 and 12 months after the procedure, they provided medical documentation with a description of symptoms and Holter ECG results.

Arrhythmia recurrence was defined as any documented episode of AF or atrial tachycardia lasting >30 seconds on ECG or Holter monitoring. When recurrence was detected, the possibility of a repeat intervention was considered. The primary endpoint of the study was the absence of atrial arrhythmias at the end of the followup period.

Statistical analysis

Sample size calculation was performed for the primary endpoint. The noninferiority margin (Δ) was set at 15%. The calculation was based on the assumption that the true efficacy in both groups was identical and approximately 80%. With a twosided significance level (α) of 5% and power (1β) of 85%, to confirm that the singlecatheter method was noninferior to the standard method, the required number of patients in each group was 105. To account for possible dropout (~10%), the total sample size was increased to 236 patients.

Normality of distribution of quantitative variables was assessed using the Kolmogorov-Smirnov test. Variables with normal distribution are presented as mean and standard deviation (M±SD) with 95% confidence intervals (95% CI). Nonnormally distributed data are presented as median and interquartile range Me [Q1; Q3].

Comparison of two independent groups with normal distribution was performed using Student's ttest. For nonnormally distributed variables, the nonparametric Mann-Whitney

Utest was used. Cumulative probability of freedom from arrhythmia recurrence during followup was assessed using Kaplan-Meier curves. Survival curves were compared using the twosided logrank test. The critical level of statistical significance was set at 0.05.

RESULTS

The proportion of procedures performed in sinus rhythm was comparable between the groups. In the singlecatheter group, 86.4% (n=89) of patients were operated on in sinus rhythm and 13.6% (n=14) in AF. In the standard group, the corresponding proportions were 83.5% (n=86) and 16.5% (n=17). The difference was not statistically significant (p=0.453).

The proportion of patients with successful firstpass PV isolation also did not differ between groups: 94.2% (n=97) in the experimental group vs. 93.2% (n=96) in the control group (p=0.874). Complete electrical isolation of all PV ostia was achieved by the end of the procedure in 100% of patients in both groups.

Total procedure time was significantly longer in the standard group than in the singlecatheter group (82.2±13.0 min vs. 65.3±20.0 min, p=0.011). Meanwhile, fluoroscopy time and RFA duration did not differ significantly between the groups (Table 2).

The median followup duration was 400 [209.8; 400.0] days. During the study, inperson followup was conducted for 112 patients (54.4%), and remote followup for 94 patients (45.6%). Treatment efficacy did not differ statistically between the inperson and remote groups (79.5% vs. 82.3%, p=0.621).

Overall treatment efficacy in the entire cohort was 81.1% (167 of 206 patients). In the first group, sinus rhythm was maintained at the end of followup in 83.5% of patients (86 of 103), and in the second group in 78.7% (81 of 103). The difference between groups did not reach statistical significance (OR 1.298; 95% CI 0.649-2.595; p=0.354). Kaplan-Meier survival analysis also showed no statistically significant differences between groups (logrank test, p=0.405) (Fig. 4).

Among patients with documented arrhythmia recurrence (n=39), repeat catheter ablation was performed in 11 patients from the first group and 14 from the second. Refusal of reintervention due to mild symptoms was recorded in 4 and 5 patients, respectively. Medical contraindications to repeat procedure were identified in 2 patients in the first group (erosive gastritis and manifestation of thyrotoxicosis) and 3 patients in the second group (thyrotoxicosis in two cases and exacerbation of gastric ulcer in one). In all cases of thyrotoxicosis, patients were not taking amiodarone.

During repeat procedures, conduction recovery was documented in at least one PV in all patients. The total number of veins with recovered conduction was 19 in the first group and 23 in the second, which did not differ statistically (p=0.612).

DISCUSSION

The results of this prospective randomised study are consistent with published data emphasising the feasibility and efficacy of simplified catheter ablation protocols.

One of the first studies to directly compare the efficacy of standard and singlecatheter RFA techniques in paroxysmal AF was that by Sebag et al. [7]. That study included 100 patients divided into two groups of 50. Safety and efficacy, as well as procedure cost, were compared between the standard and singlecatheter approaches. At oneyear followup, sinus rhythm was maintained in 86% of patients in the experimental group and 84% in the control group. The difference was not statistically significant. At the same time, the cost of the singlecatheter procedure was 31% lower than the standard technique. Thus, avoidance of the diagnostic circular Lasso catheter allowed a significant reduction in procedure cost without compromising efficacy.

Another study comparing singlecatheter and standard RFA techniques for PV isolation was that by Xhaet et al. [11]. The retrospective analysis included a cohort of 477 patients who underwent PV RFA for paroxysmal AF. Patients were divided into a standardtechnique group (n=226) and a singlecatheter group (n=251). Primary endpoints were success of PV isolation, AF recurrence rate at oneyear followup, total procedure duration, and fluoroscopy time. No statistically significant differences were found between groups in the number of isolated PVs, AF recurrence rate, or need for antiarrhythmic therapy at one year. However, the singlecatheter group showed a significant reduction in total procedure time (106±33 min vs. 125±32 min, p<0.0001) and fluoroscopy time (2.2±1.9 min vs. 2.7±2.3 min, p=0.0002).

Thus, an important practical conclusion of that study is the confirmation that the singlecatheter technique significantly reduces procedure duration and radiation exposure, suggesting a potential reduction in radiation burden

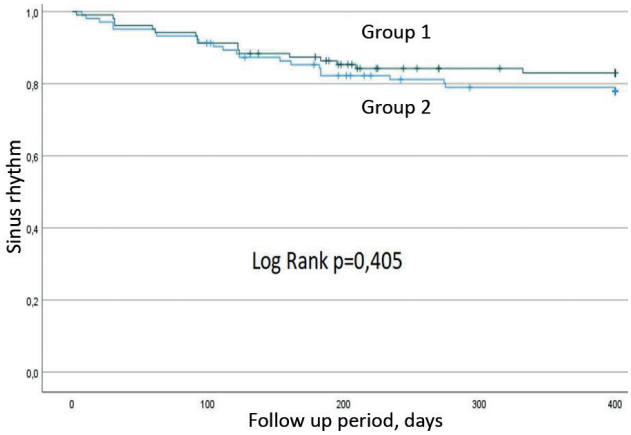

Fig. 4. Treatment efficacy in the first (single catheter method) and second (standard technique) patient groups.

Table 2.

Procedural characteristics (n=206)

	Single catheter method (n=103)	Standard method (n=103)	p
Total procedure time, min	65,3±20,0	82,2±13,0	0,011
Fluoroscopy time, s	93,1±34,3	112,5±28,6	0,083
RFA duration, min	14,9±4,0	15,7±4,9	0,271

Note: RFA - radiofrequency ablation.

for both patient and operator, as well as more efficient use of operating room resources. Despite differences in study design, their results are highly consistent with our data.

In a retrospective study by Badertscher et al., the efficacy of the singlecatheter method was evaluated using both standard ablation protocols and highpower, shortduration protocols [8]. All RFA procedures were performed through a single transseptal access using only an ablation catheter; multipolar diagnostic catheters were not used. In a cohort of 91 patients undergoing ablation for paroxysmal AF, high efficacy was demonstrated, with a success rate of 87% at 12month followup. Importantly, that study, like ours, used intraoperative criteria for conduction block verification (stimulation for exit block testing), which enhances the comparability of results. The similar efficacy rates (87% vs. 81.1% in our study) indicate the reproducibility and reliability of the singlecatheter approach when using modern technologies such as contactforce sensing and ablation index.

Another important aspect addressed in the study by Badertscher et al. is safety. In our study, three periprocedural complications were recorded: one in the singlecatheter group (haemopericardium) and two in the standard group (hydropericardium and arteriovenous fistula). Although the number of events is insufficient for statistical inference, the overall trend is consistent with the literature suggesting that procedural simplification may reduce risks. Badertscher et al. reported no serious procedurerelated complications in their cohort, also supporting the safety of the technique. Reducing the number of transseptal accesses from two to one lowers the risks of complications such as puncturerelated pericardial effusion and vascular accesssite complications.

In the study by Pedro Silva Cunha et al., the efficacy and safety of PV isolation using a single transseptal puncture and the standard technique were compared [12]. A retrospective analysis of a relatively large cohort of patients undergoing RFA PV isolation for paroxysmal AF was performed. From July 2015 to March 2020, 285 patients with a mean age of 59.5±11.6 years (36.5% women, 67.7%) underwent RFA of PV ostia. The mean CHA_2DS_2VASc score was 1.7±1.3. In 115 patients (40.3%), the procedure was performed using a single transseptal puncture; in 170 (59.6%), the standard technique was used. Operator experience (5 years of AF ablation procedures) was evenly distributed between the two groups. A significant reduction in fluoroscopy time was noted (13±6.3 min vs. 19±9.1 min for single vs. double transseptal puncture, respectively; $p<0.001$). The rate of acute major complications was similar in both groups (2.6% vs. 2.3%, p=0.799). At 2 years, the rate of sinus rhythm maintenance was similar (76.5% vs. 78.8%, p=0.646). Thus, the authors concluded that the simplified PV isolation technique using a single transseptal access is a safe and highly effective AF ablation method. This approach significantly reduced fluoroscopy time compared with the traditional technique, with a comparable safety profile.

Furthermore, the use of only one catheter in the LA cavity potentially reduces the risk of cerebral embolism by eliminating instrument exchanges during the procedure [13].

In our study, exit block verification in the singlecatheter group was performed using stimulation from the ablation electrode. This method proved reliable, as confirmed by comparable efficacy in the control and experimental groups and the absence of differences in the number of reconnections at repeat procedures. Nevertheless, it should be acknowledged that the use of a specialised diagnostic catheter may be appropriate in cases with complex anatomy. However, as our results and data from other studies show, for most patients with paroxysmal AF, the use of an ablation catheter alone is sufficient to achieve favourable longterm outcomes.

One practical advantage of the singlecatheter technique was a statistically significant reduction in total procedure time (65.3±20.0 min vs. 82.2±13.0 min, p=0.011). This has important clinical and economic implications. Shorter procedure time potentially reduces the risk of infectious complications, decreases the burden on the operating team, and enables more efficient use of operating room resources. At the same time, fluoroscopy time and actual ablation time did not differ significantly between groups, indicating comparable technical complexity of the isolation line creation and no compromise in the thoroughness of ablation.

Several limitations of our study should be noted. First, it is a singlecentre design. Second, part of the followup was conducted remotely based on submitted medical documentation, which may have led to underdetection of asymptomatic recurrences. However, the proportion of patients with remote followup and the recurrence rate in this subgroup did not differ between groups, minimising potential systematic bias. Third, the study included patients with relatively preserved atrial anatomy (no significant LA dilatation); therefore, extrapolation of the results to patients with more complex AF forms and altered anatomy requires caution.

CONCLUSION

This study demonstrates that radiofrequency ablation of the PVs using a singlecatheter method is noninferior to the traditional approach in terms of efficacy in patients with paroxysmal AF.

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REDUCTION IN PACING RATE AND PAIN DURING CARDIAC CONTRACTILITY MODULATION: AN OVERVIEW OF THE PROBLEM AND ITS SOLUTION USING DEVICE PROGRAMMING

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Aim. Evaluation of a patient group with a reduced percentage of stimulation, pain sensation, and the impact of adjusting stimulation programming parameters on achieving a positive effect from cardiac contractility modulation (CCM) therapy.

Methods. The study included 117 patients implanted with a CCM device. Personalized parameter settings were programmed intraoperatively and postoperatively. Transthoracic echocardiography (TTE) was performed before implantation and 6 months after surgery.

Results. The median age was 59.5 years, with 93.7% being male patients. The primary etiology of heart failure was ischemic heart disease (53.8%). A part of patients required a reduction in stimulation amplitude from 7.5 V (79%) to a maximum of 5 V (9%). After 6 months, the group with 7.5 V stimulation amplitude showed a significant increase in LVEF to 37 [32; 43] % (p=0.0001). However, in the group with 5 V stimulation amplitude, the increase in LVEF did not reach statistical significance during follow-up: 35 [34; 40] (p=0.211). Patients without discomfort during CCM therapy had lower LVEF (p=0.048), increased LV volumes (p=0.024; p=0.034), and a thinner LV posterior wall (p=0.028). However, the relationship between cardiac wall thickness and pain during CCM therapy requires further research. Also, in patients without stimulation discomfort, the electrodes were more frequently implanted in the middle third of the interventricular septum (p=0.025). 83.7% of patients were programmed with standard stimulation duration - 7 hours per day (hrs/day). For 5.9%, the stimulation duration was 10 to 14 hours due to failure to achieve the required stimulation percentage. In this patient group, increasing the stimulation duration achieved a stimulation percentage exceeding 70%. In 15.3% of cases, patients with a CCM device had a therapy percentage above 90%. In 68.3% of cases, the daily therapy percentage was 80-90%, and in 12% - 70 to 80%. A positive, moderate, significant correlation was noted between the stimulation percentage and the increase in LVEF (r=0.3; p=0.05).

Conclusion. CCM is an effective method of interventional treatment for patients with CHF. When programming CCM devices, it is necessary to achieve a stimulation percentage exceeding 70% per day, as the stimulation percentage directly correlates with an increase in myocardial contractility. Additionally, the stimulation amplitude should reach the target level of 7.5 V. If pain occurs, a reduction in stimulation amplitude to the minimum tolerable level is permissible. Further study of the nuances of device operation and training of specialists in programming intracardiac devices are necessary.

Key words: cardiac contractility modulation; reduced stimulation percentage; pain sensation

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Cardiac contractility modulation (CCM) is a modern treatment for chronic heart failure (CHF) in addition to optimal medical therapy (OMT) and is intended for patients without indications for cardiac resynchronization therapy (CRT), who account for about 60-70% of all CHF patients [1, 2].

The CCM method is unique because it is based on highamplitude stimulation delivered during the absolute refractory period of cardiomyocyte contraction, which does not produce subsequent contraction. It is believed that such stimulation increases phospholamban phosphorylation, which in turn may improve calcium metabolism in cardiomyocytes [3, 4]. Thus, CCM therapy exerts a positive inotropic effect on the myocardium without increasing oxygen demand.

In the current literature, the nuances of programming CCM devices are virtually not addressed. Nevertheless,

this is a fundamental process that determines the overall effectiveness of the method. To achieve maximum results with CCM therapy, proper electrode positioning and programming that ensures an adequate stimulation percentage at an appropriate amplitude are essential.

Over the entire period of development of CCM systems, programming principles have changed. Initially, both highamplitude biphasic pulses and lowamplitude monophasic pulses were used in preclinical studies [5]. Currently, the standard programming protocol for CCM devices involves the delivery of paired biphasic pulses with an amplitude of 7.5 V and a pulse duration of 5.14 ms each. In studies on isolated healthy ferret hearts stained with aequorin (a calcium-sensitive dye), highamplitude single biphasic pulses of CCM therapy were applied [6]. These studies showed that such stimulation accelerated calcium entry into the cell, which correlated with increased contractility of individual cardiomyocytes.

Table 1.

Clinical and demographic characteristics of the study patients (n=117)

Parameter	Value
Age, years	59.5 [53.5; 66]
Male, n (%)	98 (83.7)
BMI, kg/m^2	29 [26; 33]
Ischaemic CHF, n (%)	63 (53.8)
Non ischaemic CHF, n (%)	54 (46.2)
AF, n (%)	112 (95.7)
Paroxysmal AF, n (%)	56 (50)
Permanent AF, n (%)	56 (50)
Sinus rhythm, n (%)	5 (4.3)
Diabetes mellitus, n (%)	37 (31.6)
LVEF, %	31 [28; 37]
NYHA functional class	2.58±0.49
NYHA II, n (%)	48 (41.0)
NYHA III, n (%)	69 (59.0)
Transvenous ICD, n (%)	23 (19.7)
Subcutaneous ICD, n (%)	6 (5.1)
CRT D, n (%)	4 (3.4)
Pacemaker, n (%)	3 (2.5)

Note: BMI - body mass index; CHF - chronic heart failure; AF - atrial fibrillation; LVEF - left ventricular ejection fraction; NYHA - New York Heart Association; ICD - implantable cardioverter defibrillator; CRT D - cardiac resynchronisation therapy defibrillator.

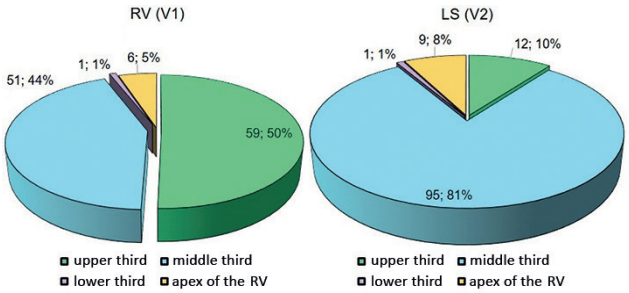

Fig. 1. Areas of electrode positioning of the CCM device.

The efficacy of highamplitude biphasic pulses was also studied in vivo. A current pulse of ±20 mA was delivered via epicardial electrodes placed on the anterior and posterior walls of the left ventricle (LV) in dogs. Based on the ratio of endsystolic pressure to volume, a global increase in LV contractility was observed. In contrast, lowamplitude monophasic pulses did not change myocardial contractility [7].

The system using the Optimizer® II (Impulse Dynamics, USA) was studied in a canine model of ischaemic CHF. Stimulation of the interventricular septum (IVS) for 2 hours with highamplitude biphasic pulses reduced LV dilation and increased LV ejection fraction (LVEF) by 5%. However, in that study, the effect was local and did not extend to more distant myocardial regions [7]. Subsequent studies demonstrated that local effects after 3 months of CCM therapy translate into remote myocardial regions, resulting in global contractility improvement [3, 8].

In 2003, a study was published that evaluated the efficacy of CCM therapy in dogs. The programming protocol included delivery of biphasic shocks with an amplitude of 5 V and a pulse duration of 14.5 ms each. CCM therapy duration varied from 1 to 6 hours per day. A positive effect of CCM therapy was observed even in the group with only 1 hour of stimulation per day [9].

Thus, through numerous experimental studies, a programming protocol for CCM devices was established and subsequently used in all major clinical trials [10]. However, in the series of clinical studies on CCM therapy, only major complications (electrode dislodgement, pocket haematoma, tricuspid valve dysfunction, infectious complications, CHF decompensation, etc.) are mentioned, while issues such as reduced CCM stimulation percentage and painful sensations from stimulation are not addressed. In realworld clinical practice, it is not always possible to achieve the recommended target stimulation percentage. Moreover, the standard programmed amplitude of 7.5 V is often quite perceptible to patients, necessitating programme adjustments.

The aim of this study is to identify patients with reduced stimulation percentage or painful sensations from CCM therapy and to evaluate the impact of these conditions on the effectiveness of the method.

MATERIAL AND METHODS

The study included 117 patients with LVEF between 25% and 40% and narrow QRS complex who underwent implantation of a CCM system. All patients provided written informed consent to participate. Preoperative evaluation included 24hour Holter ECG monitoring and echocardiography with assessment of LVEF, LV endsystolic and enddiastolic volumes. After final determination of indications for CCM device implantation, the surgical procedure was performed.

CCM device implantation was performed via the right subclavian approach. Under local anesthesia, an incision was made along the deltopectoral groove on the right. Puncture of the right subclavian vein was performed. Through introducers, ventricular leads with active fixation

were placed in the IVS segments. The upper lead (RV - right ventricular) and the lower lead (LS - local sense) were intraoperatively tested using an analyzer. Stimulation thresholds, Rwave amplitude, and impedance were determined. Then, using the Impulse Dynamics® programmer (Impulse Dynamics, USA), preliminary programming of the CCM device was performed.

The programming protocol was standard. In all patients, the OVOLSCCM mode was set. Stimulation was delivered for 7 hours per day, with 2 biphasic pulses from each of the two ventricular leads at an amplitude of 7.5 V and a total pulse duration of 20.56 ms. The timing of pulse delivery was adjusted individually according to the electrophysiological characteristics of each patient.

Some patients with indications for CCM implantation also had indications for an implantable cardioverter-defibrillator (ICD). This study included patients who already had an ICD implanted. Patients planned for or already having a device that includes a defibrillation lead constitute a separate group. In these cases, the surgical procedure for CCM device implantation has specific features. An important point is the need to fix the CCM leads at least 2 cm away from the defibrillation lead. In addition, these patients undergo a special software test - the Crosstalk test - to rule out double sensing of the CCM signal, which could be interpreted by the defibrillator as ventricular tachycardia and trigger antitachycardia pacing or defibrillation.

In patients with a previously implanted CRTD device, it is necessary to programme the CCM device with therapy delivery both on the native QRS and on the paced complex during CRTD operation to determine the most optimal settings for both states. Initial programming of the CCM device was performed in the operating room, then on the next day after surgery and before discharge from the hospital.

Followup visits with echocardiographic assessment (LVEF, enddiastolic and endsystolic volumes and dimensions) and device programming were performed 6 months after implantation. During device interrogation, special attention was paid to the stimulation percentage and stimulation amplitude level. If painful sensations occurred, the stimulation amplitude was adjusted: the minimum value at which CCM therapy was not perceived was programmed. If the stimulation percentage was insufficient, the device operating time was extended.

Statistical analysis was performed using Excel 2010 and STATISTICA 10 (StatSoft Inc., USA). Qualitative variables are presented as absolute numbers and percentages. The Mann-Whitney Utest was used. Sample parameters presented in the tables are shown as M (sd) and Me [Lq; Uq], where M is the mean, sd is the standard deviation, Me is the median, and Lq; Uq is the interquartile range. Differences were considered significant at $p < 0.05$; p values 0.05-0.10 were interpreted as a trend.

Correlation analysis was performed using Pearson's rank correlation coefficient. The strength and direction of the relationship between variables were assessed. For positive correlations, values from +1 to +0.7 were considered strong, from +0.699 to +0.3 - moderate, and from +0.299 to 0 - weak. For negative correlations: from -1 to -0.7 - strong, from -0.699 to -0.3 - moderate, and from -0.299 to 0 - weak. Correlations are presented as scatter plots.

RESULTS

The study included 117 patients, median age 59.5 years, 83.7% male. The predominant aetiology of CHF was ischaemic heart disease (53.8%). In addition, 95.7%

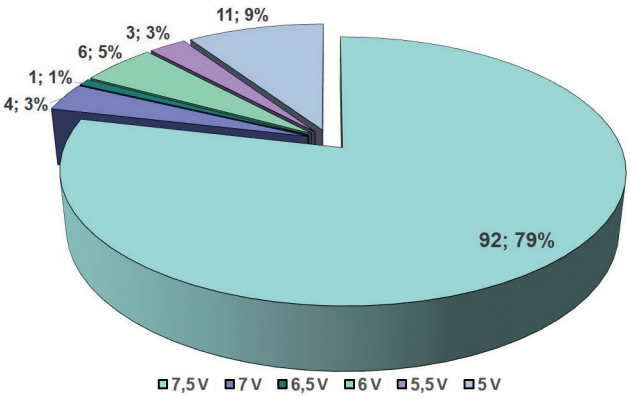

Fig. 2. Distribution of programmed stimulation amplitudes for CCM therapy.

Table 2.

Statistically significant parameters in patient groups with and without pain at the programmed CCM amplitude of 7.5 V

Parameter	Pain present (n=25)	Pain absent (n=92)	p
LV EDD, mm	63 [58; 71]	68 [62; 73]	0.05
LV ESV, mL	124 [96; 181]	148 [117; 174]	0.024
LV EDV, mL	187 [155; 251]	218 [176; 265]	0.034
LV EF, %	35 [29; 37]	30 [27; 36]	0.048
LV PWT, mm	0.9±0.15	0.8±0.15	0.028
MTIVSLP	0.8±0.4	1.08±0.3	0.025

Note: LV - left ventricle; EDD - end diastolic dimension; ESV - end systolic volume; EDV - end diastolic volume; EF - ejection fraction; PWL - posterior wall thickness; MTIVSLP - middle third interventricular septum lead placement.

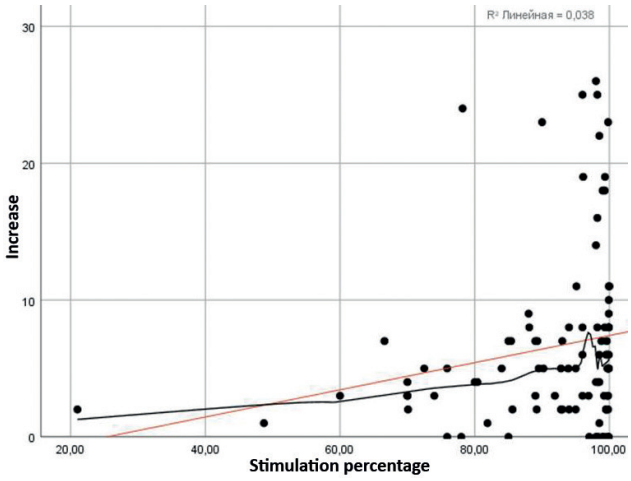

Fig. 3. Correlation between the increase in LVEF and the stimulation percentage during CCM therapy (r=0.38; p=0.05).

of patients had some form of atrial fibrillation. A subset of patients (n=36, 30.7%) had additional antiarrhythmic devices, mostly various types of ICD (29, 24.7%). Four patients had previously been implanted with a CRTD but showed no positive response to resynchronisation therapy, and therefore also received a CCM device (Table 1).

The device leads must be implanted 1.0-1.5 cm apart to correctly sense the intracardiac signal and, accordingly, to properly programme the therapy timing. In this study, leads were fixed in the upper, middle, and lower thirds of the IVS (Fig. 1). Initial programming was always performed intraoperatively with mandatory verification of stimulation tolerance by the patient. Evaluation of programming parameters and stimulation percentage was performed on the day after surgery after patient mobilisation.

In our study, some patients required a reduction in stimulation amplitude from 7.5 V (79%) down to a maximum of 5 V (9%) (Fig. 2). Both leads were active in these patients. Before surgery, LVEF in the groups with 7.5 V and 5 V stimulation amplitudes was 30 [27; 36] % and 32.5 [28; 37] %, respectively (p=0.65). After 6 months, the 7.5 V group showed a significant increase in LVEF to 37 [32; 43] % (p=0.0001). However, in the 5 V group, the LVEF increase did not reach statistical significance during followup: 35 [34; 40] % (p=0.211).

To identify possible causes of pain, we compared clinical and demographic characteristics of patients who experienced this problem with those who did not. Table 2 presents preimplant variables that showed statistical significance. According to the data, patients without discomfort during CCM therapy had lower LVEF, larger LV volumes, and a thinner LV posterior wall. In addition, in patients without stimulation discomfort, leads were more frequently implanted in the middle third of the IVS.

There are several situations in which CCM therapy may be inhibited:

- Development of a heart rate exceeding the maximum programmed threshold - usually 110 bpm.
- Frequent premature ventricular contractions - the device does not deliver a stimulus on the ectopic beat and the following complex.
- Presence of noise sensed by the leads.

During CCM device programming, use of information from the “Statistics” window helps determine the cause of stimulation inhibition.

In our study, 83.7% of patients had a standard stimulation time of 7 hours per day. In 5.9%, the stimulation time was 10 to 14 hours due to failure to achieve the required stimulation percentage. In this group, increasing the stimulation duration achieved a stimulation percentage exceeding 70%. During followup, one patient in this group experienced excessive heating of the device during battery recharging.

In patients with a CCM device, 15.3% had a therapy percentage above 90%. In 68.3%, the daily therapy percentage was 80-90%, and in 12% - 70 to 80%. A positive, moderate, significant correlation was observed between the stimulation percentage and the increase in LVEF (Fig. 3).

DISCUSSION

The use of CCM requires careful attention both to patient selection and to postimplant management.

Although device programming is fundamentally based on classical electrophysiological principles, there are a number of nuances that should be known to the implanting surgeon and the physician who will subsequently adjust the device parameters.

Protocols describing the principles of CCM device programming are virtually nonexistent and are limited to experimental studies [7-10]. Based on the results of this study, several key conclusions can be drawn. Stimulation amplitude influences the increase in LVEF, however, to improve tolerability, the amplitude can be reduced to 5 V according to patient perception.

A key factor affecting the increase in LVEF during CCM therapy is the stimulation percentage. It is known that with a standard stimulation time of 7 hours per day, pulses are delivered according to the algorithm: 1 hour of device operation followed by a 2hour25minute pause [11, 12]. The target stimulation percentage should exceed 70. To achieve the required daily stimulation percentage, the stimulation time can be increased beyond 7 hours, but values above 10 hours should be avoided, as this may cause excessive heating of the device during recharging.

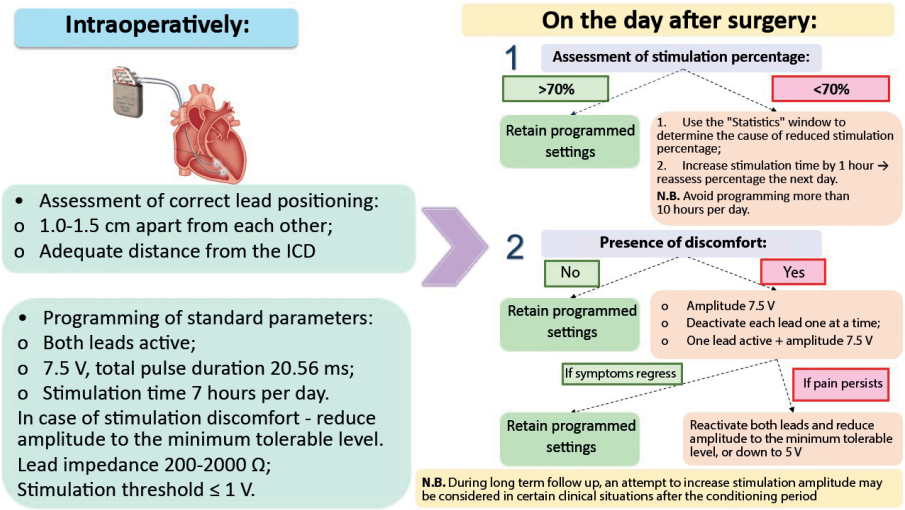

Fig. 4. Algorithm for programming CCM devices.

In our study, both leads were active for delivery of the cardiac-modulating signals in all patients. There is a study that compared the efficacy and safety of one versus two active ventricular leads. The results showed improvement in functional class ($p<0.001$) and quality of life ($p=0.002$ and $p=0.003$) at 6 months after implantation, with improvement observed equally in both the single-lead and duallead groups. Thus, this study provides another mechanism for eliminating CCM therapy discomfort if necessary. A brief algorithm for CCM device programming is presented in Fig. 4.

CONCLUSION

Cardiac contractility modulation is an effective interventional treatment for patients with chronic heart failure. With careful patient selection and meticulous postoperative followup, maximum results can be achieved. Further study of device operational nuances and training of specialists in intracardiac device programming are necessary.

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EFFICACY AND SAFETY OF PROLONGED-RELEASE LAPPACONITINE HYDROBROMIDE IN PREMATURE ATRIAL CONTRACTIONS: PILOT OBSERVATIONAL STUDY

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Aim. To evaluate the efficacy and safety of the prolonged-release formulation of lappaconitine hydrobromide at the minimum dose of 25 mg twice daily in patients with premature atrial contractions (PACs) and no structural heart disease.

Methods. This retrospective open-label non-randomized observational study included 52 patients (20 men) aged 31-79 years with symptomatic PACs and/or paroxysmal atrial fibrillation requiring antiarrhythmic therapy. All patients underwent two Holter ECG recordings: before treatment initiation and after 2-3 weeks of therapy with prolonged-release lappaconitine hydrobromide 25 mg twice daily. All quantitative indices of atrial ectopic activity were normalized to 24 hours. Efficacy was assessed by changes in the number of single, paired, and grouped PACs, episodes of paroxysmal focal atrial tachycardia (AT), the ectopic burden index, and the distribution of responders. Safety was assessed by changes in heart rate, P-wave, QRS complex, PQ, QT and QTc intervals duration. Analysis of individual forms of atrial ectopic activity was performed only in patients in whom the corresponding types of arrhythmia were present at baseline and for whom complete data were available to assess their changes during therapy.

Results. Therapy was associated with a statistically significant reduction in all forms of atrial ectopic activity, including single PACs, paired PACs, grouped PACs, and episodes of paroxysmal focal AT (all $p<0.001$). In most patients, the reduction in arrhythmia frequency was ≥75%. A similar effect was observed in the subgroup with a high baseline PAC burden (>500 PACs per 24 hours). Heart rate decreased moderately; a statistically significant but clinically insignificant increase in the PQ interval was observed. No significant changes were found in P-wave duration, QRS duration, or QT and QTc intervals.

Conclusion. The prolonged-release formulation of lappaconitine hydrobromide at the minimum daily dose of 50 mg provides a statistically significant reduction in atrial ectopic activity in patients without structural heart disease and is characterized by a favorable safety profile when administered twice daily.

Key words: premature atrial contractions (beats); single premature atrial contractions; paired premature atrial contractions; grouped premature atrial contractions; paroxysmal atrial tachycardia; prolonged-release lappaconitine hydrobromide; Holter ECG monitoring; efficacy; safety

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Premature atrial contractions (PACs) are among the most common cardiac rhythm disorders detected by Holter ECG monitoring in both patients with cardiovascular disease and apparently healthy people [1-4]. For a long time, PACs were considered predominantly a benign ECG phenomenon without independent clinical significance. However, this view now appears overly simplistic. First, PACs may be accompanied by pronounced subjective symptoms: palpitations, a feeling of irregular heartbeats, internal discomfort, anxiety, reduced exercise tolerance, which can significantly impair patients' quality of life [5-8]. Therefore, symptomatic PACs in itself may be regarded as a rationale for prescribing antiarrhythmic therapy (AAT). Second, PACs play an important role in the pathogenesis of atrial fibrillation (AF). Classic electrophysiological studies have shown that AF paroxysms are initiated by atrial ectopic impulses arising predominantly from the pulmonary vein ostia [9]. Subsequent studies have demonstrated that a high PAC burden is associated with an increased risk of AF and is considered a marker of atrial electrical instability [10-14]. Moreover, a reduction in PAC frequency may reflect decreased activity of the arrhythmic trigger mechanism. Thus, reducing PAC frequency has not only symptomatic significance but may also potentially lower the likelihood of AF occurrence.

At the same time, assessing the efficacy of AAT and catheter ablation in AF is a complex task [15-18]. In clinical practice and research, various approaches are used, including subjective symptom assessment by the patient, standard ECG recording during an arrhythmia episode, periodic Holter monitoring, wearable event recorders, implantable loop recorders, etc. [19-24]. Each of these methods has certain limitations. Subjective symptoms do not always reflect the true arrhythmic burden, since a significant proportion of AF episodes are asymptomatic [25, 26]. Moreover, after treatment initiation or catheter ablation, the proportion of asymptomatic episodes may increase [25]. Standard ECG recording during an episode has high diagnostic accuracy but depends on the ability to capture the arrhythmia at the time of occurrence. Intermittent monitoring methods also cannot guarantee detection of rare and short AF episodes [19-24, 27, 28]. Therefore, assessment of treatment efficacy based solely on recording AF paroxysms may be incomplete. In this context, quantitative assessment of atrial ectopic activity (AEA) as an additional indicator of AAT efficacy is of interest. It should be emphasised that this is an addition rather than an alternative to the generally accepted criteria for AF treatment efficacy. The likelihood of AF paroxysm is determined not only by the presence of PAC triggers but also by the state of the atrial substrate, i.e., the extent of electrical and structural atrial remodelling [10-18]. Nevertheless, a reduction in PAC count may reflect decreased activity of a key arrhythmia mechanism.

For suppression of AEA in patients without structural heart disease, antiarrhythmic drugs of all four classes according to the E.M. Vaughan Williams classification (modified by B.N. Singh and D.C. Harrison) may be used [29, 30]. However, class IC drugs are considered the most effective: ethacizine, lappaconitine hydrobromide in its immediaterelease and prolongedrelease forms (Allapinin®, Allaforte®), propafenone (Ritmonorm®, Propanorm®, etc.), flecainide (Tambocor®, Fleicardil®, etc.). Despite a similar mechanism of action predominantly mediated by blockade of fast sodium channels, each of these drugs has a number of individual pharmacological features.

The efficacy and safety of most class IC drugs have been studied in considerable detail. This applies primarily to propafenone and also to flecainide, and to a lesser extent to ethacizine [31-47]. At the same time, the prolongedrelease formulation of lappaconitine hydrobromide (PRLH) appeared much later and remains substantially less studied: its efficacy and safety are reflected only in a limited number of publications [48-52]. Additional interest in studying this formulation is related to its pharmacokinetic properties. According to pharmacokinetic studies, the time to reach maximum concentration of PRLH is about 4.43±3.54 hours, and the elimination halflife is 8.45±5.10 hours [48]. These characteristics suggest the possibility of effective use with a twicedaily dosing regimen. Meanwhile, the official Instructions posted on the State Register of Medicines portal recommend administration of the prolongedrelease form three or even four times daily, which does not correspond to its pharmacokinetics and may be associated with an increased risk of adverse effects and proarrhythmic potential.

In view of the above, the aim of this study was to evaluate the efficacy and safety of PRLH at the minimum dose of 25 mg twice daily in patients with PACs and no structural heart disease.

MATERIAL AND METHODS

This retrospective openlabel nonrandomised observational study of the efficacy and safety of PRLH included 52 patients (20 men), mean age 63.1±9.1 years, left atrial diameter 40.0±4.4 mm, volume 74.0±19.2 mL, left ventricular ejection fraction 62.5±5.4%. In 46 patients, the main diagnosis was hypertension; in 1, autonomic nervous system dysfunction. In 5 patients, cardiac arrhythmias were idiopathic in nature in the absence of any underlying disease. The study was conducted in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki and was approved by the local ethics committee of the Multidisciplinary Medical Centre “Family Doctor” (AntMed LLC, Saint Petersburg, Russia).

Inclusion criteria were:

- presence of symptomatic PACs and/or paroxysmal AF requiring AAT;
- use of PRLH at a dose of 25 mg twice daily;
- availability of two Holter ECG recordings (before AAT prescription and after 23 weeks of treatment);
- absence of structural heart changes on echocardiography;
- absence of contraindications to PRLH.

Table 1.

Efficacy of prolonged release lappaconitine hydrobromide at a dose of 50 mg/day in the treatment of premature atrial contractions

	All patients				Patients with baseline PACs >500 per day			
	n	Before treatment	On therapy	p	n	Before treatment	On therapy	p
Single PACs	52	138 [58-3081]	18 [8-92]	<0.001	22	4430 [1623-10651]	424 [21-1625]	<0.001
Paired PACs	36	13 [3-64]	0 [0-7]	<0.001	20	38 [12-602]	5 [0-14]	<0.001
Grouped PACs	30	5 [1-26]	0 [0-3]	<0.001	19	5 [1-146]	0 [0-4]	<0.001
PAT	30	3 [1-15]	1 [0-2]	<0.001	21	2 [1-35]	1 [0-1]	0.005

Note: PACs - premature atrial contractions; PAT - paroxismal atrial tachycardia

Of the 52 patients included, paroxysmal AF was documented in 35, symptomatic PACs in 13, and another 4 had both AF and symptomatic PACs. In full accordance with realworld clinical practice, PAC "symptomaticity" was defined as a combination of patient complaints (feeling of "fading" or "irregularity" of heartbeats reducing quality of life) and a high PAC burden on baseline Holter monitoring. Of the 46 patients with hypertension, 42 received standard antihypertensive therapy (dihydropyridine calcium antagonists, ACE inhibitors, angiotensin II receptor blockers, thiazide diuretics), which was unchanged between the two Holter recordings. Among these, five received low doses of selective betablockers (bisoprolol or metoprolol succinate). In full accordance with the 2025 Clinical Guidelines "Atrial Fibrillation and Flutter", these were not discontinued when PRLH was initiated, and their dose was not changed. The remaining 10 patients received no other treatment besides antiarrhythmic therapy. Analysis of individual forms of AEA was performed only in patients in whom the corresponding types of arrhythmia were recorded at baseline and for whom complete data were available to assess their changes during therapy.

Since in realworld clinical practice the duration of Holter ECG monitoring ranged from 21 hours to 7 days, all quantitative indicators of AEA were recalculated (normalised) to 24 hours. The study did not include patients with AF or focal atrial tachycardia (AT) paroxysms lasting ≥1 hour in at least one of the two Holter recordings. If shorter paroxysms were present, this time was subtracted from the actual Holter duration before normalising the parameters to 24 hours. Table 1 presents a brief clinical characterisation of the patients.

Efficacy of AAT was assessed by changes in the number of single, paired, and grouped PACs and paroxysms of focal AT, normalised to 24 hours, as well as the ectopic burden index (number of PACs per 1000 heartbeats) and the proportion of responders (reduction in PACs and focal AT episodes by ≥50% and ≥75%, respectively) during therapy compared with baseline.

Safety of AAT was assessed by changes in heart rate (HR), Pwave duration, PQ interval, QRS duration, QT and QTc intervals during therapy compared with baseline.

Statistical processing was performed using standard descriptive and comparative statistics methods. Preliminary analysis of the distribution of quantitative variables demonstrated pronounced skewness; therefore, nonparametric statistical methods were used. Quantitative variables are presented as median and interquartile range - median [Q1-Q3], where Q1 corresponds to the 25th percentile and Q3 to the 75th percentile. Comparison of quantitative variables before treatment initiation and during treatment was performed using the Wilcoxon signedrank test. Analysis of AAT efficacy was conducted only in patients in whom the corresponding forms of AEA were recorded at baseline. Consequently, the number of patients included in the analysis for individual arrhythmia forms could differ. For additional assessment of treatment efficacy, for each patient the relative change in the number of corresponding AEA forms during treatment compared with baseline was calculated. Based on the magnitude of relative reduction, patients were categorised into three therapeutic response categories: reduction in arrhythmia frequency <50%, reduction by 5074%, and ≥75%. To exclude the possible influence of HR changes on the overall AEA burden, the total number of AEA per 1000 heartbeats was additionally analysed. In all cases, differences were considered statistically significant at $p<0.05$.

RESULTS

Data on the efficacy of PRLH in the entire cohort are presented in Table 1. Analysis of AAT efficacy based on Holter monitoring was performed in all patients in whom the corresponding forms of AEA were recorded at baseline. During treatment, a marked reduction in the frequency of all analysed AEA forms was observed. Single PACs were recorded at baseline in all 52 patients; their reduction during therapy was statistically significant ($p<0.001$) and accompanied by a substantial narrowing of the interquar-

Table 2.

Relative change in atrial arrhythmia frequency during treatment compared with baseline

	n	Reduction <50%	Reduction 50-74%	Reduction ≥75%
All patients				
Single PACs	52	15 (28.8) 95% CI 18.3-42.3	6 (11.5) 95% CI 5.4-23.0	31 (59.6) 95% CI 46.1-71.8
Paired PACs	36	6 (16.7) 95% CI 7.9-31.9	5 (13.9) 95% CI 6.1-28.7	25 (69.4) 95% CI 53.1-82.0
Grouped PACs	30	6 (20.0) 95% CI 9.5-37.3	0 (0.0) 95% CI 0.0-11.4	24 (80.0) 95% CI 62.7-90.5
PAT	30	9 (30.0) 95% CI 16.7-47.9	4 (13.3) 95% CI 5.3-29.7	17 (56.7) 95% CI 39.2-72.6
PACs/1000 beats	17	3 (17.6) 95% CI 6.2-41.0	2 (11.8) 95% CI 3.3-34.3	12 (70.6) 95% CI 46.9-86.7
Patients with baseline PACs >500 per day				
Single PACs	22	5 (22.7) 95% CI 10.1-43.4	2 (9.1) 95% CI 2.5-27.8	15 (68.2) 95% CI 47.3-83.6
Paired PACs	18	3 (16.7) 95% CI 5.8-39.2	3 (16.7) 95% CI 5.8-39.2	12 (66.7) 95% CI 43.7-83.7
Grouped PACs	15	3 (20.0) 95% CI 7.0-45.2	0 (0.0) 95% CI 0.0-20.4	12 (80.0) 95% CI 54.8-93.0
PAT	17	5 (29.4) 95% CI 13.3-53.1	2 (11.8) 95% CI 3.3-34.3	10 (58.8) 95% CI 36.0-78.4
PACs/1000 beats	10	2 (20.0) 95% CI 5.7-51.0	2 (20.0) 95% CI 5.7-51.0	6 (60.0) 95% CI 31.3-83.2

Note: n - number of patients; data are n (%); the slightly lower numbers for paired/grouped PACs and paroxysmal AT compared with Table 1 are due to inclusion only of patients with complete data to calculate relative changes.

tile range. Paired PACs were detected at baseline Holter in 36 patients, and grouped PACs in 30; during treatment, a marked reduction in the frequency of these arrhythmia types was observed, with high statistical significance. Among all forms of AEA, the most clinically significant was paroxysmal focal AT, detected in 30 patients; the reduction in its episodes was also statistically significant. Thus, PRLH administration was accompanied by a significant and highly significant decrease in the frequency of all analysed forms of AEA. The most pronounced changes were observed for more complex forms - paired and grouped PACs, whose median values during therapy decreased to zero.

Since the magnitude of the antiarrhythmic effect could be related to the baseline PAC frequency, an additional analysis of AAT efficacy was performed in patients with a higher AEA burden. For this purpose, a subgroup of patients with >500 single PACs per day on baseline Holter was identified from the overall cohort. This approach allowed exclusion of cases with minimal PAC counts and more objective assessment of AAT efficacy at clinically meaningful arrhythmia burden. Data on PRLH efficacy in these patients are shown in Table 1.

As follows from the table, this subgroup included 22 patients. Of these, paired PACs were found in 20, grouped PACs in 19, and paroxysmal AT in 21. Although the baseline PAC count in these patients exceeded the overall cohort value by more than 30fold, the therapeutic effect remained equally pronounced and significant. Thus, even in patients with high baseline AEA burden, AAT was accompanied by a multiple reduction in arrhythmia frequency: the median number of single PACs decreased more than 10fold, paired PACs more than 8fold, and the median grouped PAC value decreased almost to zero.

Thus, AAT efficacy was maintained regardless of baseline AEA. However, analysis of median values does not allow assessment of individual response variability. Therefore, to detail the treatment efficacy, an additional analysis was performed: the distribution of individual responses to treatment. For each patient, the relative change in each AEA variant during AAT compared with baseline was calculated. Depending on the magnitude of effect, patients were categorised into three groups: reduction in arrhythmia frequency <50%, 5074%, and ≥75%. The results for the entire cohort are presented in Table 2.

As shown, a marked therapeutic effect was observed in most patients. A ≥75% reduction in single PACs was observed in 31 of 52 patients (59.6%), while a reduction of <50% occurred in only 15 patients (28.8%). Even more pronounced effects were observed for more complex AEA forms. A ≥75% reduction in paired PACs was seen in 25 of 36 patients (69.4%). For grouped PACs, the proportion with marked effect was 80.0% (24 of 30). A similar pattern was observed for AT episodes: a ≥75% reduction occurred in 17 of 30 patients (56.7%), while a reduction <50% was seen in 9 patients (30.0%). Additionally, to exclude possible influence of HR changes on overall AEA burden, comparison of total AEA per 1000 heartbeats at baseline and during AAT was performed. As can be seen, a marked antiarrhythmic effect was observed in the majority of patients (70.6%). A similar analysis was conducted in the subgroup with baseline high PAC burden (>500 single PACs per day) (Table 2).

As shown, in this subgroup the distribution of response to AAT was comparable to the overall cohort. A marked reduction in single PACs (≥75%) was observed in 68.2% of cases. For paired PACs, the proportion with such an effect was 66.7%. The most pronounced effect was for grouped PACs, where a ≥75% reduction was noted in 12 of 15 patients (80.0%). A similar trend was observed for AT, where a marked response was seen in 10 of 17 patients (58.8%). In the analysis of total PACs per 1000 heartbeats, the most significant reduction was observed in 6 of 10 patients (60.0%). Thus, a marked AAT effect was found both in the overall cohort and in patients with high AEA burden, independent of baseline counts.

For a more illustrative demonstration of the therapeutic response structure, the results are also presented graphically in Fig. 1. The figure shows the distribution of patients by response category for different AEA forms.

The graphical representation clearly demonstrates that patients with marked reduction in AEA frequency (≥75%) predominate in all analysed groups, whereas the proportion of patients with no clinically significant effect (<50%) is substantially smaller. Thus, the results indicate a

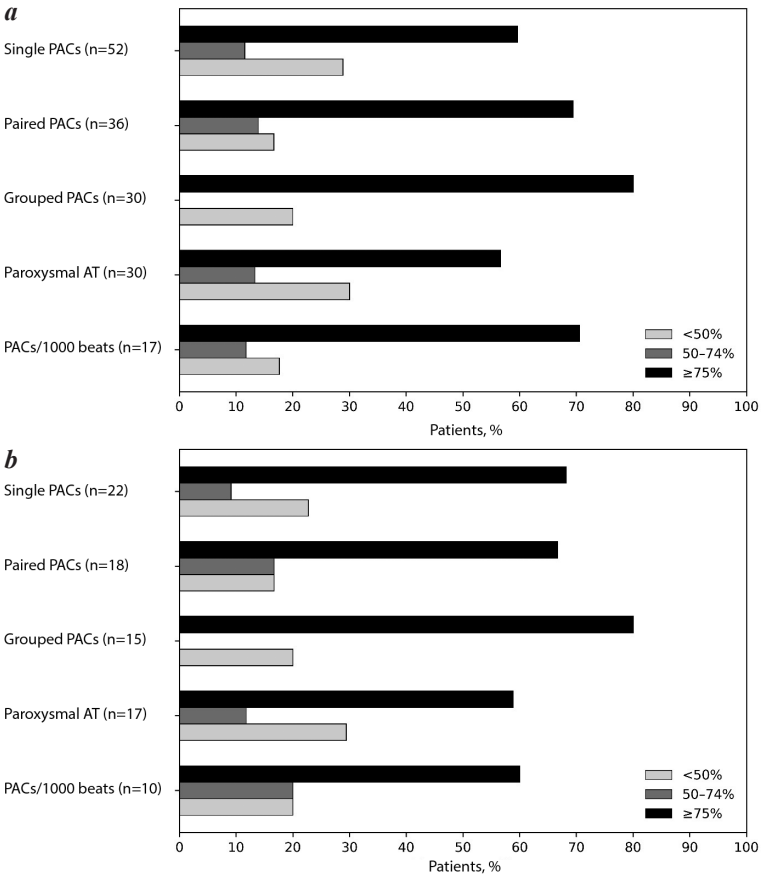

Fig. 1. Distribution of patients by categories of antiarrhythmic effect for various forms of atrial ectopic activity: a - entire cohort; b - patients with high arrhythmia burden.

marked reduction in various forms of AEA during AAT. A significant reduction was observed both in the overall cohort and in the highburden subgroup. Individual response analysis also showed that the majority of patients experienced a marked reduction, with the proportion of marked responders (≥75%) prevailing in all groups. These results testify to the high efficacy of therapy for various PAC and AT forms.

Alongside the efficacy assessment, treatment safety was evaluated, i.e., the effect of therapy on key ECG parameters. The analysis included baseline and ontreatment assessment of HR, Pwave duration, QRS duration, PQ interval, and QT and QTc (Bazett) intervals from Holter data. Results are presented in Table 3. Quantitative data are shown as median and interquartile range [Q1Q3]. The Wilcoxon test was used for statistical significance.

As can be seen, median HR on therapy was slightly reduced compared with baseline: from 72 [6879] to 69 [6275] bpm. The difference was statistically significant (p=0.001). Pwave duration did not change substantially: 100 [100103] ms before and 100 [100110] ms on therapy. The PQ interval slightly increased during AAT (p=0.017), but its median values remained within physiological ranges. QRS duration did not change: 90 [9090] ms before and 90 [9095] ms on therapy (p=0.080). QT interval remained stable and showed no changes: 410 [400420] ms and 410 [405420] ms, respectively (p=0.072). A similar picture was observed for QTc, with median values of 430 [425440] ms at baseline and 430 [430445] ms on therapy (p=0.492). Notably, the electrical systole characteristics could not change substantially, since class IC drugs are known not to affect them. Thus, ECG parameter analysis revealed no clinically significant effect of therapy on major conduction and repolarisation parameters.

Summarising the above, the study demonstrated a marked reduction in various AEA forms during AAT. The efficacy of PRLH with twicedaily administration at the minimum dose was observed both in the overall cohort and in the highburden group. At the same time, ECG assessment showed no clinically significant changes in major conduction and repolarisation parameters, indicating a satisfactory safety profile.

DISCUSSION

The study results showed that PRLH at the minimum dose of 25 mg twice daily is associated with a significant reduction in AEA. During therapy, a statistically significant decrease in the number of single, paired, and grouped PACs, as well as paroxysms of focal AT, was observed. An identical result was obtained in the group of patients with a high baseline PAC burden. The clinical significance of these findings is determined by the fact that PACs may cause pronounced symptoms and significant deterioration in quality of life [58]. Reducing PAC frequency in such cases is an independent therapeutic goal. This study shows that PRLH effectively suppresses not only single PACs but also more complex forms of AEA. Furthermore, PACs are regarded as one of the beststudied triggers of AF [9]. Current concepts of AF pathogenesis are based on the interaction of trigger factors and the arrhythmogenic substrate [1014]. PACs, especially those arising from the myocardial sleeves at the pulmonary vein ostia, can initiate AF paroxysms, whereas arrhythmia persistence is determined by the severity of structural and electrical atrial remodelling. From this perspective, a reduction in PAC frequency during AAT may be considered a reflection of decreased trigger activity.

Table 3.

Safety of prolonged release lappaconitine hydrobromide at a dose of 50 mg/day in the treatment of atrial arrhythmias

	Before treatment	On therapy	p
HR, bpm	72 [68-79]	69 [62-75]	0.001
P, ms	100 [100-103]	100 [100-110]	0.416
PQ, ms	180 [160-200]	180 [160-220]	0.017
QRS, ms	90 [90-90]	90 [90-95]	0.080
QT, ms	410 [400-420]	410 [405-420]	0.072
QTc, ms	430 [425-440]	430 [430-445]	0.492

At the same time, PAC dynamics cannot be regarded as an independent efficacy criterion for AF treatment. Even pronounced suppression of AEA does not exclude the possibility of AF paroxysms, since their occurrence is determined not only by the trigger but also by the atrial substrate condition [1018]. Therefore, quantitative PAC assessment should be considered an additional efficacy indicator. This approach seems particularly useful given the limitations of traditional methods for assessing AF treatment efficacy [1528]. A significant proportion of arrhythmia episodes are asymptomatic, and intermittent monitoring methods cannot always detect rare or short paroxysms. Under these conditions, analysis of AEA dynamics may serve as an additional characteristic of the antiarrhythmic effect. Of particular note is the fact that marked PAC reduction was also observed in patients with high baseline AEA. It is in such patients that PACs are more often associated with clinical symptoms and may be closely linked to AF risk.

The dosing regimen deserves separate discussion. This study evaluated the efficacy of PRLH at the minimum dose of 25 mg twice daily. The results are of practical interest because they demonstrate the possibility of achieving a marked antiarrhythmic effect at a relatively low dose. Moreover, a twicedaily regimen for the prolongedrelease form appears pharmacokinetically justified [4852]. An important aspect is also therapy safety. This study did not reveal clinically significant changes in major ECG conduction and repolarisation parameters. Despite a statistically significant decrease in HR and a slight increase in the PQ interval, the median values remained within physiological ranges. QRS duration, QT, and QTc intervals did not change substantially. For class IC drugs, such data are particularly important, since their use requires careful assessment of conduction effects [29, 30].

Study limitations

The study was conducted in a retrospective, openlabel, nonrandomised, observational format without a control group, and the number of patients in individual subgroups was small. Moreover, the study did not aim to directly assess the effect of therapy on AF recurrence rate. Also, no standardised quantitative symptom assessment

using validated questionnaires was performed, which does not allow evaluation of the clinical effect of therapy, since the aim was to assess AEA dynamics by Holter monitoring rather than clinical efficacy.

An important limitation is the absence of data on adverse drug effects generally characteristic of class IC drugs, since most patients were included retrospectively and their medical records contained no information on adverse effects. The results obtained require confirmation in controlled studies.

CONCLUSION

The use of PRLH is associated with a significant reduction in the frequency of various PAC forms as assessed by Holter ECG monitoring. During therapy, a statistically significant decrease in the number of single, paired, and grouped PACs, as well as AT episodes, was observed. Individual response analysis showed that most patients experienced a marked therapeutic effect with substantial reduction in arrhythmia frequency. These results were maintained in the subgroup of patients with high baseline PAC burden. At the same time, therapy was not accompanied by clinically significant changes in key ECG parameters, including QRS duration and QT/QTc intervals. The data indicate high efficacy and a favourable safety profile of PRLH in the treatment of frequent and/or symptomatic PACs.

In the studied cohort of patients without structural heart pathology, PRLH demonstrated significant efficacy in AEA, with high antiarrhythmic activity achieved with a minimum dose of 25 mg twice daily. PRLH is characterised by a favourable safety profile, with only minor effects on HR and atrioventricular conduction.

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BIOENGINEERING GENERATION OF HEART RHYTHM: THE ROLE OF BIOPACEMAKER CELLS

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This review summarizes the anatomical and physiological characteristics of the sinoatrial node as a model for biopacemakers and analyzes current approaches to their development, including sinoatrial node cell transplantation, the use of pluripotent stem cells, gene therapy (HCN overexpression, IK1 suppression, TBX18 transduction, and others), as well as combined and reprogramming strategies Special attention is given to the authors' own experience and achievements in tissue engineering. Key obstacles to clinical translation are outlined, including safety concerns, stability of therapeutic effects, adequacy of experimental models, and control of biological pacemaker activity. Despite existing limitations, progress in gene engineering, stem cell technologies, and biomaterials offers promising opportunities for the development of fully physiological alternatives to electronic pacemakers.

Key words: bradyarrhythmia; pacemaker; artificial; biological pacemakers; genetic engineering; stem cells

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Bradyarrhythmias, including sick sinus syndrome and atrioventricular blocks, remain a leading cause of sudden cardiac death and impaired quality of life [1, 2]. According to the data of the Profile Commission on "Arrhythmology" of the Ministry of Health of Russia and the Bakulev National Medical Research Center for Cardiovascular Surgery, 53,386 permanent pacemaker (PPM) implantations were performed in the Russian Federation in 2023, corresponding to a rate of 364.9 procedures per 1 million population, reflecting a further increase in pacing volumes compared with 2021 [3]. Despite significant technological progress, PPMs remain invasive systems with limited longevity and a number of potential complications: infectious risks, mechanical failures, dyssynchronous pacing, and unresponsiveness to autonomic regulation [4].

The problem is particularly acute in paediatric practice and young patients, where regular device and lead replacements may become a source of severe complications [5]. These circumstances drive the search for alternative approaches capable of providing physiological myocardial stimulation without mechanical components.

One such direction is the development of biological pacemakers - cellular or gene constructs that can replace the function of the sinus node. An ideal biopacemaker should possess spontaneous electrical activity, ability to adapt to physiological load, safety, stable integration into the myocardium, and long-lasting effect [6].

The aim of this review is to analyse current approaches to the creation of biopacemakers, their functional characteristics, limitations, and clinical prospects.

Limitations of electronic pacing as a prerequisite for biopacemaker development

Despite continuous technological improvements, modern electronic cardiac pacing devices still have serious limitations and complications in clinical use. Among the problems associated with their use are:

1. Infection risk - about 12% of PPM implantations are complicated by device pocket infection or endocarditis. If system removal is required, risks increase sharply, especially in elderly patients with concomitant diabetes mellitus or immunosuppression. These situations require expensive treatment and carry a mortality rate of up to 10% [710];
2. Limited battery life - repeat surgeries carry additional risks;
3. Lead fractures or dislodgements - common causes of premature system failure. In young patients, this requires multiple reimplantations over a lifetime, associated with adhesion formation, venous thrombosis, and repeat surgical risks [11, 12];
4. Unresponsiveness to the autonomic nervous system - electronic devices do not fully adapt to autonomic regula-

tion; during physical or emotional stress, heart rate may not match metabolic demands, which is particularly critical in active patients;
5. Interference from other electrical devices (metal detectors, MRI magnets, power lines) that can affect PPM function;
6. Risk of heart failure due to chronic right ventricular pacing, especially with apical lead placement [13];
7. Paediatric problems related to the need to adapt the pacing system to the child's growth and development [14].

Even with considerable progress in device engineering, these limitations remain unresolved, highlighting the need for alternative approaches. Hence, the question arises about the creation of alternative pacing means, such as biological pacemakers.

Anatomy and physiology of the sinus node

The sinoatrial or sinus node (SAN) is the primary physiological pacemaker of the heart, initiating action potentials (AP) and ensuring the regularity of cardiac contractions. It is a heterogeneous specialised structure located subepicardially in the terminal groove, at the junction of the right atrium and the superior vena cava.

Cellular composition of the SAN:
• specialised pacemaker cells (Pcells) - the main rhythm generators, initiate automatic activity;
• transitional cells (Tcells) - ensure impulse conduction and transmission;
• fibroblasts - form and maintain the connective tissue framework (stroma of the SAN), surrounded by dense fibrous tissue.

Distinctive features of pacemaker and transitional cells are presented in Table 1.

The physiological basis of SAN function is automaticity - the ability to generate AP without external stimulation. The main electrophysiological feature of pacemaker cells is spontaneous diastolic depolarisation, driven by the interaction of several key ion currents and intracellular calcium mechanisms [15, 16].

1. Ion currents («membrane clock»):
• *If* ("funny current") through HCN1/4 channels is activated upon hyperpolarisation (from 100 to 40 mV) and provides the early phase of diastolic depolarisation due to Na^+ entry;
• *ICa,T* - Ttype calcium current (Cav3.1/3.2), activated at less negative potentials (50 mV) and contributing to further depolarisation;
• *INaCa* - sodiumcalcium exchanger current (NCX1), where extrusion of one Ca^{2+} is accompanied by entry of three Na^+;
• *ICa,L* - Ltype calcium current (Cav1.2/1.3), providing the rapid depolarisation phase of the AP;
• *IK* - potassium currents (particularly through ERG channels), responsible for repolarisation and restoration of resting potential [1719].

2 Calcium «clock»:
• spontaneous local Ca^{2+} releases (LCR) from the sarcoplasmic reticulum through RyR2;
• activation of NCX enhances membrane depolarisation and brings it closer to the AP threshold [20].

SAN automatic activity is strictly regulated by the autonomic nervous system. Sympathetic stimulation via βadrenergic receptors activates adenylyl cyclase, increases cAMP levels, which enhances HCN4 channel activity, increasing firing rate and heart rate. Conversely, parasympathetic stimulation (via acetylcholine and muscarinic receptors) suppresses these channels and slows heart rate.

Neurohumoral regulation:
• Sympathetic activation: β1receptors → ↑cAMP → activation of HCN4 and PKA → ↑If and ↑LCR → increased heart rate.
• Parasympathetic regulation: acetylcholine → M2receptors → ↓cAMP → ↓HCN4 and ↓Ca^{2+} entry → slowed rhythm.

Anatomically, the SAN artery plays an important role - most often it is the first branch of the right coronary artery. The node also has a sensory function due to its proximity to the aorta and dense autonomic innervation. The SAN artery not only nourishes pacemaker cells but also provides a direct link to systemic arterial pressure, allowing rapid responses to haemodynamic changes. Dense autonomic innervation, represented by both efferent and afferent fibres, forms reflex arcs for rapid rhythm regulation. Thus, the SAN functions not just as an isolated generator, but as an integrated sensory centre that perceives mechanical and chemical signals from atrial stretch and blood chemistry. This integrative function allows the SAN to finely adjust heart rate to the body's current metabolic demands [21, 22].

For normal SAN function, a delicate balance must be maintained between the relatively small number of pacemaker cells (source) and the surrounding atrial myocardium (sink), so that the SAN drives the larger surrounding myocardium without being overwhelmed by the hyperpolarising influence of the myocardium [23].

The presence of unique ion channels, such as HCN4, and weak electrical coupling with neighbouring cardiomyocytes allows the SAN to maintain its own potential and generate impulses without being depolarised by surrounding tissues. HCN4 channels act as an "electrical barrier": maintaining the Pcell membrane potential at 35...60 mV (vs. 90 mV in working cardiomyocytes).

Table 1.

Distinctive features of pacemaker and transitional cells

Characteristic	Central zone (P cells)	Peripheral zone (T cells)
Expression	HCN4↑, Cav1.3↑, NCX1↑	Cav1.2↑, Cx43↑
Function	Impulse generation	Impulse conduction
Unique features	Low Kir2.1, absence of Nav1.5	High electrical connectivity

Note: P cells - pacemaker cells; T cells - transitional cells; HCN4 - hyperpolarisation activated cyclic nucleotide gated channel type 4; Cav1.3 - voltage gated calcium channel L type, alpha 1D subunit; NCX1 - sodium calcium exchanger; Kir2.1 - inward rectifier potassium channel; Nav1.5 - integral membrane protein forming voltage gated sodium channel; Cav1.2 - voltage gated calcium channel L type, alpha 1C subunit; Cx43 - major gap junction protein in the heart, plays a critical role in synchronising cardiac contractions.

Low expression of connexin43 and its replacement by Cx30.2 and Cx45, which have higher electrical resistance, limit electrical coupling with atrial myocardium and contribute to functional isolation of the SAN.

The anatomy and ion profile of the SAN, including dominance of HCN4 (the subtype forming the pacemaker current If), weak coupling with the myocardium, and dual automaticity mechanisms, make it a reference model for the development of biological pacemakers. The dual oscillator system consists of membrane and calcium clocks, ensuring stable and rhythmic depolarisation processes. Diastolic depolarisation is formed by the pacemaker current If through HCN4 channels, early activation of Ttype Ca^{2+} current (ICaT), subsequent activation of Ltype Ca^{2+} current (ICaL), and reduction of potassium conductance (IK - repolarisation currents). In parallel, the calciumbased automaticity mechanism operates, based on cyclic Ca^{2+} accumulation by the sarcoplasmic reticulum, spontaneous local Ca^{2+} releases (LCR), and activation of the Na^{+}/Ca^{2+} exchanger (INCX), which adds a depolarising contribution to late diastole. Synchronous interaction of membrane and calcium "clocks" ensures a stable rhythm of spontaneous depolarisations. Weak electrical coupling of SAN cells with the surrounding atrial myocardium (low gap junction density, predominance of connexin45 - Cx45) reduces electrotonic load and enhances the efficacy of small depolarising currents, triggering the AP. Any cell or genebased strategy must consider these key parameters, including autonomic regulation and zonal organisation of the node.

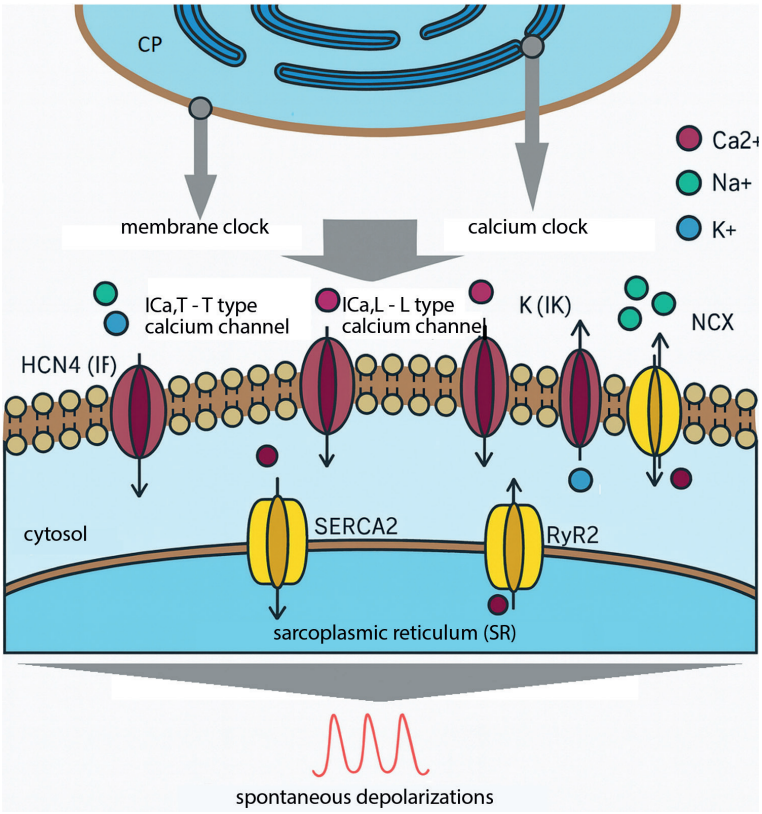

Fig. 1. Mechanism of sinus node automaticity. HCN4 - hyperpolarisation activated cyclic nucleotide gated channel type 4; If - funny current; NCX - sodium calcium exchanger; RyR2 - ryanodine receptor 2; SR - sarcoplasmic reticulum; SERCA2 - sarcoplasmic reticulum Ca^{2+} ATPase 2; ICaT - T type calcium current; ICaL - L type calcium current; IK - potassium currents.

Features of the SAN should be replicated in biological pacemakers. Ion channel proteins of membrane and calcium clocks must be expressed in biological pacemakers to provide sustained and reliable AP formation. Pacemaker cells should ideally be embedded in appropriate extracellular matrix proteins and surrounded by transitional cells and other key cell types. The sourcesink mismatch must be overcome, and APs should propagate to the surrounding myocardium; cells must be able to maintain rhythm for a long time. Finally, biological pacemakers must respond to autonomic influences (sympathetic and parasympathetic stimuli) to provide reliable rhythm generation in patients (Fig. 1).

HISTORY OF BIOPACEMAKER CONCEPT DEVELOPMENT

The history of biological pacemaker development dates back to the 1920s, with subsequent waves of research in the 1960s1980s. Early experiments attempted to use pieces of conducting tissue (e.g., the SAN itself), autografted, allografted, or xenografted into the ventricular myocardium. Autologous transplantation was most successful, sometimes restoring rhythm for 6 hours to 5 days. However, allo or xenotransplantation gave only temporary results due to inevitable fibrous degeneration.

The main problems that determined the failure of this approach were:

- pronounced immune reaction to foreign tissue;
- impaired blood supply leading to necrosis of the central part of the graft ("core necrosis");
- lack of functional electrophysiological integration with the recipient myocardium, preventing the graft AP from effectively exciting the cardiac muscle.

Thus, although these pioneering works showed the fundamental possibility of biological pacing, they clearly demonstrated the futility of simple mechanical transplantation of readymade bioexcitable conducting tissue. Awareness of these limitations became the next stimulus for the search for more refined and targeted rhythmrestoring technologies based on deep understanding of cell biology and electrophysiology [24-26].

MAIN STRATEGIES FOR CREATING BIOLOGICAL PACEMAKERS

The development of biological pacemakers represents an evolution from genetic modification of ion channels to the creation of autonomous cells capable of rhythmic depolarisation (Fig. 2).

Cellbased approaches

Use of native SAN cells: after failures with wholetissue transplantation, researchers moved to transplantation of isolated node cells, often mixed with atrial cardiomyocytes. The idea was that these cells, possessing innate electrogenicity, could become ectopic pacemakers upon establishing connection with recipient myocardium. A. Ruhparwar et al. demonstrated electrical coupling of foetal

cardiomyocytes in dogs; G. Lin et al. achieved functional connection of human cells in porcine hearts; H. Zhang et al. revealed a strong influence of the microenvironment on phenotype and activity of transplanted autologous SAN cells in dogs [2729]. These works proved the principal feasibility of biopacing but did not lead to clinical success, stimulating the development of stem cellbased approaches.

Modern approaches to creating biological pacemakers are based on regenerative medicine methods, particularly using embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). ESCs and iPSCs are considered the most promising cell source due to their ability to differentiate into any cardiomyocyte type, including pacemaker cells. Differentiation protocols mimic embryonic heart development in vitro (formation of embryoid bodies, 2D cultures with biochemical signals). The key problem remains obtaining pure populations of SANlike cells.

The work of I. Kehat et al. first demonstrated the possibility of differentiating ESCs into functional cardiomyocytes that not only engrafted in pig hearts but also functionally stimulated contractions [30]. An important step was made by T. Xue et al., who recorded and confirmed direct spread of depolarisation wave from the graft to the myocardium [31]. The group of S.I. Protze et al. achieved generation of SANlike cells from human iPSCs without genetic modification, using only combinations of growth factors (BMP4, Activin A, etc.) [32].

To enhance specificity, chemical treatments (e.g., 1EBIO), fluorescently labelled lines (e.g., selection of *NKX2.5/ISL1*+ progenitors), transgenefree protocols, and CRISPR platforms (e.g., selection of *TBX5+/NKX2.5* cells) are used. Clinical steps were taken in the ESCORT study with ESCderived progenitors in heart failure; and in the Japanese study NCT04696328 with allogeneic iPSCs in ischaemic cardiomyopathy [33, 34].

Genebased approaches

The SAN develops from a group of progenitor cells that express the *Tbx18* gene. This gene acts as a master regulator, directing these cells into right atrial structures, including the SAN itself. The further fate of pacemaker cells depends on another key factor - the *Shox2* gene. It initiates a cascade of genes (including *Isl1* and *Tbx3*) that regulate the synthesis of HCN4 channel proteins, Tchannels, gap junction proteins connexin Cx30.2, etc. It is this set of proteins that allows the cell to generate the cardiac impulse and transmit it to neighbours [35] (Fig. 3).

Genebased approaches are based on the idea of "teaching" ordinary cardiac muscle cells to perform the pacemaker function. For this purpose, viral or nonviral vectors are used to deliver genes responsible for generating electrical impulses to the myocardium. The main strategies can be outlined (Fig. 4).

Suppression of IK1 current - "unlocking" latent automaticity in ordinary cardiomyocytes. Miake et al. first showed that suppression of *Kir2.1* gene expression (via dominantnegative Kir2.1AAA) in cardiomyocytes leads to diastolic depolarisation similar to SAN cells, "unlocking" latent automaticity [36].

Expression of β2adrenergic receptor genes - increasing sensitivity to natural rhythm stimuli. Edelberg et al. showed that transfer of the human β2adrenoceptor gene into the atrium increases heart rate by 4050% due to enhanced catecholamine sensitivity [37, 38]. However, this approach provides only a chronotropic effect, not full rhythmogenesis.

Expression of *HCN* family genes (hyperpolarisationactivated cyclic nucleotidegated). The *HCN* genes, encoding channels of the "funny" current (If) - hyperpolarisationactivated cation channels - play a central

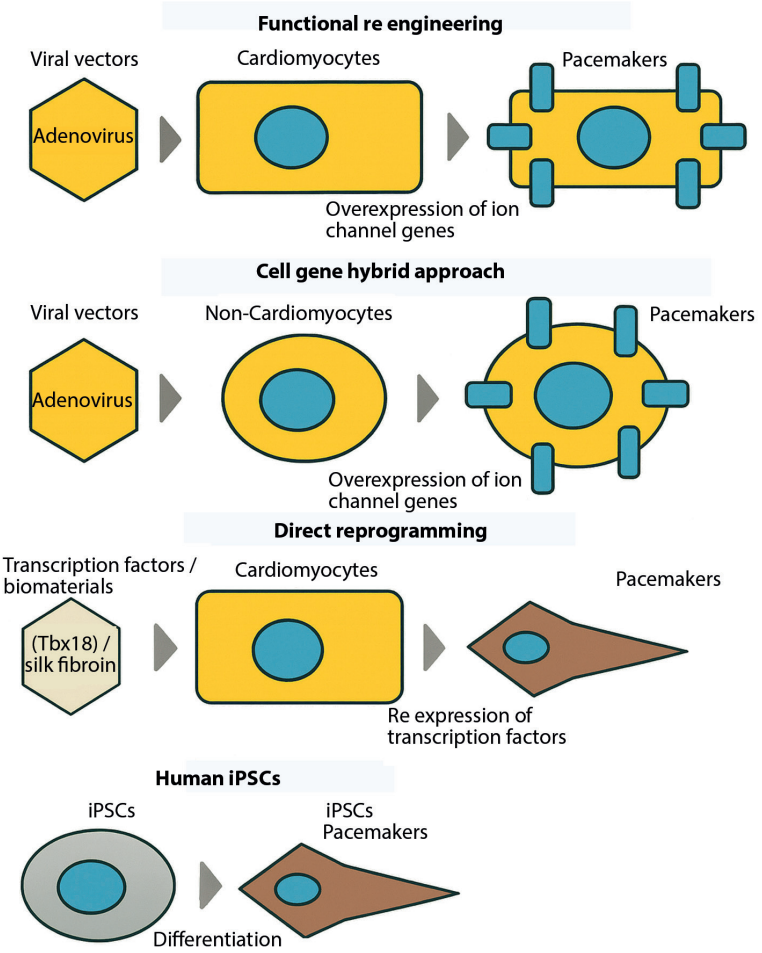

Fig. 2. Approaches to creating biological pacemakers. Tbx18 - T box transcription factor 18, plays an important role in pacemaker cell differentiation; iPSC - induced pluripotent stem cells; functional re engineering - use of adenoviral vectors for overexpression of genes encoding ion channels in cardiomyocytes to create automaticity; cell gene hybrid approach - use of adenoviral vectors for overexpression of genes encoding ion channels in non cardiomyocytes (mesenchymal, iPSCs, fibroblasts) to create automaticity; direct reprogramming - changing cardiomyocytes into pacemaker cells with integral changes in morphology, structure, function, and transcription through re expression of transcription factors (Tbx18) or biomaterials (e.g., silk fibroin); human iPSCs - differentiation of human iPSCs or embryonic stem cells into pacemaker cells.

role in forming spontaneous diastolic depolarisation in SAN cells.

Experimental data from largeanimal models confirm the functional efficacy of *HCN* gene modifications:

- delivery of the *HCN2* gene restored heart rate during SAN arrest, demonstrating the ability to restore stable cardiac rhythm in a canine model of vagal SAN arrest [39];
- use of a modified *HCN1* gene created a stable rhythm in pigs with sick sinus syndrome [40].

To make the new rhythm not only stable but also physiological (i.e., accelerating under load), genes are combined:

- *HCN2* combined with the sodium channel gene (*SkM1*) improves impulse conduction [41];
- combination of *HCN2* with the adenylyl cyclase gene allows creation of a rhythm that responds to autonomic signals, accelerating under stress like the natural one [42].

MicroRNAbased therapy. This is a newer, more refined approach. MicroRNAs are molecules that regulate gene function. It has been found that in some forms of SAN dysfunction, the activity of microRNAs (*miR4235p* and *miR3703p*) that suppress the main pacemaker gene *HCN4* is increased. The strategy of inhibiting pathologically elevated expression of *miR4235p* and *miR3703p* with antimiR oligonucleotides opens new possibilities for pathogenetic therapy of SAN dysfunction by restoring physiological *HCN4* expression and normalising pacemaker activity [43].

While direct *HCN2* gene delivery induces If current formation in the myocardium, a more fundamental approach is to reprogramme the phenotype of mature cardiomyocytes. The most promising and fundamental approach is not just to add one gene, but to “retrain” the mature cell, making it recall its embryonic past. For this, the *TBX18* gene is used - the main conductor of SAN development during the embryonic period. The study by N. Kapoor et al. became one of the proofs of this concept,

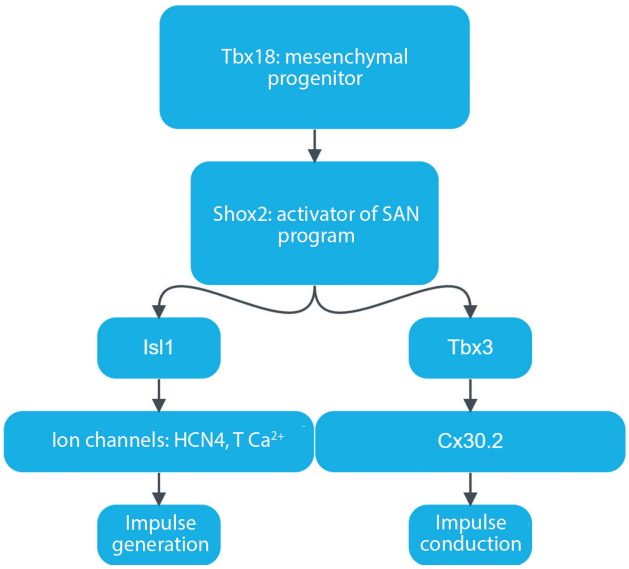

Fig. 3. Embryonic formation of the sinus node. Tbx18 - marker of sinoatrial node progenitor cells; Shox2 - factor necessary for sinoatrial node development; Isl1 - participates in formation of HCN4, T Ca^{2+} ion channels of the heart, ensuring impulse generation; Tbx3 - activation of Cx30.2 ensures impulse conduction.

demonstrating that delivery of *TBX18* into ordinary cardiomyocytes turns them into pacemakerlike cells with all necessary properties [44].

The study by Y.F. Hu et al. showed that delivery of the *TBX18* gene into the ventricular myocardium of pigs with complete AV block led to generation of a stable idioventricular rhythm that persisted throughout the observation period (14 days). These results support the potential of *TBX18*mediated reprogramming as a strategy for creating biological pacemakers [45].

Combined genecell approaches

The strategy of cellgene therapy is a combined approach involving transplantation of carrier cells (most often mesenchymal stem cells (MSCs) or cardiac progenitor cells (CPCs)) genetically modified to express key pacemaker ion channels, such as HCN1, HCN2, HCN4, and the skeletal muscle sodium channel SkM1. In this context, cells function as biological platforms for targeted and temporally controlled delivery of ion channels to the target myocardial zone.

In vitro and in vivo experiments have confirmed the feasibility of this approach. Transplantation of human MSCs expressing HCN2 induced pacemaker activity in cell culture and restored rhythm in dogs with a bradyarrhythmia model, with the effect lasting up to 6 weeks [46, 47]. Similarly, MSCs modified with *HCN1* and *HCN4* genes demonstrated the ability to influence contraction synchronisation of rabbit cardiomyocytes in vitro and induce stable idioventricular rhythm in vivo in rats and rabbits [4850]. An alternative strategy using SkM1 normalised conduction velocity in the postinfarction scar zone in dogs without provoking arrhythmias [51]. To improve integration and longterm survival of transplanted cells, human CPCs coexpressing *HCN2* and *SkM1* were used, showing higher efficacy than MSCs [52]. Furthermore, the principal possibility of creating functional hybrid cells with pacemaker properties by fusing *HCN1*expressing fibroblasts with cardiomyocytes was demonstrated [53].

Despite promising results, the method faces several technological challenges, including the risk of migration of transplanted cells from the implantation site, for which cell encapsulation in biocompatible hydrogels is being explored. The problem of insufficient electrical coupling between carrier cells and cardiomyocytes is addressed by using electromechanically integrating CPCs. The potential oncological risk associated with viral vectors stimulates the development of nonviral delivery systems and optimisation of constructs for transient and controllable transgene expression.

Reprogramming of somatic cells with transcription factors

The most fundamental approach to creating biological pacemakers is the direct reprogramming of mature somatic cells, such as cardiomyocytes or fibroblasts, into cells with a pacemaker phenotype. This strategy is based on inducing the expression of key transcription factors that regulate embryonic SAN development, allowing direct reprogramming of the target cell transcriptome.

The most effective factor in inducing the pacemaker phenotype has been *TBX18*. The study by N. Kapoor et al. showed that *TBX18* expression in rat ventricular car-

diomyocytes in vitro initiates their transdifferentiation into cells morphologically and functionally similar to SAN cells [44]. This process was characterised by suppression of genes typical of working myocardium (including the sodium channel Nav1.5 and connexin43 (Cx43)) and simultaneous activation of *HCN4* expression, generation of pacemaker If current, and appearance of spontaneous pacemaker automaticity. Importantly, in vivo delivery of *TBX18* to the ventricular myocardium of pigs with complete AV block resulted in a stable idioventricular rhythm.

In addition to *TBX18*, several other critical regulators exist:

- *SHOX2* acts upstream in the reprogramming cascade, suppressing expression of the transcription factor Nkx2.5 - a repressor of SAN pathway differentiation - and activating *HCN4*and *TBX3* expression;
- *TBX3* plays a key role in maintaining the pacemaker phenotype by actively repressing the working myocardial gene program;
- *ISL1* serves as a marker of conduction system progenitor cells and is important for their development and potential cell regeneration;
- *TBX5* is a key regulator of atrioventricular node development.

To enhance efficiency and completeness of reprogramming, strategies of coexpressing several factors, e.g., combinations of *SHOX2*, *HCN2*, and *TBX5*, are being investigated [53]. The main advantage of this approach is the possibility of local creation of a biological pacemaker without cell transplantation. Relative safety and reversibility can be ensured by using nonintegrating vectors for gene delivery. However, the approach also faces serious challenges, such as risk of incomplete or heterogeneous reprogramming, potential oncogenicity associated with viral vectors, and the need to develop systems for precise spatiotemporal control of transcription factor delivery and expression.

Problems and limitations identified at the development stage

Despite impressive preclinical successes, no biological pacemaker has yet been introduced into clinical practice. The main barriers include:

Safety (risk of ectopic activity and lifethreatening arrhythmias from offtarget delivery or uncontrolled expression, potential immunogenicity of transplanted cells or vectors, oncological risks associated with viral vectors (insertional mutagenesis) and longterm culture / use of PSCs (genomic instability).

Stability and durability of effect. A biopacemaker must provide reliable, physiologically synchronised activity for years. Most preclinical effects (especially gene therapy) last weeks to months, incomparable with decades of electronic device operation. Causes include immune elimination, loss of gene expression, cell dedifferentiation.

Control. Data obtained in rodents, whose electrophysiology (high heart rate, ion currents) differs substantially from human. Longterm studies in large animals (pigs, sheep) are needed, considering differences in microenvironment, metabolism, and innervation.

Reversibility. Lack of reliable mechanisms for control, modulation, or complete shutdown of biopacemaker activity, particularly critical for gene therapy.

Ethical issues. Particularly relevant for ESCbased approaches.

OWN EXPERIENCE IN BIOPACEMAKER DEVELOPMENT (20162018)

Within a project supported by the Russian Science Foundation (No. 161510322), our centre's team obtained

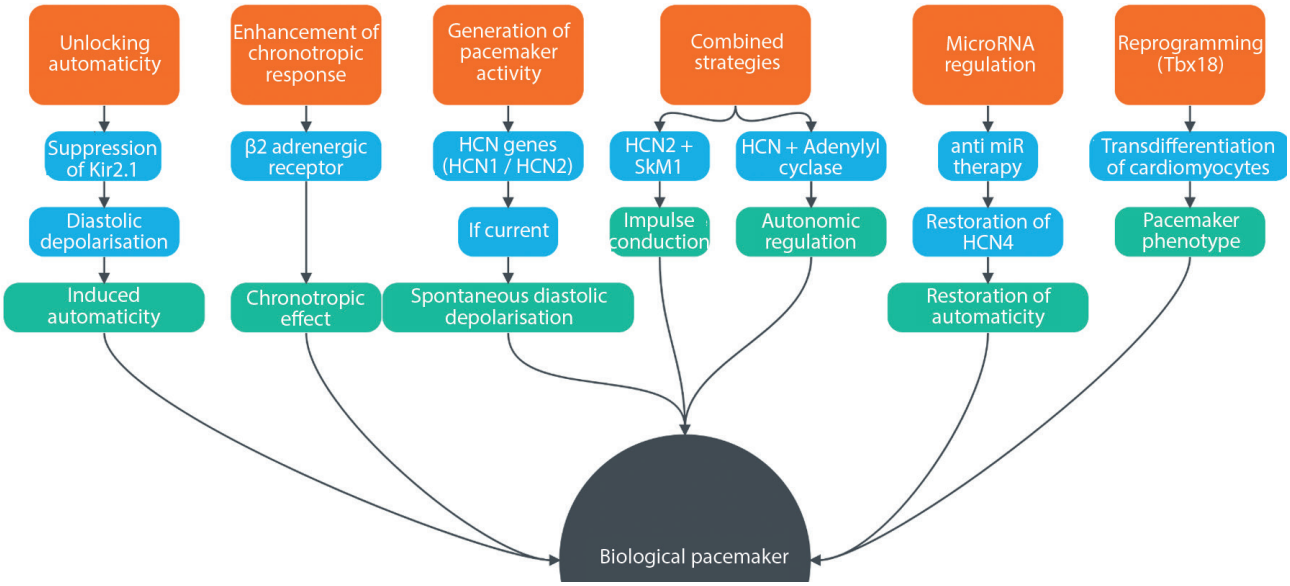

Fig. 4. Genetic strategies for creating a biological pacemaker. Kir2.1 (IK1): potassium channel protein forming the IK1 current (if blocked, working cardiomyocytes may begin to spontaneously generate impulses, like pacemaker cells); HCN genes (HCN1, HCN2, HCN4) - gene family encoding channels that conduct the If current; If current - the main pacemaker current flowing through HCN channels; HCN2 provides the slow diastolic depolarisation phase (If current), while SkM1 (skeletal sodium channel) adds a fast inward sodium current; adenylyl cyclase - enzyme that produces cyclic AMP, which directly binds to HCN channels and shifts their activation curve positively, causing channels to open more frequently; anti miR therapy - a modern therapeutic method using synthetic oligonucleotides to inhibit pathological microRNAs.

a set of significant results that form the basis for developing a new generation of tissueengineered biological pacemakers.

Key achievements

Engineering of biomimetic polymer matrices. Optimisation of electrospinning technology allowed the creation of nanofibrous scaffolds with controlled architecture based on polycaprolactone, polylactic acid (PLA), and recombinant spider silk (spidroin). Surface modification with fibronectin was found to statistically significantly enhance cardiomyocyte adhesion, while spidroinbased matrices demonstrated superior elastic properties without additional processing. Functional competence of the constructs was confirmed in experiments with neonatal rat cardiomyocytes, which, when cultured on these matrices, maintained synchronous contractile activity and conduction, visualised by optical mapping using the calcium indicator Fluo4.

Differentiation of pacemaker cells from iPSCs. Protocols for directed differentiation of human and rat iPSCs into pacemakertype cardiomyocytes were developed via modulation of the WNT/βcatenin signalling pathway (using CHIR99021 and IWP2 porphyrin). The efficiency of differentiation into pacemaker cells (*TnT+/Nkx2.5* phenotype) was increased from 0.5% to 14% through synergistic action of the morphogen BMP4 and sitespecific activation of key transcription factors SHOX2 and TBX5 using the CRISPR/Cas9 system. To create a controllable pacemaker system, hybrid cell cultures were formed combining the obtained iPSCderived cardiomyocytes with optically controllable ChR2HL1 cardiomyocytes, which demonstrated stable rhythmic activity in response to light stimulation.

Development of transplantation and integration technologies. To improve survival of transplanted cells, biocompatible micropatterns based on PLA/collagen composite were developed. It was experimentally shown that using thrombin gel as a carrier for cell suspension extended the persistence of cardiomyocytes in porcine myocardium to 10 days, twice as long as transplantation without carrier (5 days). In preclinical studies in minipigs, transplanted iPSCderived cardiomyocytes did not induce ectopic activity, but enhanced immunosuppression was required to prevent rejection.

Future directions

The accumulated data allowed the formation of a prototype platform for a tissueengineered biological pacemaker, integrating three key components: (1) biocompatible matrices with controlled architecture, (2) optimised cell products, including lines with optogenetic control, and (3) targeted delivery methods ensuring improved integration with recipient tissue. The strategic direction of further research is to enhance pacemaker phenotype stability and ensure longterm functional activity of the constructs in vivo [54-57].

Thus, the studies conducted in 20162018 created a scientific and technological foundation for further development of biological pacemaker research. The obtained results validated key tissue engineering and cell biology approaches for cardiac pacing, and also identified priority directions for subsequent work aimed at improving pacemaker phenotype stability, enhancing myocardial integration, and transitioning from shortterm preclinical models to longterm in vivo studies.

CONCLUSION

The development of biological pacemakers remains one of the most dynamic and promising areas of regenerative cardiology, integrating embryology, molecular biology, genetic engineering, and tissue engineering. Significant evolution has occurred: from primitive SAN tissue transplantation, through genetic engineering and iPSC technologies, to complex combined delivery and direct cell reprogramming methods.

Although clinical translation requires overcoming serious safety and efficacy barriers, the experimental evidence is compelling. The future likely lies not in complete replacement of electronic pacemakers, but in their integration with biological components or the use of biopacemakers in specific niches:

1. In patients with contraindications to implantation (infections, vascular anomalies);
2. As a temporary solution (e.g., in children requiring pacing until adulthood);
3. In combination with microelectronics and biosensors to create “smart” hybrid systems maximally adaptive to the body’s needs;
4. Use of allogeneic “universal” iPSC lines with low immunogenicity.

Modern technologies (CRISPR editing, cardiac organoids, 3D bioprinting, biodegradable scaffolds, targeted delivery) are actively being explored to solve existing problems. Despite difficulties, clinical application of biopacemakers appears achievable in the foreseeable future.

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POSSIBILITIES OF STEREOTACTIC BODY RADIOTHERAPY FOR THE TREATMENT OF VENTRICULAR ARRHYTHMIAS. CURRENT STATE OF THE ART

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This review article examines current approaches to the use of Stereotactic Arrhythmia Radioablation (STAR) in patients with sustained ventricular tachycardia refractory to medical therapy and catheter ablation. The biophysical and molecular mechanisms of the therapeutic action of the method, experimental data, principles of target planning and imaging, as well as international and our own clinical experience with the method in patients with ventricular tachycardias are presented. Technical aspects of the method, unresolved issues, limitations, and the potential for implementing STAR into Russian clinical practice are discussed separately.

Key words: stereotactic arrhythmia radioablation; non-invasive ablation; cardiac radiotherapy; stereotactic body radiotherapy; refractory ventricular tachycardia; SBRT; STAR.

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Ventricular tachyarrhythmias (VTs) are lifethreatening cardiac rhythm disorders characterised by pathologically accelerated and, as a rule, irregular electrical activity originating in the ventricular myocardium or the conduction system below the bundle of His. Prolonged persistence of VT may lead to haemodynamic instability and cardiac arrest [1].

Sudden cardiac death (SCD) remains one of the leading causes of mortality in developed countries: according to epidemiological studies in the USA, its annual incidence is estimated at 185-450 thousand cases (7-18% of all deaths) [2]. In the majority of cases, SCD is caused by malignant ventricular arrhythmias - sustained VT or ventricular fibrillation, especially in the presence of structural myocardial damage. According to 2023 data from the Russian Federation, surgical interventions for ventricular arrhythmias were performed in 5,369 patients, including 3,578 cases of endovascular destruction of the arrhythmic substrate and 1,791 patients receiving antiarrhythmic device implants. Repeat catheter procedures were performed in 9.6% of patients [3].

Currently, the main treatment modalities for VT are pharmacotherapy, implantation of cardioverterdefibrillators (ICDs), and catheter ablation. Implantable devices effectively prevent SCD by promptly terminating lifethreatening arrhythmias via antitachycardia pacing or electrical defibrillation. However, multiple ICD activations, particularly with frequent VT episodes, are associated with a marked decline in quality of life, increased anxiety and depression, and worse heart failure prognosis [4].

Catheter ablation of VT can achieve sustained arrhythmia control in a significant proportion of patients. Nevertheless, its success rate is lower in cases of deep intramural or subepicardial foci, extensive scarrelated myocardium, and repeated catheter ablations. According to the literature, VT recurrence after ablation may reach 20-50%, often requiring multiple reinterventions. Moreover, some patients are not candidates for ablation due to severe comorbidities, haemodynamic instability, or low myocardial contractility [5].

A particular challenge is presented by cases where VT is not controlled or recurs even after ablations, or where ablation is difficult due to anatomical features (large postinfarction scar, involvement of intramural and epicardial surfaces, etc.) [6]. In this context, there is growing interest in noninvasive treatment modalities that can address the limitations of traditional approaches [7-9]. There remains a clinical need for alternative therapies for patients with refractory or recurrent VT, in whom standard approaches are ineffective or inapplicable, driving the search for novel techniques [5, 10, 11].

One of the most promising directions is stereotactic arrhythmia radioablation (STAR), which is attracting increasing attention as a potential noninvasive alternative when invasive treatment options are limited. As of today, a PubMed search for “stereotactic arrhythmia radioablation” shows a steady growth in the number of scientific publications: from 24 articles in 2021 to 126 articles in 2025, reflecting the growing research interest in STAR technology.

STAR involves a singlesession, targeted delivery of highdose ionising radiation to the arrhythmogenic substrate [12, 13]. This approach is based on the principles of stereotactic body radiation therapy (SBRT), which is widely used in oncology, including the treatment of localised lung tumours, liver tumours, and oligometastases [14-16]. The quality and effectiveness of STAR are determined by consensus technical requirements originally developed for stereotactic radiotherapy in oncology. The accumulated experience of highdose irradiation of thoracic organs, including cardiac structures, has allowed the adaptation of the technique for arrhythmia treatment and served as the basis for the first experiments in radiation therapy for arrhythmology [17, 18].

Initial clinical results of STAR have been promising, demonstrating a marked reduction in arrhythmia frequency in patients with refractory VTs [19, 20]. A systematic review showed that the technique reduces the number of VT episodes by more than 85% with an acceptable safety profile in more than 40 patients, demonstrating high efficacy in patients with refractory VTs that do not respond to standard therapies [21-23]. These data have driven further development of the method: the number of STAR procedures has increased significantly, and the number of publications, including clinical cases, small series, and prospective studies, has grown. Currently, active clinical trials are ongoing to evaluate the efficacy and tolerability of STAR. However, the biological mechanisms of its therapeutic action remain a subject of scientific debate.

In this review, several terms are used that reflect historically established approaches to naming the method. “Stereotactic arrhythmia radiosurgery” emphasises the singlefraction nature of the intervention and corresponds to the concept of radiosurgery as a singlefraction, highdose, geometrically precise radiation delivery. “Radioablation” highlights not so much the technical parameters of delivery, but rather the biological goal - the creation of a controlled radiation lesion of the arrhythmogenic substrate. The term SBRT (stereotactic body radiation therapy) originated in oncological radiotherapy and is used for highprecision hypofractionated irradiation. The abbreviation STAR (stereotactic arrhythmia radioablation) was introduced by a group of authors led by P. Cuculich and P. Robinson and it is currently the most widely used specific term in the arrhythmological literature. In this review, the term “stereotactic arrhythmia radioablation (STAR)” is used as the main designation.

The aim of this review is to systematise and analyse current scientific and clinical data on the use of STAR in the treatment of VTs refractory to conventional therapies.

This review is based on a structured analysis of the contemporary literature on the use of STAR in refractory VT. Publications were searched in the PubMed and Scopus databases using the following keywords: “stereotactic arrhythmia radioablation”, “STAR”, “ventricular tachycardia”, “cardiac radioablation”, “SBRT”, “noninvasive VT ablation”. The search identified more than 200 publications.

The analysis included publications from 2020-2025 in English or Russian, including prospective clinical studies, cohort series, systematic reviews and metaanalyses, preclinical experimental studies, as well as clinical guidelines and consensus documents. Studies in which the population consisted of patients with sustained VT refractory to pharmacotherapy and/or catheter ablation were considered. Clinical outcomes, including VT recurrence rate, safety and complication rate, and overall survival, were evaluated.

Excluded were publications in languages other than English and Russian, conference abstracts without full text, single clinical case reports (n=1), and duplicate publications of the same cohorts. Due to the descriptive nature of the review, a formal PRISMA selection scheme was not constructed. Publication selection was performed by two independent authors based on eligibility criteria; disagreements were resolved by discussion. A total of 99 sources were included in the final analysis. The authors’ own clinical observations were not part of the literature search and are presented separately as illustrative material.

PATHOPHYSIOLOGY OF RADIATION-INDUCED MYOCARDIAL DAMAGE

The pathophysiological basis of electronbeam myocardial damage in STAR involves several mechanisms. Ionising radiation acting on the arrhythmogenic substrate leads to structural and functional changes that suppress pathological electrical activity. Key mechanisms include radiationinduced fibrosis and molecular remodelling of the conduction system components. Together, these processes create an area of altered electrical conductivity that disrupts reentry circuits and reduces the likelihood of arrhythmia recurrence.

It was initially hypothesised that the antiarrhythmic effect of STAR is mediated by apoptosis induction and subsequent fibrosis in the arrhythmogenic cardiac tissue. However, accumulating preclinical and clinical evidence suggests a more complex, multifactorial myocardial response to ionising radiation. One of the main effects is the development of radiationinduced fibrosis, triggered through oxidative stress, microvascular damage, inflammatory infiltration, and myofibroblast activation [24]. Fibrotic transformation electrically isolates the pathological reentry pathways, analogous to the goal of catheter ablation. However, the clinical effect of STAR sometimes occurs much earlier than mature fibrosis develops (which typically takes ≥6 months), indicating the presence of additional nonhistological mechanisms.

The study by D.M. Zhang et al. (2021) expanded understanding of STAR mechanisms, showing that, alongside fibrosis, molecular changes - particularly remodulation of intercellular contacts and increased connexin expression - may play a key role [25]. Irradiation of myocardial areas adjacent to scar tissue was associated with increased expression of the sodium channel Nav1.5 and connexin43 (Cx43) protein. The Notch signalling pathway, activated in response to radiation, is thought to play an important role in Nav1.5 activation. Thus, radiotherapy may induce electrophysiological remodelling of the cardiac conduction system, opening new possibilities for noninvasive targeting of VT zones. The same study presented pathomorphological data from four patients (after heart transplantation or autopsy 17-478 days after irradiation), confirming the

absence of pronounced myocardial fibrosis after a single 25Gy dose. Despite this, these patients showed a significant reduction in VT episodes, highlighting the clinical importance of alternative, nonfibrotic mechanisms [25].

Furthermore, studies by M. Amino et al. demonstrated that cardiac irradiation can increase the expression of connexin43, a transmembrane protein that mediates electrical coupling between cardiomyocytes. Increased Cx43 levels were observed both within and outside the irradiated zone; the effect varied depending on the type of radiation (photon, proton, or carbon ions) [26]. It has also been reported that postirradiation reduction in mitochondrial density facilitates more efficient calcium signalling within cardiomyocytes, which may represent a potentially novel mechanism of radiotherapy action [27].

Relationship between VT mechanisms and myocardial scar

VT developing in the context of structural heart disease is predominantly associated with reentry circuits forming in fibrotic myocardial areas. Such changes typically occur after myocardial infarction (MI), inflammatory or infiltrative processes, or cardiac surgery.

In ischaemic cardiomyopathy, scar zones usually follow coronary artery distribution and predominate in the subendocardial layers, sometimes extending through the entire myocardial thickness. In nonischaemic cardiomyopathy, scar transformation may be more heterogeneous - involving endocardial, intramural, or subepicardial layers with focal or diffuse distribution [24, 28]. The most critical areas for initiating and sustaining reentry arrhythmias are zones of slow conduction within scar tissue. These areas serve as the main targets during catheter ablation [29]. The arrhythmogenic substrate may be located on the endocardial or epicardial surface, but often is partially or entirely intramural. This limits mapping to a single side (epi and/or endocardial) and complicates complete anatomical visualisation of the arrhythmic pathway. In patients with scar-related VT, programmed stimulation often induces several morphological variants of sustained monomorphic tachycardia. This may result from multiple reentry circuits, different exit sites, or separate pathways from the same scar zone. Since the scar area is not necessarily the arrhythmia source, accurate localisation and delineation of arrhythmogenic myocardial regions are critical for effective treatment planning.

Animal experimental studies; preclinical studies

The first preclinical study that initiated experimental investigation of the method was the work of A. Sharma et al. (2010). Using a CyberKnife linear accelerator, the authors performed noninvasive STAR and demonstrated the feasibility of delivering precise damage to the electrophysiological arrhythmic substrate [30]. Subsequently, a number of experimental studies investigated the consequences of SBRT in various models: mice, rats, rabbits, pigs, and dogs. The aim was to evaluate morphological and functional cardiac changes after singlefraction irradiation, including in the setting of induced MI. Followup usually lasted up to 8-10 months, with different radiation types used: photon, proton, and heavy ions [31-37].

In most preclinical studies, irradiation targeted either healthy animals or animals after experimentally induced MI [25, 34, 35]. The main targets were pulmonary veins, the atrioventricular (AV) junction, the cavotricuspid isthmus, and (less frequently) the ventricular myocardium. Typically, irradiation was delivered as a single dose of 25-40 Gy. Information on immediate acute cardiac radiation effects is limited, since significant AV node conduction depression was observed only at extremely high doses (≥90-160 Gy), far exceeding clinical levels [35].

Early radiation effects (two to six weeks)

Signs of local radiation myocardial damage may appear in the first weeks after irradiation. For example, local βirradiation of pulmonary veins (pigs, 60 Gy) at 2-6 weeks histologically showed necrosis of the venous wall and destruction of elastic vascular fibres [38]. In a rabbit MI model, heavyion irradiation (performed on day 14 after MI) increased connexin43 expression in the border zone and remote myocardium as early as 2 weeks after treatment [26]. This was accompanied by a reduction in inducibility of VT and ventricular fibrillation compared with untreated controls [25]. Similarly, in mice after experimental infarction, γirradiation at 15-25 Gy accelerated conduction in both intact and damaged myocardium; these changes were associated with enhanced expression of sodium channels and Cx43 at 6 weeks after therapy at doses ≥15 Gy [25]. Notably, in healthy rabbits, increased Cx43 expression after irradiation persisted up to 1 year, whereas in infarcted animals the effect was less pronounced [26].

Rat studies showed oedema, vacuolisation, and widening of intercalated discs within the first month after irradiation (20-50 Gy). These phenomena intensified at doses ≥30 Gy and were accompanied by prolongation of PR and QTc intervals, despite the absence of morphological necrosis, suggesting the involvement of other conductionmodulating mechanisms at early stages [32].

In several largeanimal experiments (minipigs) using STAR with subsequent repeat mapping of targets (25-196 days), a dosedependent reduction in signal amplitude on mapping electrodes was shown, with electrophysiological verification of targets performed after irradiation. The minimum effective dose was ≥25 Gy. Bidirectional cavotricuspid isthmus block was achieved 30 days after 40 Gy, and complete AV block after 49 days with 70 Gy [30].

Late effects (3-9 months)

Cardiac morphological changes due to irradiation are strongly dosedependent. For example, βirradiation of the pulmonary vein intima at 60 Gy in pigs caused acute endothelial damage, elastic fibre breakdown, and myocardial necrosis, which in subsequent months were replaced by marked fibrosis (on average at 81±27 days) [38]. Delayed fibrosis is probably explained by a combination of processes, including apoptosis and necrosis, that gradually transform into connective tissue. Some pathological changes (microvascular disturbances, haemorrhages, inflammatory infiltration, fatty degeneration) appear gradually, starting around 3 months after irradiation [25, 31, 32].

For instance, M. Amino et al. showed that after γirradiation of the left atrium and pulmonary vein ostia, myocardial fibrosis developed at doses >30 Gy, whereas at 20-27.5 Gy only mild fibrotic changes were observed at 6 months [36, 39]. In an experiment with targeted proton irradiation of the AV node (40-50 Gy) in pigs, AV conduc-

tion slowing was recorded at 10-12 weeks, and histological examination at 3 months revealed areas of fibrosis and necrosis in the node region [33].

Adverse effects of cardiac radiotherapy

Preclinical studies, mainly in pigs, demonstrate dosedependent cardiotoxicity of stereotactic radiotherapy. At relatively low doses (<35 Gy), only moderate adverse changes - e.g., transient mild reduction in myocardial contractility and limited pericardial effusions - are seen [32].

In contrast, doses >35 Gy are associated with more severe lesions: development of pronounced arrhythmias, acute coronary events, and sudden death in animals, as well as damage to adjacent organs. In one experiment, irradiation of the cardiac region with 37.5 Gy led to the formation of a bronchomediastinal fistula [39]. Additionally, targeted proton irradiation of coronary arteries (up to 40 Gy) caused acute radiation damage to the vessel wall and subsequent luminal occlusion [33].

In addition to foreign data, a Russian research group led by A.Sh. Revishvili and A.V. Golanov conducted an experimental study in domestic pigs to evaluate the safety and efficacy of STAR at different dose levels. The results confirmed high accuracy and conformality of dose delivery and demonstrated a marked dosedependent therapeutic effect (Fig. 1). Irradiation of the AV node at 40-45 Gy led to complete thirddegree AV block (including fatal asystole), whereas 35 Gy did not cause persistent conduction disturbance. Equivalent doses applied to atrial and ventricular myocardium caused transmural changes in the form of focal fibrosis, haemorrhages, and calcification, without involvement of adjacent structures. These results indicate a threshold dose necessary for a reliable electrical effect and simultaneously underscore the need for caution when increasing radiation exposure [40].

Despite encouraging results, questions remain regarding the duration of clinical effect, the sufficiency of the identified mechanisms to explain the early therapeutic response, and the universal applicability of STAR for different aetiologies of tachyarrhythmias. In this regard, a prospective study is underway to evaluate the impact of increasing radiation dose on STAR efficacy and VT recurrence rate [41].

Nevertheless, even with existing uncertainties, in the setting of electrical storm and when no other effective therapeutic options remain, STAR is considered a salvage strategy capable of controlling arrhythmia and significantly improving patient quality of life.

PRINCIPLES OF TARGET PLANNING AND IMAGING IN RADIATION THERAPY

Noninvasive imaging of the treatment substrate

Imaging modalities play a key role in STAR planning, allowing precise identification of arrhythmogenic zones. The most widely used is late gadolinium enhancement cardiac magnetic resonance imaging (LGEMRI), which depicts areas of macroscopic fibrosis [42-44]. However, the diagnostic yield of MRI is reduced in the presence of implanted ICDs and in nonischaemic cardiomyopathies. Comparative studies have shown that LGEMRI may outperform invasive electroanatomic mapping in identifying intramural and heterogeneous scar areas, although the imaged fibrotic zones may contain viable myocytes [45-47].

Radionuclide techniques, such as positron emission tomography (PET) and perfusion singlephoton emission computed tomography (SPECT), provide functional assessment of perfusion and metabolic activity and may be useful for refining target boundaries in STAR planning, though they have not yet entered routine navigation practice. Recent studies show that the use of ^{99m}TcSPECT and ^{82}Rb or ^{13}NammoniaPET allows additional characterisation of ischaemic and functional myocardial features [48, 49]. Despite lower spatial resolution compared with CT and MRI, fusion of CT anatomical data with radionuclide images improves target localisation and enhances interdisciplinary planning consistency.

For quantitative assessment and localisation of target areas, the AHA17 segment model (2017) is used, taking into account dominant coronary blood supply [50]. The radiopharmaceutical ^{123}Imetaiodobenzylguanidine (^{123}IMIBG), a norepinephrine analogue, is used to assess myocardial sympathetic innervation with SPECT and scintigraphy in heart failure patients. Although studies are limited, an association between regional innervation defects

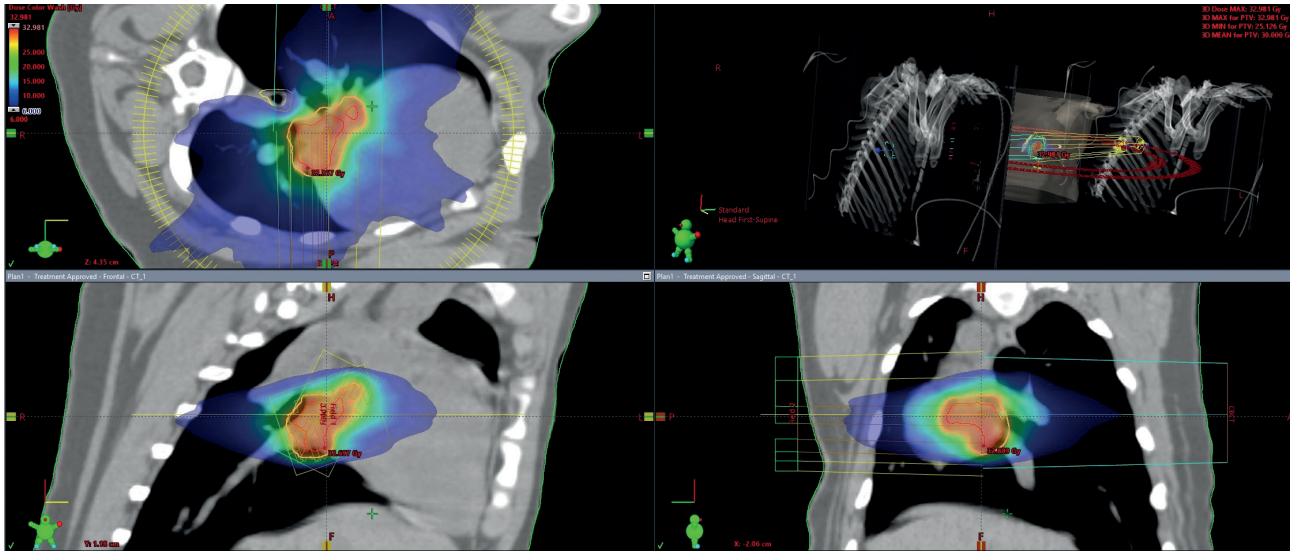

Fig. 1. Dose distribution visualisation, projection of the target area at the left ventricular summit onto native cardiac CT of a pig in the Precision treatment planning system.

and clinical outcomes in VT has been noted [51]. While some data indicate no significant changes in MIBG imaging after STAR [52], others suggest that a reduction in perfusionMIBG mismatch may correlate with successful ablation in ischaemic patients [53]. ^{11}Chydroxyephedrine, a more accurate method for sympathetic imaging, is a promising direction. Radionuclide imaging is noninvasive, allows disease tracking, and may in the future contribute to standardisation of target selection for STAR therapy.

Among the promising and already clinically implemented methods is the noninvasive cardiac activation mapping system AMICARD. Surface ECG mapping involves simultaneous recording of unipolar ECGs from multiple points on the chest, visual representation of results as isopotential and other isoparametric maps, and their diagnostic interpretation with display on an anatomical heart model. Surface ECG mapping is increasingly used for diagnosing cardiac rhythm disorders and predicting life-threatening ventricular tachyarrhythmias. This method identifies the localisation of critical reentry sites, including epicardial arrhythmogenic substrate zones, and defines the concept of noninvasive arrhythmia treatment - from topical diagnosis to therapy.

Invasive electroanatomical mapping (EAM)

Invasive electroanatomical mapping currently remains the primary method for localising the arrhythmogenic substrate in STAR preparation and is considered the gold standard in this field [54, 55]. When standard approaches are insufficient, additional techniques such as noninvasive ECG mapping, epicardial mapping during EPS, and various imaging methods are applied.

A key preparatory step is the integration of anatomical and electrophysiological data (EAM, CT, MRI) to create a unified 3D cardiac model, which serves as the basis for radiation treatment planning [56-58]. In several studies, the irradiation volume was defined by merging EAM data with CT and, when necessary, contrastenhanced MRI. However, the multicentre RAVENTA study identified discrepancies in clinical target/tumour volume (CTV) determination between EAM and CT, highlighting existing standardisation difficulties [59].

Particular difficulties arise in patients with hypertrophied myocardium, e.g., hypertrophic cardiomyopathy - in such cases, volumes determined by EAM and CT may not match. Additionally, saline infusion during catheter ablation may distort CT visualisation of left ventricular volume.

Artifacts and technical solutions

The use of delayedenhancement CT and MRI is hampered by ICDrelated artifacts and high cardiac mobility, which can reduce dosimetric planning accuracy [60, 61]. Various technical solutions are used to minimise these limitations: singleenergy metalartifactreduction CT, secondgeneration cardiac motion compensation algorithms, neural networkbased image reconstruction, automated segmentation of anatomical structures, and photoncounting CT [62-70].

Target volume and dosimetric approaches in STAR

In the context of STAR, there is active accumulation of evidence on imaging and electrophysiological criteria used to delineate arrhythmogenic zones, as well as technical treatment parameters - such as irradiated volumes, dosing regimens, and constraints on critical structures. However, current data indicate substantial heterogeneity in approaches to target volume definition, methodologies used, and completeness of preparation descriptions [71].

In clinical practice, the main contours in STAR planning are the clinical target/tumour volume (CTV), which includes the presumed VT substrate (e.g., fibrosis zones, slow activation areas), and the planning target/tumour volume (PTV), formed by expanding the CTV to account for possible positioning errors, respiratory, and cardiac motion. Some protocols also use an internal target/tumour volume (ITV) - CTV with a margin for motion amplitude determined from 4DCT. The PTV is typically obtained by adding 5-10 mm to the ITV, depending on the technique and guidance system.

According to data from several studies, PTV volumes in STAR ranged from 3.5 to 345 mL (median 81.2 mL), CTV from 6.75 to 108.7 mL (median 34.6 mL), while GTV was reported less frequently (median 25.1 mL) and lacks standardised delineation criteria in the context of VT treatment [72]. This is due to the absence of an imaging method that can accurately encompass the entire arrhythmogenic substrate without including viable myocardium, hence safety concerns dominate CTV definition.

The standard STAR dosing scheme is a single fraction of 25 Gy, with at least 95% of PTV volume covered by this dose. At the same time, dose constraints for critical anatomical structures, especially myocardium and coronary arteries, are extremely important. Historically, dose limits were based on cardiotoxicity data from chemoradiotherapy for mediastinal tumours. According to AAPM TG101 recommendations, the heart volume receiving ≥16 Gy (V16) should not exceed 15 cm^3, and the maximum point dose (Dmax) to the heart should not exceed, by various estimates, 22 Gy [17, 73, 74] (Fig. 2).

Sources of uncertainty in targeting

STAR planning involves several sources of uncertainty that can affect dose delivery accuracy. The main ones include:

- Accuracy of arrhythmogenic substrate localisation. Electroanatomical mapping (EAM) is a key targeting component, but its informative value depends on point density and spatial resolution. It should be noted that the scar zone does not always fully correspond to the VT substrate.
- Integration of multimodal data. Fusion of EAM with CT, MRI, or PET requires precise registration of anatomical landmarks. Registration errors - including rotational and translational - have been shown to occur more frequently when targets are located on the lateral wall or in the interventricular septum [71].
- Transfer of data to the planning system. Manual contour transfer has limited accuracy and may introduce geometric errors. Direct integration of registered datasets improves reproducibility but requires specialised software.
- Cardiorespiratory motion. Cardiac motion and respiratory excursions create overall positional uncertainty, hindering conformal dose distribution.

Accurate targeting and uniform dose delivery require consideration of both respiratory and cardiac motion. Car-

diac pulsations, unlike respiration, are usually incorporated into the ITV or PTV.

Management of respiratory motion

The following strategies are used to compensate for respiratory motion: forming ITV based on 4DCT or multiphase CT encompassing all predicted target positions; gating - synchronising the beam with a specific respiratory phase (e.g., expiration) using external respiratory monitors; tracking - robotic realtime target position tracking (e.g., CyberKnife matches LED markers on the patient's chest with target position); breathhold - irradiation during a fixed respiratory phase. VMAT allows fast procedure execution and may be preferred in unstable patients, whereas CyberKnife permits more precise dose limitation to critical structures, including heart valves [72].

Accounting for cardiac motion

Cardiac motion is an independent source of uncertainty. Unlike respiratory motion, it is related to cardiac cycle phases and is not eliminated by immobilisation methods. The following approaches have been described in the literature:

ECGgated gating - irradiation activated in a specific cardiac phase (usually diastole) using realtime ECG signal; experimental studies on dynamic phantoms demonstrated improved dose delivery accuracy compared with nongated mode [75].

Use of intracardiac landmarks for tracking - ICD or pacemaker leads, which move synchronously with the myocardium, can serve as radiopaque markers on robotic radiosurgery systems [76].

ECGsynchronised CT - multiphase cardiacgated CT allows quantification of cardiac displacement amplitude and its incorporation into target volume.

Formation of cardiac ITV - in the absence of gating or tracking systems, the range of cardiac motion is included in the ITV based on multiphase or 4DCT; in clinical practice, this remains the most practically feasible approach. Currently, commercial full cardiac motion tracking systems on standard linear accelerators are not available.

One promising direction is performing radioablation during a stable paced rhythm with cardiacphase synchronisation, potentially increasing target motion predictability. C.Q.M.Reis et al. (2025) demonstrated the feasibility of this approach at heart rates up to 120 bpm and confirmed dose delivery stability under highfrequency gating [75].

Thus, STAR planning requires a balanced approach, ensuring optimal coverage of the arrhythmogenic zone while strictly adhering to dose constraints. Advances in imaging, motion management algorithms, and planning technologies allow more precise definition of CTV, ITV, and PTV, enhancing both safety and efficacy.

INTERNATIONAL EXPERIENCE WITH STAR

The clinical evidence base for STAR in VT is currently under development. Most published data come from small singlecentre series and prospective cohort studies with limited followup. Randomised comparative studies are few, and their results are pending. Therefore, the data below are structured by increasing level of evidence - from initial clinical series to prospective studies, multicentre initiatives, and ongoing randomised projects.

Clinical series

The first clinical study of STAR for VT was published in 2017 by P. Cuculich and colleagues, including five patients with ischaemic and nonischaemic cardiomyopathy [19]. The work demonstrated the fundamental feasibility of noninvasive targeting of the arrhythmogenic substrate and launched the clinical development of the method.

The largest singlecentre experience to date is a series of 36 patients treated in the Czech Republic since 2014; all cases received a single 25Gy dose [20].

The first Asian clinical experience of STAR for refractory VT was reported from Taiwan [77]. Planning used 3D electroanatomical mapping, delayedenhancement MRI, and dualenergy CT to refine arrhythmogenic substrate localisation. Irradiation was delivered with a single 25Gy fraction using the Varian TrueBeam/Edge system. The study (20192023) included 11 patients with VT refractory to pharmacotherapy and at least one catheter ablation. At a median followup of 53 months, the reduction in VT episodes in the first 6 months was 88%; some patients experienced late recurrences requiring repeat catheter ablation. Oneyear survival was 83%.

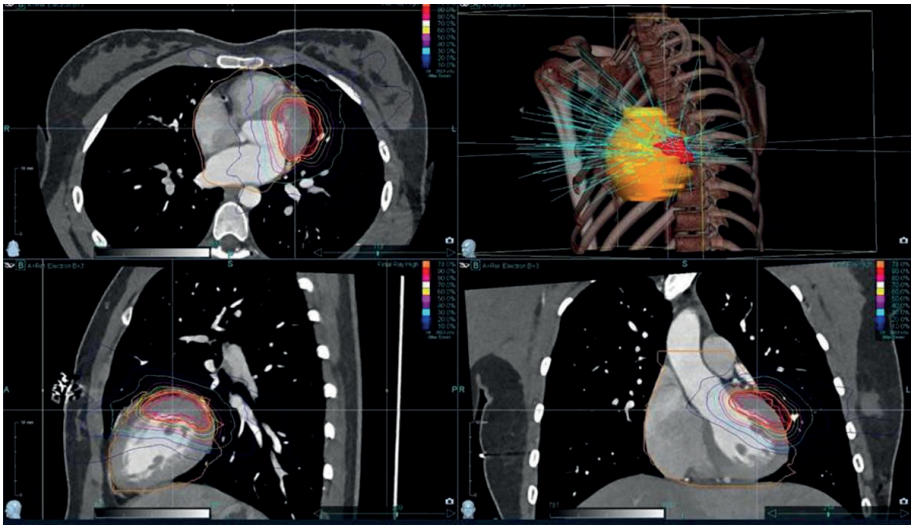

Fig. 2. Dose distribution visualisation, projection of the target area in the left ventricle onto native cardiac CT of a patient in the Precision treatment planning system.

At the early stage of clinical implementation, the evidence base was limited: studies included small numbers of patients, no control groups, and relatively short followup. Nevertheless, the initial series demonstrated clinical feasibility and served as a starting point for subsequent transition to prospective studies and international multicentre initiatives.

Prospective studies

Clinical application of STAR began in 2018 and rapidly spread internationally. A key milestone was the phase I/II prospective trial ENCOREVT (ElectrophysiologyGuided Noninvasive Cardiac Radioablation

for Ventricular Tachycardia), whose results were published in 2019. This work showed that STAR technology in refractory VT patients reduced VT episodes by 94% and significantly reduced ICD activations [78].

Multicentre initiatives and standardisation

The method's development continued within the largescale panEuropean initiative STOPSTORM (Standardized Treatment and Outcome Platform for Stereotactic Therapy Of Reentrant Tachycardia by a Multidisciplinary consortium) - a consortium aimed at standardising STAR approaches. It includes 31 clinical and scientific institutions from eight European Union countries with significant experience in radiotherapy and interventional arrhythmology. At the time of STOPSTORM launch, 84 STAR procedures had been performed, with 8 of 22 participating centres simultaneously conducting their own national clinical trials. Most centres used 25 Gy in one fraction. Targeting approaches varied: the most common were EAM during VT (96%), pacemapping (75%), and analysis of late potentials and lowvoltage areas in sinus rhythm [48].

Experience from German centres within the consortium reflects not only high clinical interest but also efforts towards harmonisation and standardisation of key aspects of STAR, including targeting, planning, and quality control [1]. Research within STOPSTORM continues: interim reports are regularly published to refine efficacy, safety, and optimise treatment planning.

A significant step was the multicentre STAR benchmark planning study involving 20 clinical centres [79]. Sixtyseven treatment plans were developed for three typical clinical scenarios of sustained VT, covering a wide range of anatomical and technical features, including proximity to critical structures and metal artifacts from implanted devices. Unlike traditional validated protocols, this study intentionally allowed variability to reflect real clinical practice. Based on pooled analysis and expert discussions, STAR planning recommendations were formulated. Expert groups reached consensus on key parameters: prescribed dose (25 Gy single fraction), procedure duration, general requirements for radiation technique, dose calculation methods, and approaches to tradeoffs between PTV coverage and critical structure constraints. However, discussion continues on several technical and clinically relevant aspects. This study also reflected the heterogeneity in STAR treatment planning approaches across European centres and confirmed the need for further harmonisation of both technical and clinical parameters. Given the limited safety and efficacy data in large cohorts, reaching consensus on optimal methodology remains a priority.

Current and planned randomised controlled trials

The largest ongoing international multicentre randomised trial, approved by US regulatory authorities, is RADIATEVT (Cardiac RADIoablation versus repeat catheter Ablation: a pivotal randomized clinical Trial Evaluating safety and efficacy for patients with highrisk refractory Ventricular Tachycardia, NCT05765175), initiated by Washington University in St. Louis. The trial plans to enrol 380 patients in 30 centres to directly compare noninvasive STAR with repeat invasive ablation in patients with refractory monomorphic VT (ischaemic or nonischaemic aetiology) with reduced LVEF (≤49%) and amiodarone failure or intolerance. Patients will be randomised 1:1 to repeat catheter ablation or noninvasive radioablation using the experimental Varian platform. The procedure requires close interdisciplinary collaboration between interventional arrhythmologists and radiation oncologists. The primary endpoint is to prove noninferiority of STAR with superior safety compared with repeat catheter ablation; secondary endpoints include quality of life and arrhythmia event rate. Although RADIATEVT results are not yet published, its mere conduct underscores the growing interest in STAR as a promising alternative to traditional methods.

Systematic reviews and metaanalyses

A comprehensive analysis of clinical studies on STAR for refractory VT was performed by Gupta et al. [80]. The authors conducted a systematic literature search up to March 2024. The aim was to identify clinical studies describing STAR use in VT patients. Only studies with at least three patients who underwent STAR and provided quantitative data on recurrence rates of arrhythmias and/or ICD interventions were included. Reviews, metaanalyses, duplicate publications, and individual case reports were excluded. Ultimately, 23 studies published between 2017 and 2024, covering 225 patients, were included. The main analytical approach was to calculate rate ratios of VT episodes, antitachycardia pacing activations, and ICD shocks before and after STAR, using a randomeffects model. The time boundary between "before" and "after" was set after a sixweek blanking period to exclude shortterm procedural effects. In addition to efficacy, complication rates and overall survival data were analysed.

Demographic characteristics: mean age 67 years, majority male (~85%), ischaemic cardiomyopathy as aetiology in about half (52%). All patients had severe refractory VT not responding to antiarrhythmic drugs and multiple catheter ablations (mean 1.9 procedures per patient). Several studies emphasised that SBRT was used as a last resort, palliative measure when other options were exhausted.

Almost all cases used a standard radiation dose of 25 Gy in a single fraction; only a few studies reported variations (e.g., 2223 Gy). Mean PTV volume was 84 mL. Followup after procedure ranged from 5.8 to 28 months, average about one year. Thus, this metaanalysis represents the most comprehensive summary of clinical data on STAR for refractory VT to date.

Reports of severe adverse events were relatively rare. The most common were pericardial complications (8%), including radiation pericarditis, effusion, and fibrosis, and pulmonary manifestations such as pneumonitis and interstitial fibrosis (5.8%). Nevertheless, several severe late complications were recorded, notably fistulas between pericardium and oesophagus. Two such cases were reported: oesophagopericardial fistula [81] and gastropericardial fistula, both developing several months after STAR. Despite adverse outcomes, overall STAR demonstrated marked clinical benefit. Before irradiation, the pooled VT episode rate was 25.7 per patientmonth, and ICD interventions were 29 (including ATP and shocks). After STAR, these decreased significantly to 2.3 VT episodes and 3.9 ICD interventions per patientmonth, respectively - roughly a tenfold reduction. The rate ratios (after/before) were 0.10

for VT, 0.09 for ICD shocks, all statistically significant ($p<0.00001$).

Despite this significant overall reduction, complete remission was not achieved in all patients. Within the first six months after treatment, nearly half of patients experienced recurrent VT, about 30% received ICD shocks, and 20% required repeat ablation - either invasive or another STAR course. Nevertheless, the substantial reduction in arrhythmic burden and painful ICD discharges suggests improved quality of life for most patients.

Importantly, no worsening of left ventricular systolic function was observed: mean LVEF before SBRT was 30.9%, after 32.4% ($p=0.3$, not significant). Given the short followup and severity of patient conditions, these data are encouraging. Pooled survival estimates showed overall survival at 12 months of 72%, and at 24 months 57%, corresponding to approximately 43% deaths over two years. As the authors emphasised, the main cause of death was not arrhythmic events but progression of heart failure [82].

Thus, cardiac STAR demonstrates high potential as a noninvasive treatment for refractory VT in patients with limited therapeutic options. Despite the severity of baseline status and certain risks, a significant reduction in arrhythmia burden without deterioration of cardiac function is observed in most cases. However, the high mortality in this population underscores the need for further studies to assess longterm efficacy and survival impact.

SERIES OF CLINICAL CASES FROM THE AUTHORS' PRACTICE

The first clinical case of STAR for refractory VT in Russia was performed under the leadership of A.Sh. Revishvili and A.V. Golanov [83]. The transition to human application was based on own largeanimal experimental studies and the international data accumulated by that time confirming the efficacy and safety of the technology [40]. Below are clinical observations obtained within the local clinical pilot programme. Treatment was approved by the local ethics committee; all patients provided informed consent for the procedure and for use of anonymised data in scientific publications.

Radiosurgical treatment was performed in a 57year-old patient with ischaemic cardiomyopathy and recurrent VT refractory to antiarrhythmic therapy and repeated radiofrequency ablations. Preprocedure electrophysiological mapping allowed precise localisation of arrhythmogenic areas in the interventricular septum and posterolateral apical segments of the left ventricle, forming the basis for target planning. Irradiation was delivered on a TrueBeam linear accelerator (Varian Medical) under respiratory con-

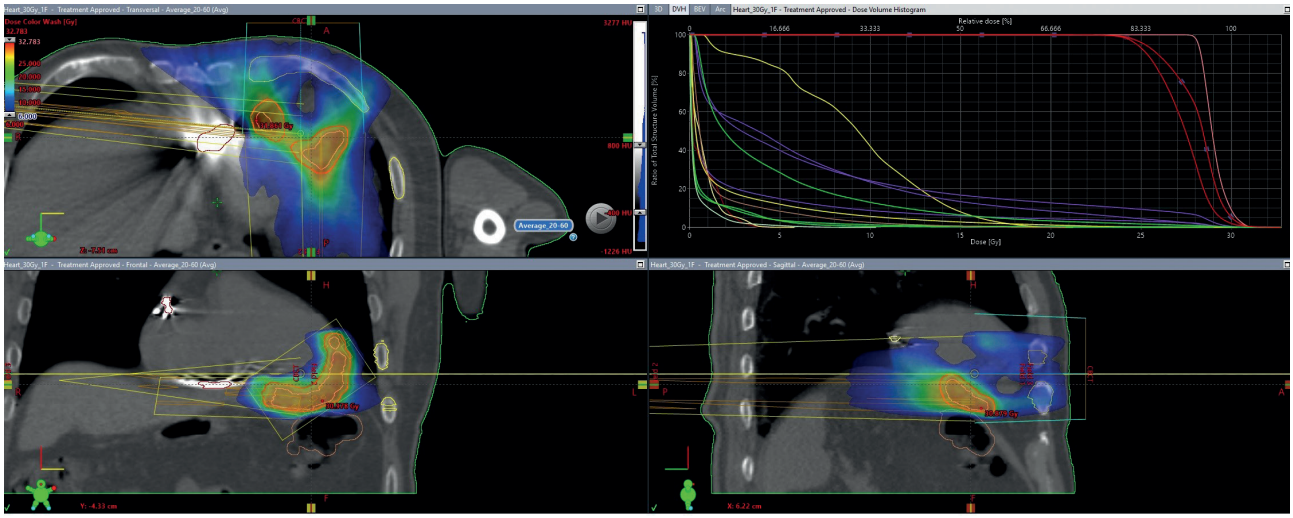

Fig. 3. Dose distribution visualisation, projection of the target area in the left ventricle onto native cardiac CT of a patient in the Eclipse treatment planning system.

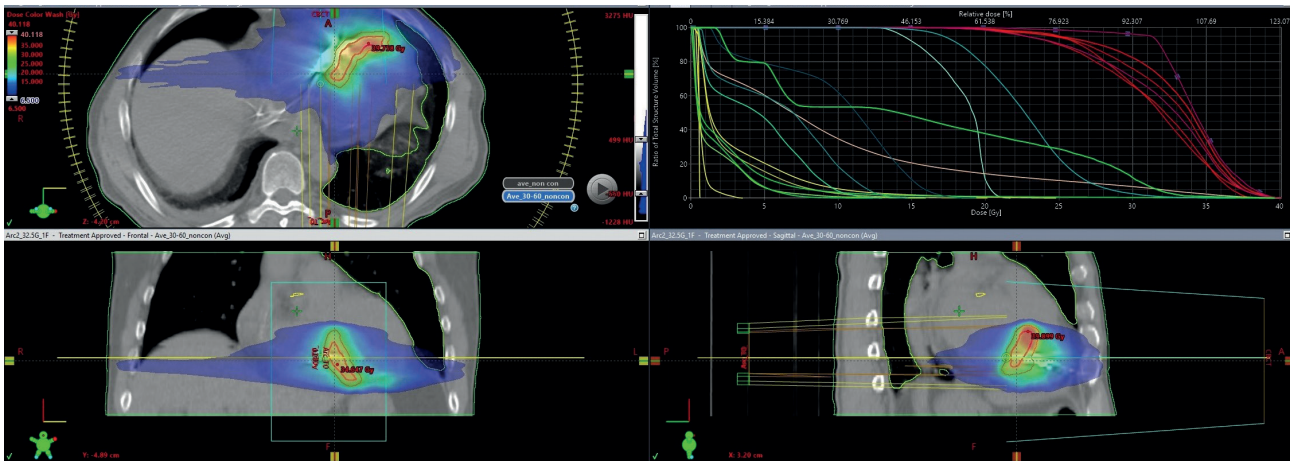

Fig. 4. Dose distribution visualisation, projection of the target area in segments 1416 of the left ventricle onto native cardiac CT of a patient in the Eclipse treatment planning system.

trol, as a single fraction of 25 Gy to 95% of the PTV (46 cm³) via two coplanar arcs. All dose constraints for critical structures were met; dose distribution visualisation is shown in Fig. 3. In the first weeks, rare arrhythmic episodes persisted, but from day 64 and throughout follow-up (450 days), no VT episodes were recorded. No adverse effects or signs of radiation damage to surrounding tissues were observed.

The second patient treated within the local STAR pilot programme was a 60yearold man with severe ischaemic cardiomyopathy. History included MI, coronary artery bypass grafting, and implantation of a CRTD device (Brava DR). Despite pharmacotherapy and prior RFA, sustained VT episodes persisted, including forms with ventricular rates >110 bpm. Recurrent paroxysms impaired quality of life and increased the risk of adverse outcomes. Given refractory arrhythmia and lack of response to conventional methods, noninvasive STAR was performed. As in the first case, treatment was carried out by a multidisciplinary team led by A.Sh. Revishvili and A.V. Golanov using a TrueBeam linear accelerator [83]. Planning targeted the arrhythmogenic substrate in segments 1416 of the left ventricle. GTV volume was 18.5 cm³, PTV 40.9 cm³. The prescribed dose was 30 Gy in a single fraction, respecting all dose constraints (Fig. 4). The plan consisted of two full coplanar arcs (Fig. 5). From the date of the procedure (07.02.2022), the patient experienced no VT episodes, indicating potential efficacy even in the most complex clinical situations.

These results demonstrate not only technical feasibility but also clinical viability, opening prospects for further application of STAR in Russian arrhythmological practice.

DISCUSSION

STAR is an innovative noninvasive treatment for refractory VT, primarily in patients with postinfarction myocardial scars. The method is at an active stage of investigation, and issues of optimising STAR efficacy and safety continue to be debated.

At the preclinical level, two main mechanisms of antiarrhythmic action of singlefraction cardiac irradiation have been described. First, at doses above about 30 Gy, radiationinduced myocardial fibrosis and coagulation necrosis develop in the target zone, potentially electrically isolating the arrhythmogenic substrate. Second, at “moderate” doses (2025 Gy), electrophysiological modulation occurs without gross scar formation - through activation of signalling pathways (Notch, etc.) that alter ion channel expression. However, clinical data on STAR mechanisms remain heterogeneous, hindering the development of a universal approach to optimal dose and volume selection. This underscores the complexity of radiobiological effects and the need for individualised treatment planning for each patient.

Attempts are being made to standardise STAR internationally. In particular, the STOPSTORM project has developed recommendations for unifying the irradiation methodology and outcome reporting. Preliminary agreement has been reached on the advisability of detailed documentation of STAR procedures according to the ICRU №91 international radiotherapy standard (target volumes, doses, control points, etc.). Undoubtedly, further experience accumulation will refine technical parameters and improve reproducibility across centres.

STAR efficacy in clinical studies is mainly assessed by reduction in VT recurrence rate in patients with previously refractory arrhythmia. In most studies, a reduction in episodes is observed after 6 weeks postirradiation [84-86]. One study reported an 88% reduction in VT burden within 6 months [77].

The largest metaanalysis to date, by A. Gupta et al., showed a statistically significant reduction in VT episodes, ATP activations, and ICD shocks after STAR (approximately 10fold, $p<0.00001$), confirming the method’s pronounced antiarrhythmic effect [80].

Importantly, the reduction in arrhythmic activity was not accompanied by worsening of systolic function - LVEF remained stable after irradiation, suggesting not only efficacy but also functional safety of the approach. Nevertheless, recurrences persisted in some patients, sometimes requiring repeat ablation, including another STAR course.

The high mortality in the analysed cohort, mainly due to heart failure progression, underscores the need for better patient selection and further study of longterm outcomes. Also, standardisation of the technique remains an issue: different studies used varying targeting and irradiation protocols, which may affect reproducibility.

Against this background, technical aspects of plan-

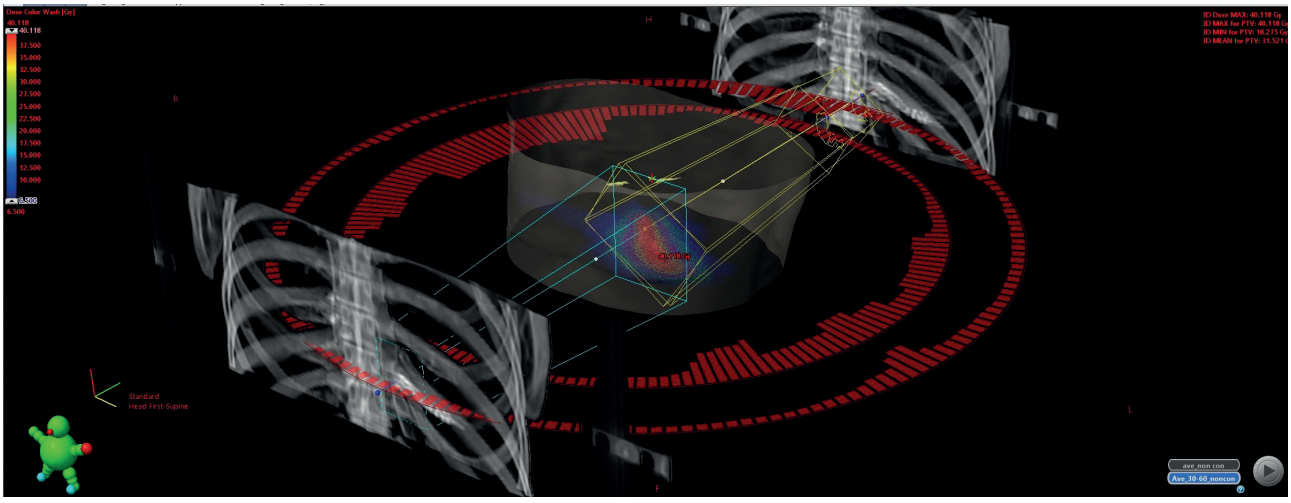

Fig. 5. Irradiation scheme with two full coplanar arcs.

ning and dose delivery gain particular relevance. However, there remains a high risk of recurrence, especially with heart failure progression or new arrhythmogenic substrates [47, 57]. Moreover, the 25Gy dose to the ITV may be insufficient at the periphery of the target, especially with cardiac and respiratory motion. This is confirmed by the detection of reentry mechanisms at the edge of the irradiated scar in patients who underwent repeat catheter ablation.

Historically, cardiac irradiation was limited due to cardiotoxicity risks, particularly observed in nonsmall cell lung cancer treatment [87, 88]. According to AAPM TG101, the heart volume receiving 16 Gy (V16) should not exceed 15 cm³, and the maximum dose 22 Gy [17, 73, 74]. These constraints are particularly relevant when considering STAR in patients with significant systolic dysfunction.

Irradiation of large heart volumes in such patients may lead to further deterioration of contractile function. Ionising radiation affecting extensive myocardial areas carries the risk of cardiomyocyte loss and loss of contractility of remaining viable tissue. Accumulated data indicate a correlation between increased irradiated volume (ITV) and worsening pump function, up to heart failure decompensation. Therefore, caution is required in target selection, especially in patients with already reduced EF.

Complications and safety of STAR

In published studies, acute toxicity of STAR is described as relatively low, while late complication rates may be underestimated due to short followup (usually up to 1 year). The most commonly described complications are transient nausea, pericarditis, oesophagitis, and pneumonitis (mild to moderate severity) [74]. In the vast majority of cases, they regress with conservative therapy and do not lead to permanent disability.

Pericardium

Pericarditis is a manifestation of acute toxicity and has been described in clinical series, occasionally requiring medical therapy [74]. Pericardial fibrosis has also been reported [89]. In animal studies, sterile pericardial effusions were observed, typically decreasing over time [32].

Oesophagus and gastrointestinal tract

Oesophagitis is a critical complication due to the anatomical proximity of the oesophagus to the posterior heart wall. Severe complications have been reported, including fatal oesophagopericardial fistula and gastropericardial fistula requiring surgery [90]. Currently, no evidence supports pharmacological prevention of these rare but serious complications. Emphasis is placed on careful planning: strict dose constraints for the oesophagus and stomach, use of diaphragmatic breathing, and other beamsparing measures.

Lungs and bronchi

Radiation pneumonitis is among the most frequently reported acute complications after STAR and is detected on followup CT, usually at 3 months. According to K. Banfill et al., lung changes occur in about 2030% of patients, mostly benign, with only a few requiring corticosteroids [74].

Risk is higher in patients with preexisting interstitial lung disease. Data from radiotherapy for cancer patients show that the probability of radiationinduced lung injury, including pneumonitis and subsequent fibrosis, depends on total dose and irradiated lung volume (Nuyttens et al., 2016), which should be considered in STAR planning [91].

In experimental settings at high doses (37.5 Gy), severe bronchial complications, including bronchomediastinal fistula, have been described [39].

Coronary arteries and valves

Development of coronary atherosclerosis 23 years after STAR has been reported, especially when vessels are close to the PTV. In such cases, longterm followup with planned ischaemia assessment is advisable.

In the Czech study (Hašková et al., 2024), 25% of patients showed worsening of mitral regurgitation several months after STAR, three requiring surgery [20]. Another observation (M.H. Van der Ree et al., 2023) showed deterioration of valve function by ≥2 grades in some patients at one year [92].

Rapid progression of aortic stenosis has also been reported [89]. Therefore, regular echocardiography is recommended, especially if valves are near the irradiation zone [73].

Interaction with implantable devices

According to a multicentre study, STAR at the employed doses is not associated with clinically significant ICD dysfunction: sensing, pacing thresholds, and impedance remained stable, and a single device reset had no clinical consequences [93].

Nevertheless, distal electrode location should be considered during planning. Irradiation of myocardium at the contact site could theoretically raise pacing thresholds and lead to loss of capture, potentially limiting device therapy.

According to published data, maximum dose to ICD electronic components varied from 0.04 to 0.603 Gy, with mean values around 0.02 Gy. Some authors (e.g., Blanck et al., 2020) recommend limiting the maximum dose to electronics to ≤0.5 Gy [75]. Monitoring dose to device components should be a mandatory part of planning [94].

Mortality

Patients with VT refractory to catheter ablation are at high risk of death. In several studies, oneyear mortality reached 28%, comparable to 32% observed with early VT recurrence after ablation [95]. VT itself may be both a cause of death and a marker of progressive heart failure. In the VANISH trial comparing ablation with pharmacotherapy, oneyear mortality was 1015%, with no significant difference between groups [96]. Similar data are reported by a metaanalysis, whereas an individualised metaanalysis showed a significant mortality reduction after ablation [97, 98]. Most patients included in recent SBRT studies had previously undergone multiple ablations, reflecting the severity of their condition. Many were not considered candidates for further procedures and thus could not be included in traditional randomised trials. According to a metaanalysis, more than half of deaths within one year after STAR were due to heart failure progression, and only 6.5% to arrhythmia recurrence [82]. Therefore, the impact of STAR itself on survival remains to be determined.

FUTURE DIRECTIONS

One of the key technical limitations of STAR is cardiac and respiratory motion. Displacement of the arrhythmogenic substrate reduces dose delivery accuracy and may lead to underdosing of PTV periphery. This is especially critical when using high doses on small volumes.

In an experiment by C.Q.M. Reis et al., a gating system (beam delivery synchronised with a specific respiratory or cardiac phase) synchronised with ECG was tested using a dynamic phantom simulating heart and lung motion [75]. Results showed high concordance of delivered dose with the plan (up to 9899% gamma pass rate) with ECG gating, whereas without motion management accuracy dropped to 5567% (especially with combined heart and respiration).

These findings underscore the importance of implementing gating and/or tracking in clinical STAR, particularly when the target is near radiosensitive structures. The authors noted stable operation of the TrueBeam linear accelerator in highfrequency intermittent mode, critical for singlefraction delivery. Although the study used a physical model (no living patient) and limited scenarios, it convincingly demonstrates the advantages of motion management technologies. Clinical implementation of such systems - ECG synchronisation, optical myocardial tracking, robotic tracking systems - may improve precision and safety, especially for targets near critical structures.

STAR is an innovative and rapidly evolving method whose clinical potential requires thorough investigation in wellcontrolled studies. Its efficacy should be evaluated in the context of current progress in invasive electrophysiology, including the introduction of pulsed field ablation and ultralow temperature cryoablation.

A key nearterm priority remains the conduct of highquality prospective and comparative studies. These should include detailed characterisation of patient clinical profiles, description of antiarrhythmic therapy used, ablation data, and selection criteria. Standardised monitoring of arrhythmia recurrence, survival, and other clinically relevant cardiac outcomes is essential. Special attention should be paid to longterm monitoring of cardiac and valve function, as well as systematic recording of radiotherapy complications using unified terminology. In this context, international initiatives such as the STOPSTORM consortium can play a leading role in harmonising methodological approaches and standardising reporting.

Despite accumulated evidence, several fundamentally important unresolved questions remain. First, a deeper understanding of the molecular and electrophysiological mechanisms of STAR action is required - including effects on the conduction system, ion channel expression and function, microcirculation, inflammatory response, and neurocardiac interactions. Second, the optimal dosing and fractionation regimen, including the possibility of reirradiation for recurrences, needs to be defined. Determining the radiosensitivity of the arrhythmogenic substrate and the timing of clinical effect is of paramount importance.

Furthermore, the choice of optimal target and targeting strategy remains open. Is it more appropriate to irradiate the entire scar zone or only the critical reentry circuit components? Validation of methods for integrating imaging data with electrophysiological and functional studies, including assessment of noninvasive EAM (ECGI) accuracy compared with invasive guidance, is needed.

Detailed analysis of the effect of STAR on myocardium, coronary arteries, and valves requires longterm observation and meticulous evaluation of delayed effects. Only on the basis of such data can the true safety profile be determined.

A decisive step in proving STAR's effectiveness will be the conduct of randomised trials comparing it with conventional treatment modalities in various clinical scenarios. This includes comparison with repeat catheter ablation in patients with failed primary intervention, as well as with catheter ablation in highrisk patients. If efficacy is confirmed in these groups, STAR could be considered as a firstline therapy in certain patient categories.

Thus, while possessing significant potential as a noninvasive alternative in malignant arrhythmia treatment, STAR requires further validation based on robust, reproducible data. Expansion of its role in clinical practice should rely exclusively on results from highlevel randomised and multicentre studies.

LIMITATIONS AND PROSPECTS FOR STAR IMPLEMENTATION IN THE RUSSIAN FEDERATION

Despite encouraging clinical results from leading foreign centres, widespread implementation of STAR in routine clinical practice in the Russian Federation is currently limited by several systemic and technical factors. The procedure requires specialised equipment, primarily linear accelerators with STAR capabilities, as well as a wellfunctioning multidisciplinary team including an arrhythmologist, radiotherapist, radiologist, medical physicist, and cardiac imaging specialist [99]. Such infrastructure is currently available only in a limited number of centres, substantially reducing reproducibility.

Moreover, STAR is not yet included in the clinical guidelines of the Ministry of Health of the Russian Federation and does not have official status as an approved medical technology. This restricts its use in routine practice, precludes funding within the compulsory health insurance system, and complicates the unification of patient selection and procedural approaches. Significant challenges also relate to imaging: precise target definition considering cardiorespiratory motion requires hightech methods such as 4DCT, ECGsynchronised studies, and integration of anatomical and electrophysiological data. The absence of such capabilities in some centres negatively affects planning quality and, consequently, potential treatment efficacy.

In addition, the lack of national clinical protocols and guidelines forces clinicians to adapt foreign approaches, which is not always feasible given domestic infrastructure specifics. The absence of longterm national followup data, especially regarding delayed complications (effects on conduction system, coronary arteries, valves), necessitates particular caution in patient selection, limiting the use of the method in patients with predictably long life expectancy. Nevertheless, prerequisites for STAR development already exist in Russia. The first clinical procedure in the country was successfully performed by a multidisciplinary team led by A.Sh. Revishvili and A.V. Golanov using a TrueBeam linear accelerator.

In the future, the development of the method will be facilitated by establishing a regulatory framework, expand-

ing the number of centres with the necessary competence, and integrating Russian institutions into international research consortia. With institutional support and continued clinical piloting, STAR may occupy an important place in the therapy of refractory ventricular arrhythmias, especially when conventional approaches have been exhausted.

CONCLUSION

STAR is one of the most discussed innovative approaches for the treatment of refractory VTs. To date, published data demonstrate a marked reduction in arrhythmia burden after a single 25Gy fraction. Initial clinical results are encouraging, particularly in patient groups where other methods have failed or are technically impossible.

However, the method remains novel and insufficiently studied. In some cases, VT recurrences occur within the firstsecond year of followup, and the impact on longterm survival and cardiac function remains an open question. It must also be considered that the procedure requires a high degree of technical equipment and coordination among specialists, as well as individual patient selection with mandatory multidisciplinary discussion.

Nevertheless, the potential of the method is evident. With continued scientific support and accumulation of clinical experience, STAR may establish a solid place among treatment strategies for patients with severe, resistant ventricular arrhythmias - primarily as a noninvasive alternative in highrisk cases.

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PROFESSOR DMITRY SERGEEVICH LEBEDEV
(for the 60th anniversary)

Professor of the Russian Academy of Sciences Dmitry Sergeevich Lebedev is an outstanding arrhythmologist and electrophysiologist who laid the foundation of a scientific and practical school that transformed the approaches to diagnosis and treatment of cardiac arrhythmias in Russia. His contribution combines fundamental research, innovative technologies, and the training of a new generation of specialists.

Dmitry Sergeevich Lebedev was born on 21 June 1966 in Leningrad into a family of naval officers and surgeonphysicians. In 1989, he graduated from the First Leningrad Medical Institute named after Academician I.P. Pavlov (now the First Saint Petersburg State Medical University named after Academician I.P. Pavlov), where he continued his training in internship and residency in cardiovascular surgery. As early as 1994, he defended his Candidate of Sciences (PhD) dissertation, and in 2004 his Doctor of Sciences dissertation on the topic “Improvement and evaluation of the effectiveness of diagnosis and surgical treatment of lifethreatening cardiac arrhythmias”.

In 1997, D.S. Lebedev completed an internship at Toronto General Hospital (Toronto, Canada), where he mastered advanced methods of tachyarrhythmia treatment and research organisation. Since 2006, he has headed the Department of Arrhythmology at the Almazov National Medical Research Centre - the successor to the laboratory established in 1986 by order of Professor V.A. Almazov, director of the Leningrad Research Institute of Cardiology. During his career, Dmitry Sergeevich has personally performed over 10,000 complex interventions, annually carrying out more than 250 operations in both adults and children. His personal experience blends clinical practice with science: from an emergency physician in the 1990s to the Chief Freelance Arrhythmologist of the Ministry of Health for the NorthWestern Federal District.

Professor D.S. Lebedev is a pioneer in the introduction of radiofrequency ablation in Russia. With his participation, a pulsedmode radiofrequency ablation technique was proposed, and a device for ablation with pulsed current was developed, allowing safer and more effective destruction of arrhythmogenic foci compared with traditional methods. Hightech methods have been introduced into clinical practice: threedimensional electroanatomical mapping, cryoablation, robotassisted ablations, and noninvasive mapping, enabling visualisation of the arrhythmic substrate and the role of fibrosis. Research on neuromodulation is opening up new pathways for the treatment of heart failure and hypertension.

D.S. Lebedev is the author of 16 patents, including methods for predicting arrhythmias and optimising cardiac resynchronisation therapy. His developments have been integrated into national clinical guidelines in cardiology. With the participation of Dmitry Sergeevich, a new direction was established - the diagnosis and treatment of cardiac arrhythmias in children at the Almazov National Medical Research Centre, where more than 150 arrhythmological operations are performed annually in children.

Professor D.S. Lebedev has created a strong school of specialists in arrhythmology. Under his supervision, 5 Doctors of Sciences and 10 Candidates of Sciences have been trained in the specialties “Cardiology” and “Cardiovascular Surgery”. In 2022, he founded and heads the educational centre “Academy of Arrhythmology” at the Almazov National Medical Research Centre, with authorled courses on complex arrhythmias.

Under the leadership of Dmitry Sergeevich, regular international scientific conferences have been established - “Sudden Cardiac Death” (since 1996) and the “Saint Petersburg Arrhythmology Forum” (since 2016), as well as the annual Saint Petersburg School of Arrhythmology (since 2011). In 2021, under his guidance, the 9th AllRussian Congress of Arrhythmologists was held. Colleagues not only from all over Russia, but also leading specialists from worldclass

clinics and universities eagerly come to Saint Petersburg for joint work and friendly interaction with Dmitry Sergeevich and his team.

The professional community has highly appreciated Dmitry Sergeevich's contributions to healthcare and science: he is VicePresident of the Russian Scientific Society of Arrhythmologists and Chairman of the Saint Petersburg Branch of the Russian Scientific Society of Arrhythmologists, a member of the Board of the Russian Society of Cardiology, a member of international professional societies - the Heart Rhythm Society, the European Heart Rhythm Association, and a member of the editorial boards of prestigious journals - Russian Journal of Cardiology, Journal of Arrhythmology.

D.S. Lebedev is an Honoured Scientist of the Russian Federation (2018), a Professor of the Russian Academy of Sciences (2016), and a recipient of the Order of Pirogov (2025). In 2023, he was awarded the I.P. Pavlov Prize of the Government of Saint Petersburg in Physiology and Medicine. The author of more than 400 publications and 13 monographs, Dmitry Sergeevich is an expert of the Russian Science Foundation and the Higher Attestation Commission. His scientific and practical school is the foundation of progress in Russian arrhythmology, where fundamental discoveries translate into clinical practice, saving lives from arrhythmias, heart failure decompensation, and the risk of sudden death.

Dmitry Sergeevich's students and colleagues congratulate him on his jubilee and wish him inexhaustible energy and good health!

PROFESSOR YURY VIKTOROVICH SHUBIK
(for the 70th anniversary**)**

Yury Viktorovich Shubik, a physician of the third generation and one of Russia's leading cardiologists and arrhythmologists, was born in 1956 in Leningrad. After graduating in 1979 from the First Saint Petersburg State Medical University (First Leningrad Medical Institute) named after Academician I.P. Pavlov, he worked until 1983 as a physician on the intensive care team of the emergency medical service, and then from 1984 to 1985 as a senior resident in the intensive care unit of the infarction department of City Hospital No. 25. From 1985 to 2001 he worked at the Research Institute of Cardiology of the Ministry of Health of the Russian Federation, where he initially headed the telediagnostic cardiology center, and in 1986 he organised and took charge of the electrophysiology laboratory. Subsequently, he held positions of junior, senior and leading research fellow, and headed the department of cardiac arrhythmias. From 2001 to 2012 he worked as a professor at the Department of Cardiology of the Faculty of Postgraduate Training of the NorthWestern State Medical University (Saint Petersburg State Medical Academy) named after I.I. Mechnikov, and from 2012 to 2025 as the head of the Department of Arrhythmology of the Scientific, Clinical and Educational Centre "Cardiology" of Saint Petersburg State University. In 2001, he founded the NorthWestern Centre for Diagnosis and Treatment of Cardiac Arrhythmias, which continues to operate actively to this day. Currently, Yu.V. Shubik is its scientific supervisor. Over the 25 years of the NorthWestern Centre for Diagnosis and Treatment of Cardiac Arrhythmias, more than 150,000 patients with complex cardiac rhythm and conduction disorders have received qualified outpatient and inpatient care there - not only from Saint Petersburg and the Leningrad region, but also from other regions of Russia, the CIS countries, and beyond.

In 1988, Yu.V. Shubik defended his Candidate of Sciences (PhD) dissertation, and in 1996 his Doctor of Sciences dissertation in the specialty "Cardiology". In 2007, he was awarded the academic title of Professor in the same specialty. Yury Viktorovich is the author of 450 scientific publications, including 25 monographs and book chapters, more than 20 teaching aids and methodological guidelines. Cardiologists, internists and specialists in functional diagnostics are well familiar with the monographs written by him alone or with colleagues: «Daily ECG Monitoring in Cardiac Rhythm and Conduction Disorders», «Holter Monitoring in Arrhythmias», «Noninvasive Electrophysiological Study in Anomalies of the Cardiac Conduction System (Atlas)», «Transesophageal Electrocardiography and Pacing», «Clinical Lectures on Selected Problems of Cardiology» in 4 volumes, «Cardiology Practicum (Collection of Clinical Case Reviews) in 2 volumes, «Antithrombotic Therapy in Cardiovascular Diseases», and others. His "nonmedical" publications in the journal Zvezda, as well as the books «A Different View of Arrhythmias», «Doctor's Sausage», the collection of short stories «Sausage Scraps», «Medical Exlibris», «Optional Information about Arrhythmias for Intelligent Doctors and Patients», «About Atrial Fibrillation - for Patients and Their Relatives», etc., are also well known to physicians.

Yury Viktorovich Shubik is a member of the Board of the AllRussian Scientific Society of Arrhythmologists, a member of the Presidium of the Russian Society of Holter Monitoring, and Deputy Chairman of the Cardiac Arrhythmias Section of the Russian Society of Cardiology. For many years, he has been a member of the Editorial Board of the Journal of Arrhythmology, the editorial boards of University Therapeutic Journal and Medical Alliance, and the Chairman of the Editorial Council of the journal Cardiology: News, Opinions, Training. Yury Viktorovich is a member of working groups and expert councils involved in the development of Russian national guidelines on the diagnosis and treatment of atrial fibrillation, supraventricular tachycardias, ventricular arrhythmias, prevention of sudden cardiac death, and Holter monitoring.

Yu.V. Shubik devotes considerable attention to clinical work. In addition to his ongoing consultative practice at the NorthWestern Centre for Diagnosis and Treatment of Cardiac Arrhythmias, he serves as a consultant arrhythmologist for

a number of inpatient facilities in Saint Petersburg. As part of the mobile School of Arrhythmology, together with M.M. Medvedev, he has repeatedly travelled to most regions of Russia - from Kaliningrad to Kamchatka - providing cardiology consultations and lectures. For 25 years, Yu.V. Shubik has been one of the lecturers of the Saint Petersburg School of Cardiologists project.

Yury Viktorovich is married, has two children and four grandchildren. The Editorial Board of the Journal of Arrhythmology, his friends, colleagues and students are pleased to congratulate Yury Viktorovich Shubik on his jubilee and wholeheartedly wish him health, happiness, and continued success in his scientific, clinical and teaching work.