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# CONTENT

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# EFFICIENCY OF CARDIOVERSION IN PERSISTENT ATRIAL FIBRILLATION AND MAINTENANCE OF SINUS RHYTHM IN THE LONG-TERM PERIOD IN PATIENTS WITH MYOCARDITIS

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**Aim.** To compare the immediate and long-term efficacy of cardioversion in patients with persistent atrial fibrillation (AF) in the setting of active myocarditis versus those without myocardial inflammation.

**Methods.** The study included 80 patients with persistent atrial AF (mean age 58.39±14.3 years; 56.2% male), of whom 40 had biopsy- or magnetic resonance imaging-confirmed myocarditis, elevated antimyocardial antibody titers, and ≥3 points on a non-invasive myocarditis diagnostic algorithm (main group). The control group (n=40) consisted of patients with non-inflammatory cardiovascular diseases (coronary artery disease, hypertension). All patients with myocarditis received standard anti-inflammatory therapy. Following pre-treatment with amiodarone for 10-12 days, electrical cardioversion (ECV) was performed. The efficacy of ECV, the need for radiofrequency ablation (RFA), the incidence of persistent AF, and adverse outcomes were evaluated. Differences were considered statistically significant at $p<0.05$.

**Results:** Patients in the myocarditis group were characterized by a higher proportion of males (80.0% vs. 32.5%), younger age (49.1±12.0 vs. 67.7±9.5 years), lower left ventricular ejection fraction (LVEF) (37% [30;41] vs. 56% [52;59]), and larger left ventricular end-diastolic volume (152 ml [119;184] vs. 89 ml [76;106]), all with $p<0.001$. The duration of AF history and left atrial size did not differ significantly between groups. Only in the myocarditis group did spontaneous sinus rhythm (SR) restoration occur during amiodarone loading, observed in 17.5% of cases. ECV was successful on the first attempt in all patients of the control group and in 57.5% of patients with myocarditis; an additional 15% achieved SR with a second ECV attempt ($p<0.001$). Reversible recurrences of AF, terminated by intravenous amiodarone, were observed in 20% of myocarditis patients versus 5% in the control group ($p=0.012$). By the end of the one-week observation period, irreversible recurrences were recorded in two patients in each group. LVEF improved more significantly in the myocarditis group (to 42% [33;49], $p<0.001$). At six months post-ECV, SR was maintained in 50% of patients with myocarditis and 66.5% in the control group ($p=0.530$). Rhythm control was discontinued in 15% of patients with myocarditis and in 5% of the control group ($p=0.547$), and radiofrequency ablation was performed in 10% and 5% of patients, respectively ($p=0.509$). All-cause mortality was documented in 12.5% (n=5) of myocarditis patients. No thromboembolic events or heart transplantations were reported in either group.

**Conclusion:** AF in the context of myocarditis more commonly affects individuals of working age and worsens LV systolic dysfunction. The immediate and long-term efficacy of ECV was non-significantly lower in patients with myocarditis; however, successful restoration and maintenance of SR were associated with a more pronounced improvement in LVEF, supporting the rationale for a rhythm control strategy. Further research is planned to identify predictors of sustained SR in this population.

**Key words:** persistent atrial fibrillation; myocarditis; electropulse therapy; electrical cardioversion; antiarrhythmic therapy; left ventricular systolic dysfunction.

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According to the definition proposed by N.R. Paleev (1997), myocarditis is an inflammatory disease of the myocardium caused by the direct or immune-mediated effects of infection, parasitic or protozoal invasion, chemical or physical factors, as well as myocardial involvement occurring in allergic and autoimmune diseases [1]. In the definition provided by Russian experts in the 2023 Ministry of Health clinical guidelines, particular emphasis is placed on the wide spectrum of clinical manifestations of myocarditis, ranging “from an asymptomatic course, mild dyspnoea, and non-intense chest pain resolving spontaneously, to heart failure, cardiogenic shock, life-threatening arrhythmias, and sudden cardiac death” [2]. Among the typical complications of myocarditis, atrial fibrillation (AF) occupies a prominent place.

The same clinical guidelines state that the development of AF - either persistent or paroxysmal - in the ab-

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sence of ischaemic heart disease, a history of arterial hypertension, or valvular heart disease allows myocarditis to be suspected with a high degree of probability [2]. While the available literature includes studies assessing the incidence of arrhythmias, including AF, in the setting of active myocarditis, none specifically address the efficacy of cardioversion in this patient population.

A multicentre retrospective study conducted in the United States in 2019 demonstrated that AF was documented in 602 patients (9%) out of 6,642 individuals with acute myocarditis, with a predominance of male patients (61.3%). In this cohort, AF was associated with significantly prolonged hospitalisation, a higher incidence of acute heart failure, and increased mortality [3].

A 2021 review encompassing 65 studies showed that AF is the most common cardiac arrhythmia in patients with COVID-19, sepsis, or acute respiratory distress syndrome. Among patients with a prior history of AF, arrhythmia recurrence was observed in 23–33%, while approximately 10% developed AF for the first time [4]. Management strategies depended on the patient's clinical condition, in line with current guidelines: haemodynamically unstable patients underwent urgent cardioversion. However, in the context of coronavirus infection, myocarditis is only one of several potential mechanisms contributing to the onset or exacerbation of AF.

Since AF occurring in the setting of active myocarditis makes a significant contribution to left ventricular (LV) systolic dysfunction, aggravates the course of heart failure, and leads to recurrent hospitalisations, a rhythm-control strategy using electrical cardioversion (ECV) may be justified in this patient population. The relative simplicity of the ECV procedure and its safety, provided that the established protocol is followed, make it an attractive method for AF termination [5]. At the same time, it is essential to protect patients from unjustified attempts at cardioversion in clinical situations where the risk of early AF recurrence is predictably high.

The first attempts to predict unfavourable factors for maintenance of sinus rhythm date back to the 1960s. A.V.

***Table 1.***

***Clinical and functional parameters of patients in the main group and the comparison group at admission***

| | Main group | Comparison group | p |
|---|---|---|---|
| Follow-up duration, months | 22 [7;50] | 6 [6;7] | <0.001 |
| Age, years | 49.1±12.0 | 67.7±9.5 | <0.001 |
| Male sex, n (%) | 32 (80) | 13 (32.5) | <0.001 |
| Body mass index, kg/m$^2$ | 27 [26;32] | 31 [27;36] | 0.010 |
| Grade of arterial hypertension | 0[0;2] | 3[2;3] | <0.001 |
| NIMDA score (points) | 7[6;8] | 1[1;2] | <0.001 |
| Duration of AF history, weeks | 26 [8;58] | 24 [4;57] | 0.370 |
| Time since last AF episode, weeks | 10 [4;30] | 8 [4;16] | 0.380 |
| Number of AF episodes per year | 1 [1;2] | 1 [1;2] | 0.970 |
| History of LAA thrombosis, n (%) | 8 (20.0) | 3 (7.5) | 0.105 |
| HR on admission (AF), bpm | 104.5±23.6 | 99.8±22.6 | 0.360 |
| PVCs per 24 h | 213 [55;1300] | 44 [1;91] | 0.021 |
| Low QRS voltage, n (%) | 5 (12.5) | 0 | 0.021 |
| Low RV1-V6 amplitude, n (%) | 30% (n=12) | 0 | <0.001 |
| QRS duration, ms | 96.5[90;111] | 92.5[83;101] | 0.360 |
| Corrected QT interval (QTc), ms | 450[422;469] | 450[429;461] | 0.710 |
| LVEDD, cm | 5.9±0.7 | 4.9±0.4 | <0.001 |
| LVEDV, mL | 152 [119;184] | 89 [76;106] | <0.001 |
| LVEDV/BSA, mL/m$^2$ | 70 [59;86] | 51[44;58] | 0.013 |
| LVESV, mL, мл | 89 [66;137] | 39 [30;47] | <0.001 |
| LVEF, % | 37 [30;41] | 56 [52;59] | <0.001 |
| VTI, см | 11.2±3.1 | 16.7±3.8 | <0.001 |
| LA diameter, cm | 4.56±0.67 | 4.39±0.50 | 0.280 |
| LA volume, mL | 92 [79;104] | 84 [72;92] | 0.073 |
| LA volume/BSA, mL/m$^2$ | 42 [39;56] | 38 [45;39] | 0.370 |
| RA volume, mL | 74 [56;88] | 65 [60;79] | 0.360 |
| RV diameter, cm | 3[2.9;3.6] | 3[2.8;3.5] | 0.440 |
| Mitral regurgitation grade | 1 [1;2] | 1 [1;1.5] | 0.280 |
| mPAP, mmHg | 30 [25;40] | 33 [29;38] | 0.318 |
| Leukocytes, ×10$^9$/L | 7.1±1.9 | 6.75±1.7 | 0.350 |
| Hemoglobin, g/L | 151.7 ±2.56 | 143 ±14.8 | 0.007 |
| CRP, mg/mL | 3 [1.3;5.6]. | 2.4 [1.3;4.2] | 0.400 |
| Fibrinogen, g/L | 3.5 [3.1;4.0] | 3.0 [2.6; 3.3] | 0.011 |
| ESR, mm/h | 6.5 [5;10] | 10 [6;20] | 0.012 |
| TSH, μIU/mL | 2.5[1.8;3.5] | 2[1.8;3.2] | 0.117 |

Notes: NIMDA - non-invasive myocarditis diagnostic algorithm; AF - atrial fibrillation; LAA - left atrial appendage; LA - left atrium; HR - heart rate; PVCs - premature ventricular contractions; LVEDD - left ventricular end-diastolic diameter; LVEDV - left ventricular end-diastolic volume; BSA - body surface area; LVESV - left ventricular end-systolic volume; LVEF - left ventricular ejection fraction; VTI - velocity time integral; RA - right atrium; RV - right ventricle; mPAP - mean pulmonary artery pressure; CRP - C-reactive protein; ESR - erythrocyte sedimentation rate; TSH - thyroid-stimulating hormone.

Nedostup et al. proposed selection criteria for electroimpulse therapy of AF, in which a substantial role was assigned to anamnestic factors, including the duration of sinus rhythm maintenance during previous episodes, the number of AF paroxysms in the medical history, and other parameters [6]. Almost all contraindications to ECV identified at that time-factors reducing its effectiveness or rendering the procedure impractical or unsafe-have retained their clinical relevance to this day. Among these factors, active inflammatory processes (predominantly rheumatic in origin at that time) were considered particularly important.

Since then, the spectrum of myocarditis aetiologies has changed considerably. However, no studies have evaluated the course of AF, the appropriateness, or the efficacy of cardioversion in myocarditis in comparison with AF associated with other forms of heart disease. Moreover, there are no studies assessing long-term maintenance of sinus rhythm after ECV in patients with myocarditis or identifying its predictors. These gaps in evidence underscore the high clinical relevance of the present study.

The aim of this study is to assess the efficacy of cardioversion and long-term maintenance of sinus rhythm in patients with persistent AF and myocarditis, compared with patients with persistent AF associated with non-inflammatory heart diseases.

## MATERIALS AND METHODS

A retrospective and prospective study included 80 patients (mean age 58.39 ± 14.3 years; 43.8% women and 56.2% men) admitted to the V.N. Vinogradov Faculty Therapy Clinic of Sechenov University with persistent AF between 2017 and 2024. Patients were divided into a main group (40 patients with myocarditis) and a comparison group (40 patients with non-inflammatory heart diseases).

Inclusion criteria for the main group were age ≥18 years, persistent AF scheduled for electrical cardioversion, and a diagnosis of active myocarditis, established on the basis of:

- endomyocardial biopsy (EMB) with myocarditis diagnosed according to the Dallas morphological criteria, supplemented by immunohistochemical criteria; or
- non-invasive diagnostic criteria, including a diagnostically significant ≥3-fold increase in anticardiac antibody (ACA) titres in combination with the 2018 Lake Louise criteria for cardiac magnetic resonance imaging (MRI) and a score of ≥3 points according to the non-invasive myocarditis diagnostic algorithm (excluding ACA titres) [7-9].

Exclusion criteria for the main group included a history of acute coronary syndrome or myocardial infarction, infective endocarditis within the preceding 6 months, acquired valvular heart disease, hypertrophic, restrictive, non-compaction, or arrhythmogenic cardiomyopathy, a history of thyrotoxicosis, prior open-heart surgery of any duration, verified cardiac sarcoidosis, lymphoproliferative disorders, and prior anthracycline-based chemotherapy.

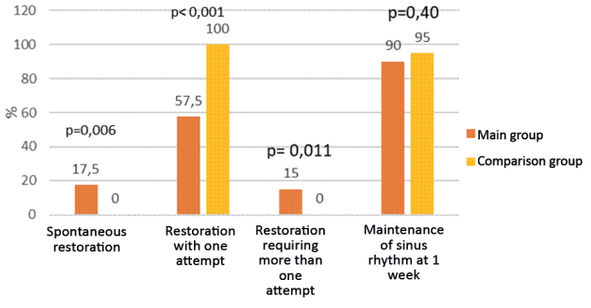


***Figure 1. Immediate efficacy of electrical cardioversion.***

Patients aged ≥18 years with persistent AF scheduled for cardioversion and non-inflammatory heart diseases were included in the comparison group. Non-inflammatory conditions comprised idiopathic AF, arterial hypertension, and coronary artery disease, excluding myocardial infarction within the preceding 6 months.

Patients were excluded from the comparison group if myocarditis was diagnosed on the basis of EMB and/or the 2018 Lake Louise MRI criteria for myocarditis, in combination with a score of ≥4 pointsaccording to the non-invasive myocarditis diagnostic algorithm (including elevated ACA titres), as well as in cases of exudative pericarditis or the presence of any of the exclusion criteria defined for the main group.

General exclusion criteria for both groups also included established contraindications to ECV, such as intracardiac thrombosis, duration of the current AF episode exceeding 3 years, thyrotoxicosis, a history of sick sinus syndrome or second- or third-degree atrioventricular block, as well as patient refusal to undergo ECV.

Non-inclusion criteria were refusal to participate in the study, pregnancy, breastfeeding, intellectual disability, legal incapacity, and decompensated psychiatric disorders.

All patients underwent clinical interview and physical examination, standard laboratory testing, assessment of thyroid hormone levels, 12-lead electrocardiography with calculation of the QTc interval, transthoracic echocardiography, and 24-hour Holter ECG monitoring. In addition, coronary angiography or multislice computed tomography (MSCT) of the heart was performed in 30 patients (37.5%).

For verification of myocarditis, ACA levels were measured using indirect immunofluorescence, cardiac magnetic resonance imaging was performed in 19 patients (47.5%), and morphological examination of myocardial tissue was carried out in 15 patients with myocarditis (37.5%), including one post-mortem specimen and EMB samples in the remaining cases.

After assessment of inclusion and exclusion criteria in both groups, patients underwent preparation for planned ECV. Amiodarone was prescribed at a loading dose of 600 mg/day. If atrial fibrillation persisted by day 10-12 of therapy, electrical cardioversion was performed, with assessment of its immediate effectiveness and the number of shocks required to restore sinus rhythm (SR).

The maintenance of sinus rhythm was evaluated at the end of the first week of treatment and at 6 months after discharge, which was considered the measure of long-term cardioversion efficacy, in both groups. In cases of early AF recurrence, intravenous amiodarone infusion was administered.

Patients in the myocarditis group additionally received background therapy for myocarditis. Methylprednisolonewas prescribed to 29 patients (72.5%) at a median dose of 16 [14; 24] mg/day, including 13 patients (32.5%)

who received combination therapy with azathioprine at 150 [88; 150] mg/day or mycophenolate mofetil (n = 3, 7.5%) at 2000 mg/day. Hydroxychloroquine was administered to 9 patients (22.5%) at a dose of 200 mg/day, including two cases in combination with corticosteroids.

Follow-up in the myocarditis group was continued beyond the initial 6 months. At the end of follow-up (mean duration 22 months [7; 50]), the incidence of long-term outcomes was assessed. The primary endpoint was death or heart transplantation. Secondary endpoints included the need for radiofrequency catheter ablation, the development of sustained forms of AF (persistent or permanent), and the incidence of thromboembolic events.

**Statistical analysis**

Data analysis was performed using IBM SPSS Statistics, version 25.0 (IBM Corp., USA). Normality of data distribution was assessed using the Shapiro–Wilk test. Continuous variables are presented as mean ± standard deviation for normally distributed data and as median with interquartile range (Me [Q25; Q75]) when the distribution deviated from normality.

Comparisons of continuous variables were performed using the Student's t-test, Mann–Whitney U test, or Wilcoxon signed-rank test, as appropriate. Categorical variables were analyzed using the $\chi^2$ test or Fisher's exact test, with construction of 2×2 contingency tables where applicable. Differences were considered statistically significant at $p < 0.05$.

The study protocol was approved by the Local Ethics Committee (Protocol No. 02-24, dated 29 January 2024). All patients provided written informed consent for participation in the study, diagnostic procedures, and interventions.

## RESULTS

Clinical characteristics at admission and after cardioversion, as well as the immediate and long-term effectiveness of cardioversion, were analysed. The main clinical characteristics of patients in both groups are presented in Table 1. Patients with myocarditis were characterised by younger age and a predominance of male sex compared with the control group. The duration of atrial fibrillation (AF) history and the time since the last AF episode did not differ between groups. In the myocarditis group, the duration of myocarditis history was 20 [10; 60] weeks.

Patients with myocarditis also demonstrated a higher prevalence of ventricular arrhythmias, low QRS voltage in standard ECG leads, and reduced left ventricular (LV) systolic function parameters prior to ECV, including left ventricular ejection fraction (LVEF) and LV outflow tract velocity–time integral (VTI). Atrial dimensions and volumes did not differ significantly between groups, whereas LV dimensions were significantly largerin the myocarditis group.

No significant differences were observed between groups in leukocyte count, leukocyte differential, or C-reactive protein levels. A higher fibrinogen level was noted in the myocarditis group; however, mean values remained within the normal range. Immunological activity of myocarditis was assessed by circulating anticardiac antibody (ACA) titres. The highest titres were observed for antibodies against smooth muscle antigens and conduction system fibres, with a mean titre of 1:160 [80; 160]. Antibodies to cardiomyocyte nuclear antigens (specific antinuclear factor) were detected in 52.5% (n = 21) of patients, with a mean titre of 1:40 [0; 80].

According to cardiac MRI, late gadolinium enhancement in patients with non-ischaemic AF was detected in 73.7% (n = 14). Myocardial oedema was identified in 2 patients (10.5%), and increased trabeculation not meeting criteria for non-compaction cardiomyopathy was observed in 2 patients (10.5%).

During amiodarone loading as preparation for ECV, spontaneous restoration of SR occurred in 7 patients (17.5%) in the myocarditis group. No association was found between spontaneous SR restoration and AF recurrence within one week after ECV (r = 0.166, p = 0.145). In the control group, spontaneous SR restoration during amiodarone loading was not observed.

If AF persisted after 10–12 days of amiodarone loading, planned ECV was performed. In the myocarditis group, SR was restored with a single 200-J shock in 57.5% (n = 23) of patients, whereas in the control group ECV was successful on the first attempt in all patients (100%). More than one shock was required in 6 patients in the myocarditis group (mean 2.7 attempts). In one of these patients SR was not restored immediately, but spontaneous restoration occurred after 2 months on continued amiodarone therapy. In another patient, ECV was ineffective with persistent AF during follow-up (Figure 1).

The number of reversible AF recurrences within the first week after ECV or spontaneous SR restoration was higher in the myocarditis group (8 cases), 2 of which required repeat ECV (Figure 2). In the control group, one episode of sustained AF paroxysm was recorded and successfully terminated with intravenous amiodarone.

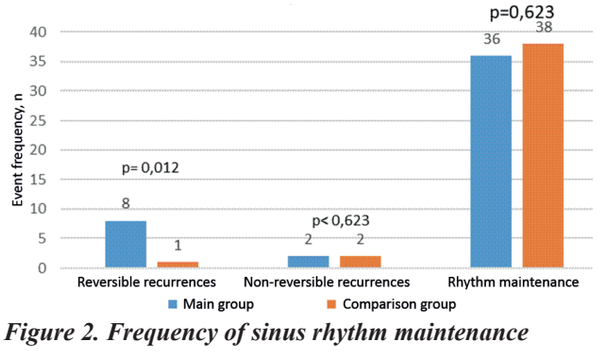


***Figure 2. Frequency of sinus rhythm maintenance one week after electrical cardioversion or spontaneous restoration of sinus rhythm.***

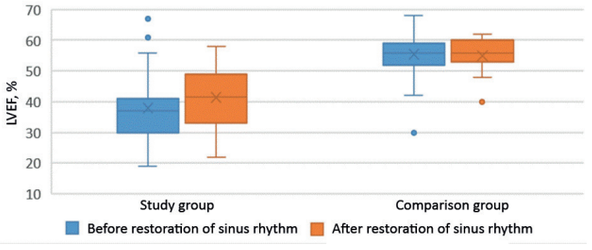


***Figure 3. Changes in left ventricular ejection fraction (LVEF) in the study groups one week after electrical cardioversion or spontaneous restoration of sinus rhythm (SR).***

Within the first week after cardioversion or spontaneous SR restoration, the number of irreversible AF recurrences at discharge did not differ between groups and amounted to 2 cases in each group. Thus, the overall rate of SR maintenance at one week was 36 patients in the myocarditis group and 38 patients in the control group.

One week after cardioversion, LVEF increased in both groups. In the myocarditis group, LVEF increased from 37 [30; 41]% to 42 [33; 49]% ($p < 0.005$), which was clinically significant, while in the control group it increased from 56 [52; 59]% to 57 [52; 60]% ($p = 0.085$) (Figure 3). In the myocarditis group, a significant reduction in LV end-systolic volume was also observed, from 89 [66; 137] to 85 [65; 136] mL ($p = 0.025$).

Long-term outcomes at 6 months after cardioversion were assessed in all patients in the myocarditis group and in 27 patients in the control group. The rate of SR maintenance was 50% (n = 20) in patients with myocarditis and 66.5% (n = 18) in the control group ($p = 0.45$). Radiofrequency ablation was performed more frequently in the myocarditis group. In the control group, rhythm-control strategy was discontinued in two cases. No thromboembolic events were recorded in either group (Table 2).

The follow-up duration in the myocarditis group exceeded 6 months and averaged 22 [7; 50] months. One year after cardioversion, atrial fibrillation (AF) recurrences were documented in 32 patients (80%) with myocarditis. In five of these patients, recurrence was associated with self-discontinuation of therapy, while in two cases it was related to documented amiodarone-induced thyrotoxicosis.

In six patients (15%) from the myocarditis group, a decision was made to abandon an active rhythm-control strategy. Radiofrequency ablation (RFA) for arrhythmia management was performed at any time during follow-up in eight patients (20%). No thromboembolic events were recorded during the long-term follow-up period.

There were no cases of heart transplantation throughout the entire follow-up period. All-cause mortality occurred in 12.5% (n = 5) of patients with myocarditis. The immediate causes of death were end-stage chronic heart failure in three cases, myocardial infarction due to late stent thrombosis in one case, and septic complications of immunosuppressive therapy in one patient.

## DISCUSSION

Atrial fibrillation (AF) is frequently a complication and, in some cases, the sole clinical manifestation of myocarditis. Both the clinical guidelines of the Ministry of Health of the Russian Federation and the multicentre study by A. Subahi et al. report a younger age and predominance of male patients among individuals with myocarditis, which is fully consistent with our findings and underscores the relevance of the present study [3].

A distinctive feature of this work was the application of maximally stringent inclusion criteria, including the exclusion of other primary myocardial diseases, toxic myocardial injury, thyrotoxicosis, as well as the active exclusion of myocarditis in the comparison group using a minimal score according to the non-invasive myocarditis diagnostic algorithm.

Analysis of baseline clinical characteristics revealed no significant differences in atrial size or volume between the two groups. In both groups, the atria were moderately enlarged, slightly more so in patients with myocarditis, but did not reach threshold values traditionally considered a contraindication to ECV or significantly reducing its clinical justification. In both early and subsequent studies, A. V. Nedostup et al. proposed a left atrial linear diameter of 5.5–6.0 cm as a critical threshold [6]. Numerous later studies have repeatedly confirmed the prognostic value of left atrial size for cardioversion outcomes in AF. Nevertheless, in our study, moderate atrial enlargement did not preclude ECV [10]. The absence of intergroup differences in this key parameter increased group comparability by eliminating the influence of one of the most extensively studied predictors of AF recurrence, although full matching of the groups was not pursued, as the primary comparison was based on AF aetiology.

A significantly larger LV volume was observed in the myocarditis group, reflecting inflammatory myocardial dysfunction and correlating with reduced LV contractility, as evidenced by lower LVEF and LV outflow tract velocity-time integral (VTI). Notably, despite a comparable degree of tachysystole (mean heart rate 100–105 bpm), similar AF history duration, and comparable duration of the current AF episode, patients in the comparison group (without myocarditis) demonstrated minimal LV dilatation and preserved systolic function. This finding further emphasizes the necessity of actively searching for the underlying aetiology of AF in patients with LV dysfunction and highlights the inadequacy of attributing LV impairment solely to “tachycardia-induced cardiomyopathy”.

The present study provides an answer to the clinically important question of the appropriateness of cardioversion in patients with persistent AF in the setting of active myocarditis. To our knowledge, no prior studies have specifically addressed this issue. Earlier investigations evaluating ECV outcomes suggested that not only high (grade II–III) activity of rheumatic inflammation, but even minimal (grade I) activity, reduced the efficacy of cardioversion and worsened prognosis [6]. In contrast, despite pronounced morphological and immunological activity of myocarditis in our cohort, the immediate success rate of

***Table 2.***

***Achievement of study endpoints at 6 months of follow-up***

| | Main group | Comparison group | p |
|---|---|---|---|
| Death, n (%) | 2 (5) | 0 | 0.376 |
| Heart transplantation, n (%) | 0 | 0 | - |
| Radiofrequency ablation, n (%) | 4 (10) | 2 (5) | 0.509 |
| Discontinuation of rhythm control strategy, n (%) | 0 | 2 (5) | 0.152 |
| Thromboembolic complications, n (%) | 0 | 0 | - |

ECV and the rate of sinus rhythm maintenance one week after cardioversionwere relatively high and comparable to those observed in patients with AF due to non-inflammatory cardiac diseases.

In addition, in patients with myocarditis and baseline left ventricular (LV) dysfunction, we observed a rapid and statistically significant increase in left ventricular ejection fraction (LVEF) within the first days following successful cardioversion, a phenomenon that was not observed in the comparison group. This finding confirms the substantial contribution of atrial fibrillation (AF) to the aggravation of LV dysfunction specifically in patients with myocarditis and provides a strong argument in favour of a rhythm-control strategy with restoration of sinus rhythm (SR).

Multicentre studies have demonstrated that elimination of AF in patients with LV dysfunction leads to a greater improvement in LVEF compared with a passive rate-control approach; however, in those studies the aetiology of heart failure was not specifically analysed, or was oversimplified as being solely a consequence of tachysystole [11]. In our cohort, following cardioversion in patients with myocarditis, LVEF increased but remained reduced, which was primarily attributable to the underlying inflammatory myocardial disease and necessitated continued cardiotropic and disease-modifying therapy.

A characteristic feature of patients with myocarditis was markedly greater rhythm instability compared with the control group. This was reflected both in a high rate of spontaneous restoration of sinus rhythm (17.5%), which was not observed in the comparison group, and in a higher number of reversible AF recurrences, most of which were successfully terminated with intravenous amiodarone. It is likely that myocardial inflammation creates a state of electrical instability and plays a central role in arrhythmogenesis in myocarditis. Among the key mechanisms of arrhythmia development in myocarditis are direct cytopathic injury with cardiomyocyte membrane lysis, myocardial ischaemia due to coronary microvasculitis, and abnormal calcium channel function, the latter bringing myocarditis closer to arrhythmogenic cardiomyopathy in terms of electrophysiological substrate [12].

Nevertheless, rhythm stabilisation was achieved in the majority of patients. During six months of follow-up, the rate of sinus rhythm maintenance in patients with myocarditis was somewhat lower than in the comparison group, and the need for radiofrequency catheter ablation (RFA) was higher (performed after suppression of inflammatory activity), which may be explained by the development of irreversible atrial myocardial fibrosis. Importantly, in a subset of patients with myocarditis, AF recurrences were related to premature and unjustified discontinuation of amiodarone, including cases where regression of LV dysfunction created a false impression of recovery. Such recurrences may potentially be prevented by more cautious long-term rhythm management.

It should also be noted that with standard preparation for planned electrical cardioversion—including transoesophageal echocardiography and anticoagulant therapy according to general principles—no thromboembolic events were observed in patients with myocarditis, as in the group with non-inflammatory heart disease. This is noteworthy given the presumed prothrombotic potential of active myocarditis, possibly related to inflammatory involvement of the mural endocardium.

Analysis of long-term outcomes in the myocarditis group revealed that heart transplantation, predefined as a study endpoint, was not required in any case. This may be explained by the arrhythmic clinical phenotype of myocarditis in a subset of patients, the reversibility of LV systolic dysfunction following restoration of sinus rhythm, and the use of comprehensive cardiotropic and immunosuppressive therapy. In cases where transplantation was considered due to therapy resistance, it was not performed because of weight-related limitations; fatal outcomes were predominantly associated with end-stage heart failure.

It is likely that specific predictors exist that allow forecasting long-term cardioversion efficacy in patients with myocarditis complicated by sustained forms of AF. Identification of such factors represents one of the objectives of the ongoing study.

## CONCLUSION

In patients with myocarditis and persistent atrial fibrillation (AF), a rhythm-control strategy aimed at restoration of sinus rhythm yields more heterogeneous outcomes than in patients with non-inflammatory heart disease. During amiodarone loading, spontaneous restoration of sinus rhythm was observed in 17.5% of patients, whereas 15% required more than one defibrillation shock, and in 5% of patients electrical cardioversion proved ineffective.

The overall rate of sinus rhythm restoration in patients with myocarditis and persistent AF reached 95%, compared with 100% first-shock cardioversion success in patients with non-inflammatory heart disease (with no cases of spontaneous sinus rhythm restoration in the comparison group).

One week after spontaneous or electrical cardioversion, sinus rhythm was maintained in 90% of patients with myocarditis (including 95% of those in whom sinus rhythm had been successfully restored) and in 95% of patients with non-inflammatory heart disease, with no statistically significant difference between groups. However, during the first week of follow-up, reversible AF recurrences were significantly more frequent in the myocarditis group than in the comparison group (21% vs 2.5%).

Six months after successful cardioversion, sinus rhythm was preserved in 53% of patients with myocarditis and 67% of patients in the comparison group ($p = 0.45$). At that time point, 62.5% and 40.7% of patients, respectively, continued amiodarone therapy. One case of spontaneous sinus rhythm restoration during ongoing amiodarone therapy was documented following ineffective electrical cardioversion. Radiofrequency catheter ablation was used more frequently in the myocarditis group, although the difference did not reach statistical significance (10% vs 5%). No thromboembolic complications were recorded in either group.

Electrical cardioversion of persistent AF in patients with myocarditis appears justified even before the full effect of disease-modifying and cardiotropic therapy becomes evident. Despite greater rhythm instability compared with patients without myocarditis, the rates of sinus

rhythm restoration and maintenance are comparable, while allowing for a rapid and statistically significant improvement in left ventricular systolic function, which is initially impaired in myocarditis. Specifically, left ventricular ejection fraction increased from 37 [30; 41]% to 42 [33; 49]% ($p < 0.05$.

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# MYOCARDIAL WORK AND MANIFESTATION OF CARDIAC DYSFUNCTION IN PATIENTS WITH PERMANENT LONG-TERM STIMULATION OF THE RIGHT VENTRICLE

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**Aim.** To evaluate the relationship between mechanical dyssynchrony, defined as myocardial work components and manifestations of cardiac dysfunction in patients with permanent right ventricular pacing.

**Material and methods.** The study included 55 patients (25 men, mean age 63±12 years) with implanted permanent pacemakers and left bundle branch block type paced QRS complex morphology and 20 healthy volunteers (15 men, mean age 32.4±7.4 years). The patients included in the study were examined twice: initially before pacemaker implantation and again at the time of study inclusion. A standard echocardiographic study was performed with an additional assessment of the degree of global longitudinal strain (GLS) and myocardial performance parameters - global constructive myocardial work (GCW), global wasted myocardial work (GWW), global work index (GWI) and global work efficiency (GWE) before and after pacemaker implantation. In all patients, segments with maximum and minimum GWI were determined. The parameters of myocardial function were analyzed depending on the localization of the pacemaker stimulating head, and a comparison was made with the parameters of myocardial function in 20 healthy volunteers.

**Results.** In 18.2% of patients, against the background of right ventricular pacing, a decrease in left ventricular ejection fraction (LVEF) from normal values to 55 (53.5; 55.8) % was recorded, in 5 (50%) of them, signs of chronic heart failure functional class II-III were recorded. An increase in the degree of tricuspid regurgitation (TR) was found in 29.9% of patients. In patients against the background of long-term pacing, the GLS, GWI, GCW and GWE indicators were statistically significantly lower than in the group of healthy volunteers, and the GWW indicator was higher than the reference values of the control group. Patients with an apical-septal localization of the stimulating electrode head have statistically lower GWI and GCW values than patients with a more “basal” location of the electrode head in the middle third of the interventricular septum (1042.23±308.85 versus 1430±514 mmHg%, p = 0.049 and 1457 (1256; 1766) versus 2089 (1831; 2186) mmHg%, p = 0.04).

**Conclusion.** The localization of the stimulating electrode head does not affect the development of negative dynamics of LVEF and TR, but has a significant effect on the myocardial performance indicators. In patients with the apical-septal localization of the electrode, the worst values of the constructive work of the myocardium were noted, and in patients with the localization of the stimulating electrode head in the right ventricular outflow tract area, the best indicators of the constructive work of the myocardium were noted.

**Key words:** pacing-induced cardiomyopathy; mechanical dyssynchrony; myocardial work; tricuspid regurgitation; left bundle branch block

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Chronic heart failure (CHF) is a highly prevalent pathological condition characterised by a substantial reduction in quality of life and high patient mortality [1-3]. Results of large prospective clinical trials, such as DAVID, PACE, and BLOCK-HF, indicate that right ventricular pacing (RVP) plays a significant role among the aetiological factors associated with the development of CHF [4-6]. Observational data from patients undergoing permanent RVP for bradyarrhythmias, as well as experimental studies in laboratory animals, demonstrate that RVP may lead to pathogenetic mechanisms similar to those responsible for CHF development in the presence of left bundle branch block (LBBB) [4, 7-10].

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Alterations in ventricular myocardial contraction mechanics during right ventricular stimulation, particularly with a high percentage of paced ventricular complexes, may result in the development of cardiac dysfunction even in individuals with preserved left ventricular ejection fraction (LVEF). This condition has been termed pacing-induced cardiomyopathy (PICM) in the literature. The reported incidence of PICM varies considerably among studies, ranging from 5.9% to 20.5% in patients with right ventricular pacing [11]. At the same time, the clinical manifestations of PICM may differ substantially from those of cardiomyopathy caused by electromechanical dyssynchrony secondary to LBBB [12].

It is conceivable that, in addition to electromechanical dyssynchrony, other factors contribute to the development of PICM and associated cardiac dysfunction. These include tricuspid regurgitation resulting from lead-leaflet interaction (compression, impingement, or adhesion) and the position of the pacing lead itself. Contemporary echocardiographic (echocardiography) techniques enable assessment of the contribution of each of these factors to the pathogenesis of PICM. In particular, evaluation of myocardial contraction mechanics has become possible through methods assessing myocardial work by constructing pressure-strain loops. This echocardiographic approach characterises left ventricular contraction efficiency by quantifying wasted energy and constructive work and may provide fundamentally new insights into the role of electromechanical dyssynchrony in the development of PICM in patients undergoing permanent RVP [13].

Thus, the aim of the present study was to assess the relationship between mechanical dyssynchrony-defined by myocardial work parameters-and manifestations of cardiac dysfunction in patients with permanent right ventricular pacing.

## MATHERIALS AND METHODS

The study protocol was approved by the local ethics committee. Written informed consent was obtained from all participants prior to enrolment.

A total of 55 patients were enrolled in the study (25 men, 45.5%; mean age 63 ± 12 years) with implanted permanent pacemakers (PPMs): 52 (94.5%) dual-chamber and 3 (5.5%) single-chamber devices. In all cases, paced QRS complexes demonstrated a LBBB morphology. Indications for PPM implantation included high-grade atrioventricular block or the brady-systolic form of atrial fibrillation.

The primary diagnoses at the time of device implantation (Table 1) were arterial hypertension in 36 patients (65.5%), coronary artery disease (CAD) in 4 patients (7.3%), iatrogenic complete atrioventricular block following radiofrequency catheter ablation of paroxysmal atrioventricular nodal re-entrant tachycardia in 3 patients (5.5%), and congenital high-grade atrioventricular block in 2 patients (3.6%). In 10 patients (18.1%), conduction disturbances were idiopathic in nature. Patients with obstructive coronary atherosclerosis (n = 4; 7.3%) underwent timely myocardial revascularisation performed either before or after PPM implantation. At the time of implantation, 6 patients (10.9%) had type 2 diabetes mellitus.

At the time of study inclusion, 4 patients (7.3%) with severe aortic valve stenosis and 2 patients (3.6%) with manifestations of heart failure secondary to tachysystolic atrial fibrillation were receiving therapy for CHF. The remaining patients were treated with ACE inhibitors / ARBs / sacubitril-valsartan for arterial hypertension. Beta-blockers were prescribed for the presence of coronary artery disease and in 12 patients (21.8%) as antiarrhythmic therapy for atrial fibrillation.

Patients with a known history of prior myocardial infarction and/or echocardiographic evidence of hypo- or akinetic myocardial segments, as well as patients with reduced LVEF of any aetiology, haemodynamically significant valvular heart disease, or other structural myocardial disorders at the time of PPM implantation were not included in the study.

At the time of device implantation, all enrolled patients demonstrated preserved global left ventricular systolic function. LVEF was ≥60% in 100% of patients, and

***Table 1.***
***Baseline characteristics of patients included in the study***

| Parameter | Value |
|---|---|
| Age (years), Me [IQR] | 63[52-76] |
| Men, n (%) | 25 (45.5) |
| Women, n (%) | 30 (54.5) |
| Coronary artery disease, n (%) | 4 (7.3) |
| Arterial hypertension, n (%) | 36 (65.5) |
| Diabetes mellitus, n (%) | 6 (10.9) |
| Paroxysmal AF, n (%) | 12(21.8) |
| Persistent AF, n (%) | 1(1.8) |
| Permanent AF, n (%) | 3 (5.5) |
| CHF functional class I*, n (%) | 1 (1.8) |
| CHF functional class II*, n (%) | 3 (5.5) |
| LV end-diastolic diameter (cm), M (SD) | 5.1±0.5 |
| LV end-systolic diameter (cm), M (SD) | 3.3±0.5 |
| LVEF (%), Me [IQR] | 60 [60; 60] |
| Paced QRS duration** (ms), M (SD) | 158±28 |
| Medical therapy at the time of pacemaker implantation | |
| ACEI / ARBs / valsartan + sacubitril, n (%) | 37 (67.3) |
| Beta-blockers, n (%) | 32 (58.2) |
| Aldosterone antagonists, n (%) | 18 (32.7) |
| Loop diuretics, n (%) | 4 (7.3) |
| Acetylsalicylic acid, n (%) | 14 (25.5) |
| Anticoagulant therapy, n (%) | 16 (29.1) |
| Statins, n (%) | 20 (36.4) |
| No therapy, n (%) | 6 (10.9) |

Note: AF - atrial fibrillation; * - assessed at the time of permanent pacemaker (PPM) implantation; CHF - chronic heart failure; FC - functional class; LV - left ventricle; LVEDD - left ventricular end-diastolic diameter; LVESD - left ventricular end-systolic diameter; LVEF - left ventricular ejection fraction; ** - paced QRS complex; ARB - angiotensin II receptor blockers; ACEI - inhibitors angiotensin-converting enzyme inhibitors.

no echocardiographic signs of regional wall motion abnormalities were detected. Cardiac chamber dimensions were within normal limits: left ventricular end-diastolic diameter was 5.1 (4.6; 5.6) cm and end-systolic diameter was 3.3 (2.8; 3.8) cm. In all patients, pacing lead tip localisation for right ventricular pacing was analysed based on operative reports. The paced QRS duration was 158 ± 28 ms. Baseline patient characteristics are presented in Table 1.

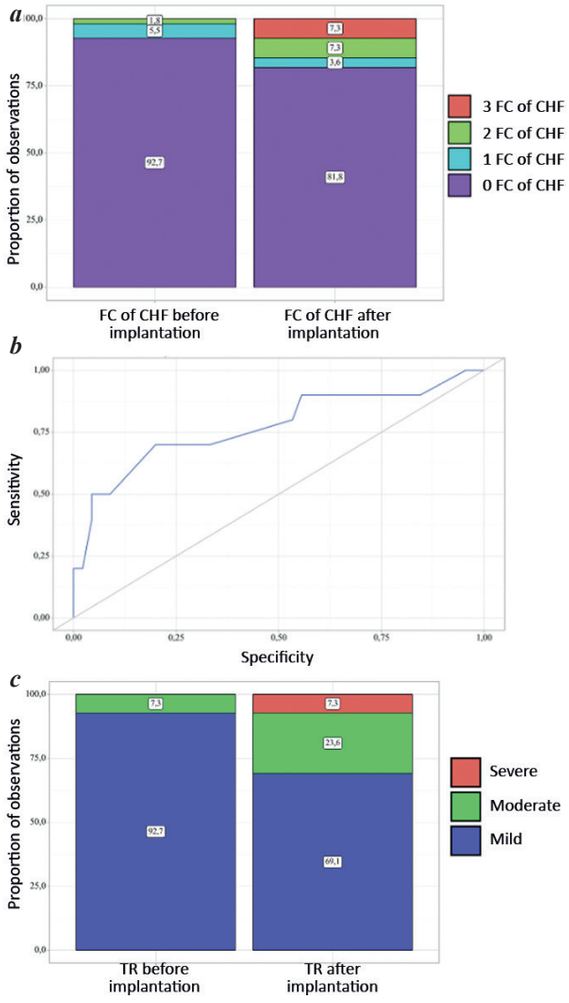


***Figure 1. Changes in the functional class (FC) of chronic heart failure (CHF )during right ventricular pacing (a); ROC curve (b) illustrating the predictive value of paced QRS duration during right ventricular pacing for left ventricular ejection fraction decline (AUC = 0.772, sensitivity 70%, specificity 80%); distribution of patients according to the severity of tricuspid regurgitation (c).***

Patients included in the study underwent examination twice: initially prior to PPM implantation and subsequently at the time of study inclusion. At inclusion, the duration of RVP was at least 6 months and amounted to 95.5 (33.5; 126.7) months. In addition, 20 healthy volunteers were included (15 men, 75%; mean age 32.4 ± 7.4 years), in whom clinical and instrumental evaluation revealed no evidence of organic cardiovascular disease and no pathological electrocardiographic findings.

**Transthoracic echocardiography with assessment of left ventricular myocardial deformation and work**

All examined patients and healthy volunteers, in addition to standard echocardiographic assessment, underwent evaluation of left ventricular (LV) global longitudinal strain (GLS, %) and myocardial work. For calculation of these parameters, echocardiographic acquisition was performed using a Vivid E9 ultrasound system (GE Healthcare, USA) equipped with an M5S phased-array transducer. Image acquisition was carried out from the apical views in accordance with current recommendations and using a previously described methodology [14].

To calculate myocardial work indices and GLS, the recorded images were analysed offline using an EchoPac PC workstation, Version 204 (GE Healthcare, USA). Based on GLS data, arterial blood pressure values, and the timing of mitral and aortic valve opening and closure manually defined on the acquired images, the software automatically constructed pressure-strain loops and calculated myocardial work indices both for each of the 17 left ventricular segments individually and for the myocardium as a whole.

The analysed myocardial work parameters included:

1. Global constructive work (GCW, mmHg%), defined as the arithmetic sum of work performed during myocardial shortening in systole and myocardial lengthening during isovolumic relaxation;
2. Global wasted work (GWW, mmHg%), calculated as the arithmetic sum of work expended during myocardial lengthening in systole and myocardial shortening during the isovolumic relaxation phase;
3. Global work index (GWI, mmHg%), corresponding to the area of the pressure-strain loop and characterising the work performed throughout systole, specifically during the time interval from mitral valve closure to mitral valve opening;
4. Global work efficiency (GWE, %), expressed as the percentage ratio of constructive work to the sum of constructive and wasted work [4].

Using the 17-segment left ventricular model (“bull’s-eye” plot), segments demonstrating maximal constructive work and maximal wasted work were identified for each patient.

***Table 2.***

***Echocardiographic parameters of myocardial deformation and myocardial work in patients with long-term right ventricular pacing (RVP) and healthy volunteers***

| | Patients with long-term RVP (n = 55) | Healthy volunteers (n = 20) | p |
|---|---|---|---|
| GLS, % | -12.7 [-13.7; -11.8] | -18.0 [-18.8; -17.5] | <000.1 |
| GWI, mmHg% | 1211 [1101; 1321] | 1588[1402; 1747] | <000.1 |
| GCW, mmHg% | 1719[1603; 1834] | 1909 [1736; 2115] | <000.1 |
| GWE, % | 82 [78; 88] | 94 [93; 95] | <000.1 |
| GWW, mmHg% | 312 [210; 432] | 108 [74.3; 137.3] | <000.1 |

Note: RVP - right ventricular pacing; GLS - global longitudinal strain; GWI - global myocardial work index; GCW - global constructive work; GWE - global work efficiency; GWW - global wasted work.

**Statistical analysis**

Statistical analysis was performed using StatTech software v.4.7.0 (StatTech LLC, Russia). Quantitative variables were assessed for normality of distribution using the Kolmogorov-Smirnov test. Quantitative variables with a normal distribution were described using arithmetic means (M) and standard deviations (SD). The representativeness of mean values was expressed by 95% confidence intervals (95% CI). In the absence of normal distribution, quantitative data were described using the median (Me) and lower and upper quartiles (Q1-Q3).

Categorical variables were described using absolute values and percentages. Ninety-five per cent confidence intervals for proportions were calculated using the Clopper-Pearson method. Comparison of proportions in contingency tables was performed using Pearson's chi-square test. The strength of association between categorical variables was assessed using Cramér's V, with values interpreted according to the recommendations of Rea and Parker (2014). Differences were considered statistically significant at $p < 0.05$.

## RESULTS

**Localisation of the pacing lead tip in patients with RVP**

Among the examined patients, the position of the RVP lead tip was basal septal in 19 patients (34.5%), mid-septal in 10 patients (18.2%), apical or near-apical (apical-septal) in 22 patients (40.0%), and located in the right ventricular outflow tract (RVOT) in 4 patients (7.3%).

Patients with different pacing lead tip localisations were comparable with respect to sex, age, baseline echocardiographic parameters (left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular ejection fraction), duration of right ventricular pacing, paced QRS duration, and comorbid conditions.

**Manifestations of cardiac dysfunction during long-term RVP**

***Dynamics of LVEF and CHF functional class (FC) during RVP***

How its indicated above, at the time of study inclusion the duration of RVP was 95.5 (33.5; 126.7) months. According to echocardiographic assessment performed during long-term RVP, a reduction in LVEF to 55.0 (53.5; 55.8)% was documented in 10 patients (18.2%); among these, 5 patients (50%) demonstrated signs of CHF of FC II-III (Fig. 1a).

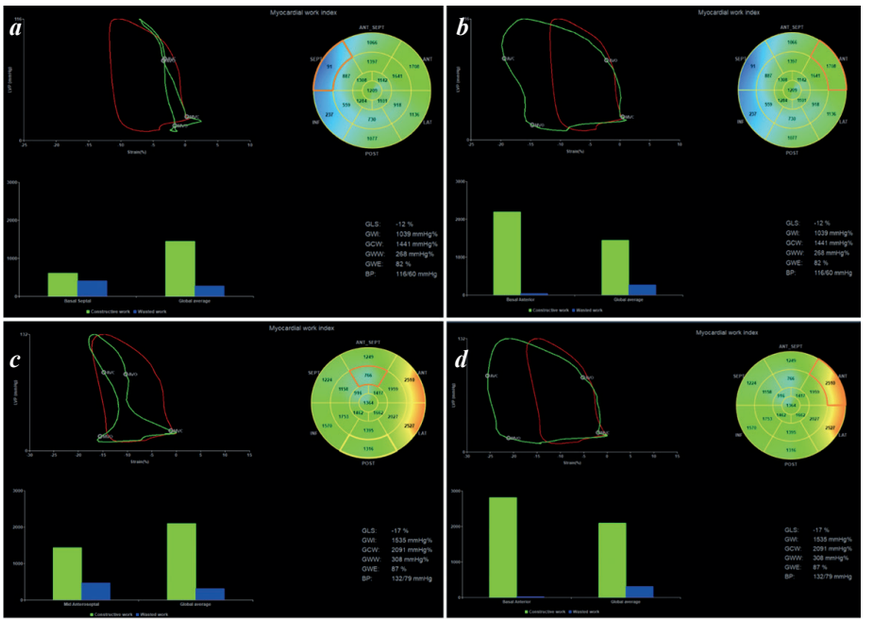


***Figure 2. Examples of myocardial work in patients with apical (a, b) and mid-septal (c, d) localization of the right ventricular pacing lead. Pressure-strain loops are shown for left ventricular segments with maximal wasted myocardial work (green curve) (a, c) and maximal constructive myocardial work (b, d), compared with global myocardial work of the entire left ventricle (red curve).***

***Table 3.***

***Descriptive statistics of quantitative variables according to right ventricular pacing lead tip location.***

| Parameter | Pacing lead location | | | | p |
|---|---|---|---|---|---|
| | Mid-septal (n=10) | Apical-septal (n=22) | Basal-septal (n=19) | RVOT (n = 4) | |
| GLS, mmHg% | -12,50 [-16,25; -10,25] | -13,00 [-14,00; -11,25] | -13,00 [-16,00; -10,50] | -15,50 [-16,50; -14,25] | 0,393 |
| GWE, mmHg% | 86 [77; 88] | 82 [79; 86] | 82 [76; 91] | 88 [82; 93] | 0,495 |
| GWI, mmHg% | 1429,70±513,93 | 1042,23±308,85 | 1228,32±399,81 | 1515,00±244,85 | 0,025 |
| GCW, mmHg% | 2089,00 [1830,75; 2186,25] | 1457,00 [1256,25; 1766,25] | 1734,00 [1397,50; 1964,50] | 2017,00 [1919,25; 2117,75] | 0,017 |
| GWW, mmHg% | 355 [262; 448] | 336 [235; 456] | 262 [151; 354] | 292 [139; 448] | 0,319 |
| Max, mmHg% | 2710±791 | 2036±588 | 2254±443 | 2508±208 | 0,023 |
| Min, mmHg% | 587,00 [121,00; 786,25] | -2,50 [-234,50; 356,50] | 337,00 [-30,50; 738,00] | 549,00 [367,50; 781,75] | 0,022 |

Note: Max - maximal constructive myocardial work; Min - maximal wasted myocardial work. Comparisons were performed using the Kruskal-Wallis test.

In addition to reduced LVEF, these patients were characterised by larger LV dimensions (LV end-diastolic diameter 5.5 cm vs 5.0 cm, p = 0.006; LV end-systolic diameter 3.8 cm vs 3.2 cm, p < 0.001), a significantly longer paced QRS duration (p = 0.002), and a higher prevalence of coronary artery disease in medical history (p = 0.016). At the same time, sex, age, duration of pacing, and pacing lead tip localisation did not have a significant impact on changes in LVEF.

Receiver operating characteristic (ROC) analysis demonstrated that a paced QRS duration ≥180 ms may be considered associated with a reduction in LVEF during long-term RVP (AUC = 0.772, sensitivity 70%, specificity 80%) (Fig. 1b). It should be noted that paced QRS duration did not depend on the localisation of the RVP lead (p = 0.373). It is likely that additional factors, such as baseline left ventricular myocardial condition and distal conduction disturbances, may also influence paced QRS duration during RV.

***Changes in tricuspid valve function during long-term RVP***

A pacing lead positioned in the right ventricle mechanically interacts with the tricuspid valve leaflets, which may potentially impair valve function. Therefore, the dynamics of tricuspid regurgitation (TR) were assessed under conditions of long-term (≥6 months) RVP. It should be noted that echocardiographic evaluation did not reveal any cases of leaflet perforation or compression by the pacing lead.

However, the proportion of patients with mild TR decreased from 92.7% to 69.1% (a reduction of 23.6%), whereas the proportion with moderate TR increased from 7.3% to 23.6% (an increase of 16.3%). In addition, severe TR was identified in 7.3% of patients during long-term RVP, whereas no cases of severe TR were present at baseline (Fig. 1c).

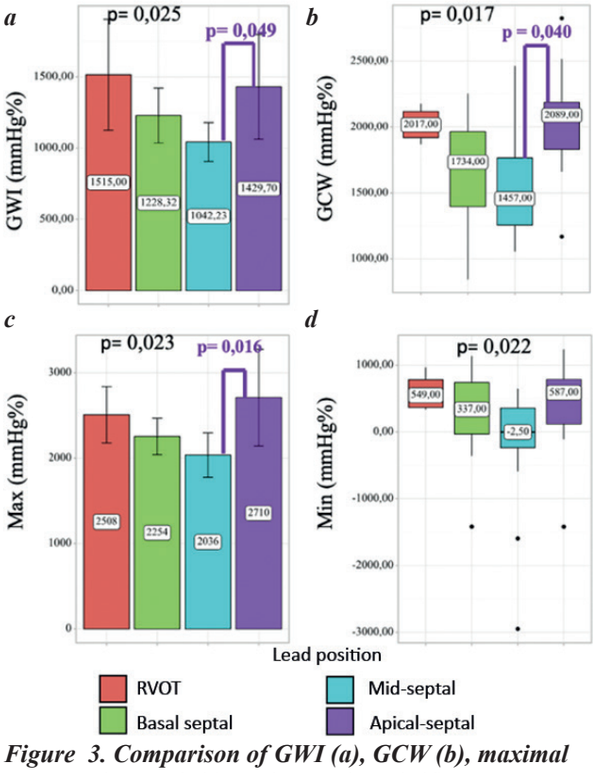


***Figure 3. Comparison of GWI (a), GCW (b), maximal constructive work (c), and wasted work (d) across different right ventricular pacing lead positions. Patients with apical-septal lead localization (blue bars) demonstrate the least favorable myocardial work parameters.***

Overall, progression of TR severity was observed in 16 patients (29.9%). Patients with and without worsening of TR differed significantly in CHF FC, while no statistically significant differences were found in other clinical or instrumental parameters.

***Myocardial work parameters in patients with long-term RVP***

When comparing myocardial work parameters and GLS calculated in the group of patients with RVP with those of healthy volunteers, substantial differences were identified. Specifically, GLS, GWI, GCW, and GWE values in the study group were significantly lower than those observed in healthy controls, while GWW was higher than the reference values of the control group (Table 2).

Thus, despite preserved LVEF in most cases, patients with RVP were characterised by less efficient myocardial work. It should be noted that segmental analysis revealed, in the same patients, LV segments with a predominance of both constructive and wasted myocardial work (Fig. 2). However, the distribution of these segments was more heterogeneous than that previously described in patients with electromechanical dyssynchrony due to LBBB [15].

The high variability of myocardial work parameters observed in the study group served as the basis for identifying factors influencing these indices. Statistical analysis revealed trends toward weak correlations between global work efficiency (GWE) and patient age (r = -0.273, p = 0.044). In addition, correlations were identified between body mass index and GLS, GWE, and GWI (r = 0.305, p = 0.025; r = -0.307, p = 0.024; r = 0.314, p = 0.021, respectively). Furthermore, correlation analysis demonstrated an association between paced QRS duration during RVP and GLS (weak positive correlation, r = 0.263, p = 0.048), as well as GWE (weak negative correlation, ρ = -0.234, p = 0.045).

Moderate correlations were also identified between RVP lead tip localisation and GWI (r = 0.407, p = 0.025), GCW (r = 0.443, p = 0.017), maximal myocardial work (Max) (r = 0.411, p = 0.023), and minimal myocardial work (Min) (r = 0.420, p = 0.022).

Comparative analysis of myocardial work parameters between patient groups stratified by RVP lead localisation (Table 3, Fig. 3) demonstrated that patients with apical-septal lead positioning had significantly lower GWI and GCW values than patients with a more “basal” lead position in the mid-portion of the interventricular septum (GWI: 1042.23 ± 308.85 vs 1430 ± 514 mmHg%, p = 0.049; GCW: 1457 [1256; 1766] vs 2089 [1831; 2186] mmHg%, p = 0.04).

At the same time, patients with apical-septal lead localisation exhibited the lowest values of both maximal constructive work (Max) and maximal wasted work (Min). In the segment with maximal wasted myocardial work in a patient with apical-septal lead positioning (Fig. 3), the value of constructive myocardial work (green bar) was nearly comparable to the value of wasted myocardial work (blue bar).

In contrast, in the segment with maximal wasted myocardial work in a patient with mid-septal lead localisation (Fig. 3), constructive myocardial work (green bar) predomi-

nated over wasted myocardial work (blue bar). Thus, the least efficient myocardial contraction was observed in patients with apical-septal pacing lead localisation. Patients with more "basal" lead positions (interventricular septum or right ventricular outflow tract) demonstrated more favourable indices of myocardial contraction mechanics (Fig. 2 and 3).

## DISCUSSION

Within this study, the role of several potential pathogenetic factors contributing to the development of cardiac dysfunction under conditions of long-term RVP was assessed. The most significant determinant in the development of CHF was a reduction in LVEF. At the same time, it was found that despite the extremely long duration of RVP (95.5 [33.5; 126.7] months), both a decline in LVEF and the emergence of CHF symptoms were observed in only 18.2% of patients. These results are fully consistent with data from a larger retrospective study by S. Khurshid et al. [16]. However, the magnitude of LVEF reduction associated with RVP in that study was considerably more pronounced (from 62.1% to 36.2% over a mean follow-up of 3.3 years) than that observed in our cohort (from >60% to 55%), despite the fact that the proportion of right ventricular pacing in our patients (96.9%) exceeded that reported in the aforementioned study (≥20%).

Given that a high burden of RVP leads to LVEF decline only in a subset of patients, we analysed several factors potentially associated with this phenomenon. First, tricuspid valve dysfunction-potentially caused by mechanical fixation of valve leaflets by the pacing lead-was excluded in all cases.

The study results indicate a substantial role of paced QRS duration in the development of adverse LVEF dynamics during long-term RVP. A paced QRS duration ≥180 ms in this patient population was associated with a high likelihood of LVEF reduction (Fig. 2b), in agreement with previously published data [16-19].

In addition, the presence of CAD was identified as a predisposing factor for LVEF decline during long-term RVP. Notably, none of the patients had a history of myocardial infarction, as this diagnosis constituted an exclusion criterion for the study. This finding suggests that an initially compromised myocardial substrate is an important prerequisite for long-term RVP-particularly in the setting of a high pacing burden and marked QRS prolongation-to exert its deleterious effect in the form of reduced LVEF.

Another manifestation of cardiac dysfunction was progression of TR, observed in 18.2% of patients, in the absence of leaflet fixation or structural damage to the valve or subvalvular apparatus. The results of the present study, as well as data from a large meta-analysis, allow one to unequivocally conclude that TR progression is not related to pacing lead tip localisation [20]. It is likely that the increase in TR severity in patients with RVP is attributable to mechanisms of electromechanical dyssynchrony that differ somewhat from those observed in patients with true LBBB. Previous studies have reported TR progression during RVP within 12 months in up to 43% of patients with leadless pacemakers [21]. These observations underscore the importance of further investigation into the mechanisms of electromechanical dyssynchrony associated with RVP.

This study is the first to provide a detailed analysis of myocardial work parameters in patients with long-term RVP and the factors influencing these indices. The results demonstrate a statistically significant reduction in GCW, GWI, and GWE in this patient population, along with a significant increase in wasted work (GWW). The decline in these parameters-reflecting myocardial inefficiency-even in patients with preserved LVEF, as was the case for the majority of our cohort, may represent an early marker of progressive myocardial dysfunction. The validity of this assumption should be confirmed in a dedicated prospective study.

In addition, pronounced asynchrony of myocardial work across different LV segments was identified, resembling the dyssynchronous contraction pattern seen in LBBB, but with greater topographic variability of asynchronous segments [15]. In this context, a targeted analysis of the impact of pacing lead tip localisation on myocardial work parameters was conducted. The poorest values of constructive myocardial work were observed in patients with apical-septal lead positioning, whereas the most favourable constructive work indices were found in patients with pacing lead localisation in the right ventricular outflow tract. This finding provides an additional pathogenetic explanation for the adverse prognostic impact of apical right ventricular lead placement in patients with RVP [6, 22-24]. As in other studies, patient age and the presence of CAD were identified as factors exerting a negative influence on myocardial work parameters [25].

**Study limitation**

A substantial limitation of the present study is its cross-sectional and retrospective design, which may have resulted in the omission of patients who experienced more pronounced clinical deterioration in the setting of PICM. It is highly likely that time represents a critical factor in the realisation of the adverse effects of electrical dyssynchrony and the development of PICM.

It should also be noted that right ventricular function was not analysed in the present study, although it may also contribute to the progression of tricuspid regurgitation.

## CONCLUSION

The results of the present study indicate that RVP is associated with a reduction in LVEF in 18.2% of patients, worsening of TR in 29% of patients, and a decrease in myocardial work parameters. Factors contributing to the development of reduced LVEF were a prolonged paced QRS duration and a history of CAD. Apical-septal positioning of the RVP lead did not contribute to adverse changes in LVEF or TR; however, it had a significant impact on myocardial work parameters. The reduction in myocardial work observed in patients with preserved LVEF suggests that this phenomenon may represent a potential early marker of subsequent cardiac dysfunction.

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# HEMODYNAMIC CHARACTERISTICS IN PATIENTS WITH PERMANENT ATRIAL FIBRILLATION ACROSS DIFFERENT HEART RATE RANGES AND LEFT VENTRICULAR EJECTION FRACTION LEVELS USING CONTINUOUS NON-INVASIVE BLOOD PRESSURE MONITORING

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**Aim.** Permanent atrial fibrillation (AF) requires rate control. However, the optimal heart rate (HR) remains a matter of debate. Hemodynamic parameters such as mean arterial pressure (MAP) and the proportion of hemodynamically ineffective beats (HIB), derived from pulse pressure (PP), may provide insight into the hemodynamic characteristics of AF at different HRs and left ventricular ejection fractions (LVEF).

**Methods.** The study included 135 patients with permanent AF (aged 37-90 years, symptom class 1-2A according to the mEHRA scale). For each patient, beat-to-beat systolic BP, diastolic BP, and PP were measured using the "volume clamp" method over a 15-minute period with the "Cardiotechnika-SAKR" system (Incart, Saint Petersburg). On each cardiac cycle, MAP and its variability were calculated using two independent metrics: Average Real Variability (ARV) and Root Mean Square of Successive Differences (RMSSD).

**Results.** The percentage of HIBs, defined per patient as deviations from the mean PP, considered as 1 («mild» <0.75, «moderate» <0.5, «severe» <0.25) - significantly increased with higher HR. Across all HR ranges (60-89 and >110 bpm), except 90-110 bpm, HIBs were more frequent in patients with reduced LVEF (<50%) than in those with preserved LVEF (≥50%) ($p<0.05$). Significant inter-individual differences in HIBs were observed among patients with similar average HRs within both the 60-89 and 90-110 bpm groups, in both preserved and reduced LVEF subgroups. MAP decreased with increasing HR; at HR >110 bpm, MAP was 80.4 ± 12.3 mmHg in the reduced LVEF group versus 94.1 ± 14.1 mmHg in the preserved LVEF group ($p<0.05$). With rising HR, MAP did not change significantly in either preserved or reduced LVEF groups, and no between-group differences were found across HR ranges ($p>0.05$).

**Conclusion.** Heart rate control in permanent AF should be individualized, hemodynamically guided, and account for LVEF. Beat-to-beat monitoring enables identification of the optimal HR that minimizes HIBs and MAP variability while maintaining MAP within accepted reference values, particularly in patients with impaired contractile function.

**Keywords:** permanent atrial fibrillation, beat-to-beat blood pressure, «volume clamp» method, hemodynamics, hemodynamically ineffective beats, mean arterial pressure, blood pressure variability, heart rate, RMSSD, ARV

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Atrial fibrillation (AF) is the most common form of cardiac arrhythmia, characterised by chaotic electrical activity in the atria, resulting in ineffective atrial contractions. The condition has a significant impact on patients' quality of life and is associated with an increased risk of stroke, heart failure, and mortality. With increasing life expectancy and the growing prevalence of risk factors such as hypertension, obesity, and diabetes mellitus, the incidence of AF continues to rise steadily [1-4].

The permanent form of this arrhythmia implies a single available therapeutic approach-heart rate (HR) control. Determination of the optimal HR in patients with AF has been the subject of numerous studies, among which RACE II, AFFIRM, and AF-CHF are considered foundational in this context [5-7]. These studies formed the basis for principles well known to every practising cardiologist and reflected in current Russian clinical guidelines and European consensus documents: achievement of an HR not exceeding 110 beats per minute in asymptomatic patients and below 80 beats per minute in patients with pronounced symptoms. These recommendations apply to patients without heart failure (HF), whereas in patients with HF, maintenance of an HR below 100 beats per minute is considered preferable.

Despite ongoing debate and published post hoc analyses highlighting limitations of existing approaches,

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these HR ranges remain target values for clinical practice, albeit with less than the highest class of recommendation [1, 2, 8-10]. A potential solution for determining optimal HR may lie in the assessment of haemodynamic characteristics of AF using a device that records arterial blood pressure (BP) on a beat-to-beat basis. Although primarily known as a tool for autonomic function testing, this method has also proven reliable for accurate BP measurement in AF, with peripheral values calibrated against synchronous brachial measurements obtained on the contralateral arm using the Korotkoff method [11, 12].

Quantification of so-called haemodynamically ineffective cardiac contractions (HICCs), which essentially represent an instrumental objectification of the well-known physical examination finding of pulse deficit, together with assessment of mean haemodynamic arterial pressure (MHAP), reflecting the degree of continuous peripheral perfusion, may provide insight into the haemodynamic features of AF at different HR levels.

Thus, the aim of this study was to analyse haemodynamic changes in patients with permanent atrial fibrillation at different heart rates and left ventricular ejection fraction values.

## MATHERIAL AND METHODS

The study included 135 patients aged 37 to 90 years (84 men and 51 women) with permanent non-valvular AF, without evidence of intraventricular conduction disturbances (QRS duration <120 ms on electrocardiography (ECG)), and with a symptom severity class according to the modified EHRA (mEHRA) scale corresponding to class 1 (asymptomatic) or class 2A (mild symptoms not interfering with daily activities). The clinical 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 medical centre. Written informed consent for participation in the study was obtained from all patients. The clinical characteristics of the study population are presented in Table 1.

The study had an observational, hypothesis-generating design. All patients meeting the inclusion criteria who presented to the clinic between September 2023 and December 2024 were consecutively enrolled. No a priori sample size calculation was performed.

**Determination of haemodynamic parameters**

Each patient underwent continuous beat-to-beat recording of systolic, diastolic, and pulse arterial blood pressure (PBP) for 15 minutes using the unloaded artery method, with simultaneous 12-lead ECG recording. Measurements were performed using the Cardiotechnika-SAKR system (Inkart JSC, Saint Petersburg, Russia; patents RU 2694737 C1 and RU 2698447 C1, V.V. Pivovarov et al.) [13-15].

**Mean haemodynamic arterial pressure**

MHAP reflects a stable level of tissue perfusion in the systemic circulation and averages approximately 100 mmHg (normal range 70-100 mmHg) [16]. Since arterial pressure changes represent a complex periodic function, MHAP is not equal to the half-sum of maximal (systolic) and minimal (diastolic) pressures, but rather corresponds to the mean of infinitesimal pressure changes from maximum to minimum over a single cardiac cycle [17]. Therefore, for automated calculation of MHAP for each cardiac cycle, the following formula was used:

$$p_{\text{cp}} = \frac{1}{\Delta t}\int_{t_1}^{t_2} p(t)\ dt$$

where $p_{cp}$ - MHAP over the time interval; $p(t)$ - instantaneous pressure at time $t$; $t_1$, $t_2$ - start and end times of the cardiac cycle; $\Delta t = t_2 - t_1$ - duration of the cardiac cycle.

**Variability of mean haemodynamic arterial pressure**

Variability of MHAP in this study was assessed using two independent indices: ARV and RMSSD. Both indices were calculated based on MHAP data obtained for each patient for every cardiac cycle. The ARV index reflects the mean absolute change in MHAP between successive heartbeats and is sensitive to short-term pressure instability, independently of its absolute value [18]. Formally, it was calculated as the arithmetic mean of the absolute differences between adjacent measurements:

$$\text{ARV} = \frac{1}{N-1}\sum_{i=1}^{N-1}|MAP_{i+1} - MAP_i|$$

where ARV - average real variability of MHAP, reflecting the mean absolute difference between successive measurements; $N$ - total number of MHAP (MAP) measurements over the analysed period; $MAP_i$ - MHAP value at the $i$-th measurement; $|MAP_{i+1} - MAP_i|$ - absolute difference between adjacent MHAP measurements.

In turn, RMSSD represents the square root of the mean of squared differences between successive MHAP values; it is more sensitive to abrupt fluctuations and is widely used in variability analysis of autonomic regulation [19]:

$$\text{RMSSD} = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N-1}(MAP_{i+1} - MAP_i)^2}$$

where RMSSD - root mean square of successive differences, an index of short-term MHAP variability; $N$ - total number of MHAP (MAP) measurements over the analysed period; $MAP_i$ - MHAP value at the i-th measurement; $(MAP_{i+1} - MAP_i)^2$ - squared difference between adjacent MHAP measurements.

Before intergroup comparisons, statistical assumptions were tested: normality of distribution was assessed using the Shapiro-Wilk test, and homogeneity of variances using Levene's test. In cases of normal distribution and variance homogeneity, one-way analysis of variance (ANOVA) was applied (for ≥3 groups) or Student's $t$-test. When normality assumptions were violated, non-parametric equivalents were used, including the Kruskal-Wallis test or the Mann-Whitney U test. A p value < 0.05 was considered statistically significant.

## RESULTS

Based on the results of 15-minute beat-to-beat blood pressure monitoring, mean values of systolic, diastolic, and pulse blood pressure (PBP) were obtained. The mean PBP was accepted as an individual reference value for each

patient (set as "1"). Deviations from this value were categorised as moderate, marked, and severe. Thus, following completion of the recording, the software automatically calculated, for each patient, the percentage of cardiac contractions corresponding to values below 0.75, below 0.5, and below 0.25 of the mean PBP taken as 1. In this manner, HICCs of varying severity were identified. Alternatively, this approach may be described as determining the proportion of cardiac contractions that are 25%, 50%, and 75% less effective than the individual mean PBP taken as 100%.

**Haemodynamically ineffective cardiac contractions**

Among the 135 patients, 33 had a reduced left ventricular ejection fraction (LVEF <50%), while 102 patients had preserved LVEF (≥50%). The absolute LVEF values in these groups were 43.67 ± 4.74% and 68.29 ± 11.05%, respectively. Patients were stratified according to mean HR ranges (60-89, 90-110, and >110 beats per minute), which allowed assessment of the effect of HR on the proportion of HICCs. This stratification reflects both physiological patterns of ventricular filling and ejection and clinically relevant HR control thresholds recommended in Russian and international guidelines for the management of AF. Groups with preserved and reduced LVEF were compared across the above HR ranges.

The proportion of HICCs increased significantly with increasing HR in both patient groups ($p < 0.001$) (Table 2). At the same time, patients with reduced LVEF demonstrated a significantly higher overall proportion of HICCs compared with patients with preserved LVEF in the HR ranges of 60-89 and >110 beats per minute. In the HR range of 60-89 beats per minute, the proportion of moderate HICCs was 17.8 ± 8.5% in the reduced LVEF group compared with 10.5 ± 5.9% in the preserved LVEF group ($p < 0.001$). The proportion of marked HICCs was also higher in patients with reduced LVEF, with mean values of 7.3 ± 6.0% versus 3.6 ± 4.0%, respectively ($p = 0.004$). Differences in the proportion of severe deviations did not reach statistical significance (3.8 ± 4.9% vs 2.2 ± 3.0%; $p = 0.09$).

At an HR of 90-110 beats per minute, no statistically significant differences between groups were observed for any of the parameters ($p > 0.5$). Pronounced differences in HICCs were again observed at HR > 110 beats per minute: the proportion of moderate HICCs was 48.2 ± 4.7% in the reduced LVEF group compared with 38.5 ± 7.0% in the preserved LVEF group ($p = 0.006$); the proportion of marked HICCs was 42.07 ± 6.52% versus 28.29 ± 9.56% ($p = 0.006$); and the proportion of severe deviations reached 34.4 ± 8.6% and 20.2 ± 9.7%, respectively ($p = 0.005$).

Given the presence of samples with non-normal distribution, statistical comparisons were additionally performed using non-parametric tests (Kruskal-Wallis and Mann-Whitney tests). No substantial discrepancies from the previously obtained results were identified.

**Mean haemodynamic arterial pressure**

When analysing mean haemodynamic arterial pressure (MHAP) in relation to HR in both patients with preserved and reduced LVEF, no statistically significant differences were identified (Table 2). In both subgroups, data distribution deviated from normality and variance homogeneity was violated; therefore, non-parametric methods were applied. According to the Kruskal-Wallis test, MHAP values did not change significantly with increasing HR either in patients with preserved LVEF ($p = 0.087$) or in those with reduced LVEF ($p = 0.081$). Comparison of MHAP values between the two LVEF groups across all HR ranges also revealed no statistically significant differences (Mann-Whitney test, $p = 0.075$-$0.65$).

The maximum individual MHAP values in the preserved LVEF group reached 126.5 mmHg at an HR of 60-89 beats per minute and 123.0 mmHg at an HR of 90-110 beats per minute. In the reduced LVEF group, maximum MHAP values also exceeded 120 mmHg, but only at HRs up to 110 beats per minute; at HR > 110 beats per minute, MHAP did not exceed 100 mmHg in any patient. Moreover, hypoperfusion profiles (MHAP − SD <70 mmHg) were observed specifically in this subgroup.

**Variability of mean haemodynamic arterial pressure**

Under sinus rhythm, variability of mean haemodynamic arterial pressure (MHAP) remains relatively stable and minimal. However, in AF, pronounced irregularity of cardiac cycles results in a substantial increase in MHAP variability. This phenomenon is likely of even greater clinical relevance than a simple increase or decrease in mean MHAP level. It is precisely the abrupt, albeit short-term, episodes of hypoperfusion characteristic of AF that may adversely affect perfusion of vital organs.

The use of two complementary variability indices (ARV and RMSSD) allows for a more comprehensive characterisation of short-term haemodynamic fluctuations. In the present study, these indices were calculated for all patients and additionally stratified by mean HR ranges (60-89, 90-110, and >110 beats per minute), enabling an

***Table 1.***
***Clinical characteristics and pharmacological therapy of patients***

| Parameter | Value |
|---|---|
| Arterial hypertension, n (%) | 131 (97.0) |
| Coronary artery disease, n (%) | 27 (20.0) |
| History of myocardial infarction, n (%) | 9 (6.7) |
| History of stroke, n (%) | 8 (5.9) |
| Type 2 diabetes mellitus, n (%) | 22 (16.3) |
| Pharmacological therapy | |
| ACE inhibitors / ARBs / ARNIs, % | 112 (83.0) |
| Beta-blockers, % | 130 (96.3) |
| MRAs, % | 33 (24.4) |
| SGLT2 inhibitors, % | 51 (37.8) |
| Statins, % | 90 (66.7) |
| Metformin, % | 22 (16.3) |
| NOACs, % | 131 (97.0) |

Note: ACE inhibitors - angiotensin-converting enzyme inhibitors; ARBs - angiotensin II receptor blockers; ARNIs - angiotensin receptor-neprilysin inhibitors; MRAs - mineralocorticoid receptor antagonists; SGLT2 - sodium-glucose cotransporter 2; NOACs - novel oral anticoagulants.

integrated analysis of dynamic blood pressure stability depending on myocardial functional status.

The analysis demonstrated that ARV and RMSSD differed significantly according to HR, but only in patients with preserved LVEF (Table 3). In this subgroup, a statistically significant increase in both ARV ($p < 0.001$) and RMSSD ($p < 0.001$) was observed when transitioning from an HR range of 60-89 beats per minute to the ranges of 90-110 and >110 beats per minute. The highest variability values were recorded during tachycardia (>110 beats per minute): ARV reached 6.0 ± 2.3 mmHg, and RMSSD reached 7.3 ± 2.8 mmHg.

In contrast, no such dependence was observed in patients with reduced LVEF: neither ARV ($p = 0.85$) nor RMSSD ($p = 0.98$) demonstrated statistically significant changes across HR ranges. When comparing patients with preserved and reduced LVEF within each of the three HR ranges, no statistically significant differences were identified (all $p > 0.05$), except for higher MHAP variability in patients with reduced LVEF at an HR of 60-89 beats per minute (ARV: $p = 0.004$; RMSSD: $p = 0.01$).

Sensitivity analysis using non-parametric tests fully reproduced the identified differences: all key comparisons retained statistical significance at level of 0.05, confirming the robustness and reliability of the obtained results.

## DISCUSSION

In the present study, haemodynamic characteristics continuously determined on a beat-to-beat basis in patients with permanent AF were, for the first time, compared not only with HR but also with left ventricular function. The obtained data help to clarify why the "universal" target HR ranges proposed in large controlled trials (AFFIRM, RACE II, AF-CHF) often prove to be clinically inadequate in everyday practice.

### Haemodynamically ineffective cardiac contractions

From a physiological perspective PBP, albeit indirectly, reflects stroke volume and vascular tone; therefore, its dynamics in AF may serve as an integral marker of cardiac cycle efficiency, reflecting both the quality of ventricular mechanical activation and the degree of peripheral resistance. Although the thresholds for HICCs were initially selected empirically, they successfully capture the patterns of haemodynamic response variability in AF, allowing quantitative assessment of the degree of reduction in contraction efficiency depending on heart rate and myocardial contractile function.

The number of HICCs increased proportionally with HR; however, the magnitude of this phenomenon was significantly greater in patients with reduced LVEF. Differences were already evident in the HR range of 60-89 beats per minute and became maximal during tachycardia >110 beats per minute (for example, severe HICCs: 34.4 ± 8.6% vs 20.2 ± 9.7%; $p = 0.005$). These findings indicate an additional contribution of impaired pump function to AF haemodynamics: rhythm irregularity combined with reduced contractility markedly increases the proportion of contractions with low stroke volume and, consequently, the risk of peripheral hypoperfusion.

Despite the presence of general trends, substantial individual deviations from the apparent overall patterns were identified. Thus, among patients with preserved LVEF in the HR subgroup of 60-89 beats per minute, despite similar mean HR values (~83 beats per minute according to 15-minute monitoring), pronounced differences in the proportion of HICCs were observed. In one patient, the proportions reached 30.9% moderate, 20.2% marked, and 13.3% severe contractions, whereas in another patient they were only 9.8%, 1.6%, and 0.1%, respectively. A similar pattern was observed in the HR range of 90-110 beats per minute: at comparable mean HR values (~100 beats per minute over 15 minutes), one patient exhibited 26.2% moderate, 22.9% marked, and 20.3% severe HICCs, while another showed only 10.0%, 5.0%, and 3.1%, respectively.

Comparable interindividual differences in HICC parameters were also observed in patients with reduced LVEF within the same HR ranges. However, at HR values exceeding 110 beats per minute, such pronounced interindividual variability in HICCs was no longer observed in either the preserved or reduced LVEF groups. This phenomenon likely underlies the difficulties encountered in determining whether a "lenient" or "strict" HR control strategy is optimal. Apparently, the individual structure of AF rhythm exerts a significant influence on haemodynamics at comparable HR values, which is particularly important to consider at HRs below the threshold beyond which rhythm control becomes ineffective and the proportion of HICCs increases sharply regardless of rhythm organisation.

***Table 2.***
***Parameters of haemodynamically ineffective cardiac contractions in patients with preserved and reduced left ventricular ejection fraction across different heart rate ranges (n = 135)***

| LVEF, % | HR, bpm | n | HICCs, % | | | MHAP, mmHg | SD BP, mmHg | p* |
|---|---|---|---|---|---|---|---|---|
| | | | Moderate | Marked | Severe | | | |
| ≥50 | 60-89 | 60 | 10.5±5.9 | 3.6±4.0 | 2.1±2.9 | 101±15 | 5.9±1.6 | <0.001 |
| | 90-110 | 28 | 21.1±6.9 | 13.1±7.2 | 8.8±6.4 | 96±13 | 6.2±1.6 | |
| | >110 | 14 | 38.5±7.0 | 28.3±9.9 | 20.2±9.7 | 94±14 | 6.3±1.8 | |
| <50 | 60-89 | 16 | 17.8±8.5 | 7.3±6.0 | 3.7±4.6 | 95±14 | 6.1±2.6 | <0.001 |
| | 90-110 | 11 | 22.2±9.0 | 12.6±9.2 | 7.4±8.2 | 98±12 | 5.7±0.7 | |
| | >110 | 6 | 48.2±4.7 | 42.1±7.1 | 34.4±8.6 | 80±12 | 6.3±1.5 | |

Note: HICCs - haemodynamically ineffective cardiac contractions; LVEF - left ventricular ejection fraction; HR - heart rate; MHAP - mean haemodynamic arterial pressure; SD - standard deviation; p - one-way ANOVA.

It is precisely in the HR range below 110 beats per minute that individual differences in rhythm structure make the greatest contribution to haemodynamic response variability, whereas above this threshold the impact of irregularity is attenuated due to overall destabilisation of the cardiac cycle and a reduction in stroke volume of virtually every contraction.

It should be emphasised that the obtained data are not proposed as "target" values for HICCs. Rather, they should be regarded as individual characteristics suitable for dynamic monitoring. Establishment of universal therapeutic targets requires large prospective studies linking these metrics to clinical outcome.

**Mean haemodynamic arterial pressure**

Unlike systolic and diastolic blood pressure, which may exhibit substantial fluctuations, MHAP is characterised by relative stability. I.P. Pavlov considered this parameter to be one of the homeostatic constants of the organism. MHAP reflects a stable level of tissue perfusion without accounting for pressure pulsations.

In AF, particularly in its chronic form, activation of the sympathoadrenal system is typical and serves as a compensatory mechanism in the setting of reduced cardiac output. This leads to peripheral vasoconstriction, an increase in total peripheral vascular resistance, and elevation of diastolic blood pressure. MHAP depends primarily on diastolic pressure; therefore, a significant increase in diastolic blood pressure results in a corresponding rise in MHAP. This effect is especially pronounced at high HR, when shortening of diastole limits the time available for arterial emptying, thereby contributing to the maintenance of elevated pressure during the diastolic phase. Thus, under AF conditions, MHAP may remain high or even increase despite a reduction in stroke volume, reflecting a mismatch between central haemodynamics and peripheral vascular resistance.

The obtained data confirm the relative stability of this parameter regardless of HR level and myocardial contractile function. In patients with preserved LVEF, a tendency toward elevated MHAP was observed in some cases, which may reflect enhanced sympathetic activation, increased vascular tone, and preserved adaptive reserves. Achievement of MHAP values exceeding 120 mmHg in individual patients may have pathophysiological consequences, including increased afterload and subsequent vascular wall remodelling.

In patients with reduced LVEF, MHAP tended to decrease with increasing HR; however, this change did not reach statistical significance ($p = 0.075$). At HR values exceeding 110 beats per minute, none of the patients demonstrated MHAP levels above 100 mmHg, which may indicate critical vulnerability of this population to tachycardia in the setting of AF.

**Variability of MHAP**

Analysis of ARV and RMSSD demonstrated that in patients with preserved LVEF, MHAP variability increased with rising HR ($p < 0.001$), whereas no comparable changes were observed in the reduced LVEF group. A plausible explanation is that under conditions of impaired pump function, pressure variability is limited by a "ceiling" imposed by low cardiac output, whereas in patients with preserved LVEF, fluctuations in preload and afterload become more pronounced at higher HR. Another potential explanation for the absence of increasing MHAP variability with rising HR in the reduced LVEF group is the presence of angiosclerosis, increased arterial wall stiffness, and reduced arterial compliance, which limit the amplitude of pressure oscillations in response to changes in stroke volume.

Thus, pharmacological HR reduction aimed at decreasing MHAP variability in patients with reduced LVEF is likely to be of less benefit than in patients with preserved LVEF. Nevertheless, monitoring of absolute MHAP values remains clinically relevant.

**Study limitations**

A limitation of the study is the relatively small number of patients with reduced LVEF, particularly in the subgroup with HR >110 beats per minute. In addition, participants received different combinations of pharmacological therapies, which may have heterogeneous effects on peripheral vasoregulation and blood pressure variability. Despite consecutive enrolment, the cohort was drawn from a single specialised centre and did not include patients with pronounced AF-related symptoms (mEHRA ≥2B) or severe heart failure (NYHA class IV). Therefore, extrapolation of the results to populations with a higher symptomatic burden and/or decompensated heart failure should be undertaken with caution and requires confirmation in future studies.

No separate statistical power calculation was performed; consequently, results obtained in small subgroups (n <10) should be considered descriptive and interpreted cautiously. Stratification by type and dose of medications was not performed, which may introduce systematic bias. The use of the domestic Cardiotechnika-SAKR system, with its specific algorithmic approach for calibrating peripheral blood pressure values against simultaneous contralateral brachial measurements, does not allow full extrapolation of the findings to other systems employing the unloaded artery method [20]. At the same time, this reflects the uniqueness of the system used, which, among currently known analogous devices, uniquely enables accurate blood pressure measurement in AF owing to its built-in mathematical algorithms referencing Korotkoff sound.

## CONCLUSION

In Western clinical practice, the physical examination finding of pulse deficit appears to have long been abandoned, based on the notion of its limited clinical util-

***Table 3.***

***Indices of mean arterial pressure variability in patients***

| LVEF, % | HR, bpm | n | ARV±SD, mmHg | RMSSD±SD, mmHg |
|---|---|---|---|---|
| ≥50% | 60-89 | 60 | 4.0±1.2 | 5.3±1.6 |
| | 90-110 | 28 | 4.8±1.5 | 6.4±1.9 |
| | >110 | 14 | 6.0±2.3 | 7.3±2.8 |
| <50% | 60-89 | 16 | 5.3±2.3 | 6.8±2.9 |
| | 90-110 | 11 | 5.5±1.7 | 6.9±1.9 |
| | >110 | 6 | 5.9±1.6 | 7.1±1.8 |

Note: ARV - average real variability; SD - standard deviation; RMSSD - root mean square of successive differences.

ity [21]. This view is partly justified, as pulse deficit assessment by physical examination is inherently subjective and depends on individual tactile sensitivity. However, the advent of non-invasive beat-to-beat blood pressure monitoring enables objective quantification of this parameter. Continuous blood pressure monitoring at each cardiac contraction allows determination of an individually optimal heart rate, adjusted for the proportion of haemodynamically ineffective cardiac contractions, mean haemodynamic arterial pressure, and MHAP variability.

The obtained findings support the rationale for an individualised, haemodynamically oriented approach to heart rate control in AF, particularly in patients with impaired cardiac pump function, and provide a justification for incorporating beat-to-beat blood pressure monitoring into clinical practice to optimise therapeutic strategies.

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# RISK STRATIFICATION OF SUDDEN CARDIAC DEATH IN YOUNG PATIENTS WITHOUT STRUCTURAL HEART DISEASE

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**Aim.** To stratify the risk of recurrent syncope and the risk of sudden cardiac death (SCD) / sudden cardiac arrest in young patients with cardiogenic syncope without structural heart disease using the Evaluation of Guidelines in Syncope Study (EGSYS score). To conduct the first retrospective analysis of the personalized risk of sudden cardiac death, as well as the sensitivity of the EGSYS scale for patients with different nosological entities.

**Methods.** The study included 63 patients with syncope aged 18 to 44 years, the average age of the patients was 25,98±6,69 years. The patients were divided into 5 groups: the first group (12 patients, average age: 21,84±4,37 years) consisted of patients with cardiac channelopathies, the second group (16 patients, average age 25,84±6,56 years) consisted of patients with sinus node dysfunction in the form of arrest of the Kiss-Fleck node, the third group consisted of patients with atrioventricular block (15 patients, the average age 26,71±7,13 years), the fourth group consisted of patients with paroxysmal monomorphic and polymorphic ventricular tachycardia (15 patients, the average age of the group was 25,74±7,79 years), the fifth group consisted of patients with syncope in the Wolff-Parkinson-White (WPW) syndrome (5 patients, average age - 25,64±3,05 years). The frequency of recurrence of syncope and SCD episodes was assessed over a 2-year period from the time of the first syncope. The EGSYS score was used to stratify the risk of recurrence of syncope and SCD.

**Results:** A total of 23 patients, or 36.5% of the study population, had an EGSYS score more than 5 points (very high), with a 2-year risk of SCD of 21% and a risk of recurrent syncope of 77%. In addition, the highest score on the EGSYS scale was associated with a higher frequency of cardiogenic syncope and SCD episodes. Patients with cardiac channelopathies had the highest EGSYS score (mean score 5.84), which was associated with the highest incidence of syncope and episodes of SCD with cardiopulmonary resuscitation over a 2-year period (r=0,58, p=0,01). The risk of developing SCD over a 2-year period in the group of patients with sinus node dysfunction (sinus node arrest) does not exceed the average population (less than 2%), which was associated with the absence of episodes of sudden cardiac death (sudden cardiac arrest) for a period of 2 years in the patients in this group. The highest validation of the EGSYS score and the frequency of syncope over a 2-year period were in patients with ventricular tachycardia ((r=0,73, p=0,002).

**Conclusion:** Thus, already at the debut syncopal state there is a possibility of determining the personalized risk of recurrent syncope and sudden cardiac death using the EGSYS scale. According to the study, the area of the highest sensitivity of the scale was patients with ventricular tachycardia (the main cause of SCD), which allows us to consider this scale as a basis for constructing a prognostic model for stratifying the risk of sudden cardiac death in young patients with cardiogenic syncope without structural heart disease.

**Key words:** sudden cardiac death, sinus node arrest, complete atrioventricular block, channelopathies, ventricular tachycardia, long QT syndrome, syncope, implantable cardiac monitor.

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The term sudden cardiac death (SCD) refers to non-violent death occurring instantaneously or within less than 1 hour from the onset of acute changes in a patient's clinical status [1-3]. This term is used in the following situations: the deceased had a congenital or acquired heart disease that was potentially life-threatening during life; autopsy revealed a cardiac or vascular disease that could have been the cause of sudden death; or autopsy failed to identify any extracardiac causes of death, and death is presumed to have been caused by an arrhythmia [1-4]. According to contemporary studies, ventricular arrhythmias account for 85% of all causes of SCD, including ventricular tachycardia (VT) and ventricular fibrillation (VF) [1, 5].

According to the World Health Organization, 30 individuals per 1 million population die each week worldwide from ventricular arrhythmias. Based on the 2015 European Society of Cardiology clinical guidelines on SCD (sudden cardiac arrest (SCA)), 4.25 million people die annually worldwide from SCD. In the Russian Federation, 200,000-250,000 individuals die each year from ventricular ar-

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rhythmias, with this number increasing annually [1, 6, 7]. Of particular concern is mortality among young patients (aged 18-44 years) without structural abnormalities of the cardiovascular system, occurring against a background of complete clinical, laboratory, and instrumental well-being [6, 7]. According to various reports, this patient group accounts for up to 10% of all SCD cases [8].

The development of SCD in young patients without structural cardiovascular abnormalities is most commonly associated with primary electrical diseases of the heart, as well as several other relatively rare conditions. Among the most prevalent primary electrical heart diseases are channelopathies, inherited forms of sinus node dysfunction, complete atrioventricular block, genetically determined progressive disorders of the cardiac conduction system, idiopathic ventricular arrhythmias, and several others [9-13].

In many cases, the only (and sometimes the first and last) predictor of SCD in young patients is a syncopal episode (syncope). Syncope is defined as a transient loss of consciousness resulting from cerebral hypoperfusion, characterised by rapid onset, inability to respond to external stimuli, short duration, and spontaneous recovery. Syncope accounts for approximately 5% of all emergency medical visits across healthcare facilities of various profiles [14, 15].

Syncope has a broad spectrum of causes, ranging from potentially benign and non-life-threatening to life-threatening conditions. Depending on the underlying mechanism, all syncopal episodes can be classified as cardiogenic and non-cardiogenic (reflex-mediated, orthostatic). Several studies have demonstrated significantly higher mortality in patients with cardiogenic syncope (CS), regardless of age. At the same time, patients with syncope may differ substantially in their risk of recurrence and in their risk of developing SCD [16, 17]. Thus, patients without a prodrome or typical triggering events; those with syncope occurring in the supine position or at peak physical exertion; those with a family history of SCD at a young age; those with a prior history of disease, including previously diagnosed rhythm or conduction disorders; or those with pathological ECG findings at the time of syncope are at high risk of cardiogenic syncope. Notably, only 4% of patients who experience a first syncopal episode seek medical attention. For the majority of these patients, risk stratification for syncope recurrence and SCD is not performed, and as many as 75% of patients after a first syncopal episode do not undergo comprehensive evaluation [3].

Several tools have been developed to date for stratifying the risk of syncope recurrence and SCD in patients with cardiogenic syncope, including the San Francisco Syncope Rule, the OESIL Risk Score, the Evaluation of Guidelines in Syncope Study (EGSYS) score, and the Canadian Syncope Risk Score. Each of these tools has its own advantages and limitations. A cohort study conducted by the developer of the EGSYS score, Italian cardiologist Attilio Del Rosso from the San Giuseppe Clinic in Empoli, demonstrated high specificity and sensitivity of the score, which was also confirmed by external validation studies. However, its prognostic value does not significantly exceed that of clinical assessment alone. Despite evidence of high specificity and sensitivity of the EGSYS score in diagnosing cardiogenic syncope, data on its prognostic value in determining personalised risk of SCD and syncope recurrence for specific nosological entities are currently lacking in the international literature. Moreover, the clinical context in which the score demonstrates the highest sensitivity has not been clearly defined. Using the present study as an example, we aim to demonstrate experience in determining personalised risk of syncope recurrence and SCD in patients with specific nosological entities, as well as to identify the setting in which the EGSYS score shows the highest validity, which may serve as a practical reference point for clinicians in stratifying SCD risk in patients with syncope [2, 18-21].

Study objective: to stratify the risk of syncope recurrence and the risk of SCD (SCA) in young patients with cardiogenic syncope without structural heart disease using the EGSYS score; to perform a retrospective analysis of personalised SCD risk; and to evaluate the sensitivity of the EGSYS score in patients with different nosological entities.

## MATERIALS AND METHODS

The study included 63 patients presenting with complaints of syncope who were followed at a medical institution between 2018 and 2025.

**Inclusion criterias**

1. Young age (18-44 years).
2. History of at least one syncopal episode.
3. Presence of diagnosed cardiac rhythm disorders in accordance with the 2015 European Society of Cardiology guidelines as causes of cardiogenic syncope: bradyarrhythmias (sinus node dysfunction, atrioventricular block), tachyarrhythmias (supraventricular and ventricular), as well as a diagnosed channelopathy [1, 2].
4. Presence of at least one high-risk feature for syncope according to the European Society of Cardiology criteria [1, 2]: syncope without prodrome; syncope without an identifiable provoking factor (except for triggers suggestive of channelopathy, such as fever, loud sounds, etc.); positive family history (sudden cardiac death in first-degree relatives or a history of frequent syncope in relatives); syncope occurring at peak physical exertion; syncope in the supine or sitting position, or syncope unrelated to body position (in cases of recurrent syncope); presence of pathological ECG changes documented during syncope or on resting ECG.
5. Written informed consent provided by the patient.

**Exclusion criterias**

1. Syncope clearly associated with food intake, change in body position, fear, hunger, or another identifiable trigger (except for factors suggestive of channelopathy, such as fever, loud sounds, etc.).
2. Presence of structural heart or vascular disease (coronary artery disease, valvular heart disease, cardiomyopathies, atherosclerosis, diffuse connective tissue diseases, myocarditis, etc.).
3. Presence of concomitant internal organ pathology (anaemia, thyrotoxicosis, autoimmune vasculitides, diabetes mellitus with micro- and/or macroangiopathy, electrolyte disturbances, etc.).
4. Diagnosed and instrumentally confirmed epilepsy with a positive response to antiepileptic therapy.

5. Presence of an established or diagnosed non-cardiogenic cause of syncope (intoxication, orthostatic hypotension, reflex-mediated syncope, etc.).
6. Informed refusal to participate in the study.

The study was conducted in several stages. At the first stage, a thorough collection of patient complaints and medical history was performed, along with assessment of clinical status. Particular attention was paid to a history of syncopal and presyncopal episodes, episodes of tachycardia and bradycardia, and associated symptoms such as general weakness and non-systemic dizziness. In the presence of a history of syncope, detailed characterisation of syncopal episodes was undertaken. Cardiogenic syncope is characterised by the following features: sudden onset and sudden termination; variable duration of episodes; a relatively small number of syncopal episodes over a lifetime (one or two); a short prodrome preceding syncope (tachycardia or a sensation of cardiac pause in the chest); possible sudden loss of consciousness without prodrome; absence of a clear trigger for syncope (or presence of a trigger in certain specific nosological entities, such as fever in patients with Brugada syndrome); pathological findings on cardiac evaluation (signs of sinus node dysfunction or prolonged QT interval in long QT syndrome); a family history of inherited cardiac disease; or SCD in first-degree relatives before the age of 50 years [2-5]. At this stage, a detailed analysis of the patient's ECG archive was also performed; when rhythm disturbances were documented, their temporal association with syncope was clarified.

At the second stage, more comprehensive laboratory and instrumental examinations were performed. All patients included in the study underwent complete clinical and biochemical blood testing, coagulation profile assessment, and immunological blood analysis. If abnormalities were identified at this stage, further diagnostic evaluation was carried out, and specialist consultation and treatment were provided when necessary. Transthoracic echocardiography and 24-hour ECG monitoring were performed, during which an active orthostatic test was conducted according to a standard protocol. Ultrasound examination to detect developmental anomalies of the brachiocephalic arteries with significant impairment of intracerebral haemodynamics was performed when indicated. Video electroencephalography was carried out for the diagnosis of epileptic activity, and brain magnetic resonance imaging was performed to detect structural pathology, when clinically indicated. Based on the results of the latter two examinations, patients were evaluated by a neurologist and, if necessary, an epileptologist.

At the third stage, transoesophageal electrophysiological study was performed according to indications, with pharmacological testing (using atropine) applied when required. Implantation of implantable cardiac monitors - Confirm Rx (Abbott, USA) and Reveal LINQ (Medtronic, USA) - was performed, followed by prolonged remote ECG monitoring for up to 2 years. Exercise stress testing was conducted according to indications. A subset of patients underwent invasive intracardiac electrophysiological study. When necessary, pharmacological tests with atropine and procainamide were used. Molecular genetic testing was performed only in accordance with clinical guidelines specific to the corresponding nosological entity.

A retrospective assessment of the frequency of syncope and episodes of SCD over a 2-year period from the first syncopal episode was performed using the EGSYS score. Based on the obtained results, risk stratification for syncope recurrence and SCD was carried out for each patient. The total EGSYS score, as well as the calculated probabilities of SCD and syncope recurrence expressed as percentages, were then compared with the actual observed frequency of syncope and SCD episodes. Subsequently, correlation analysis was performed to assess the relationship between the final EGSYS score and the frequency of syncope and SCD episodes within each patient group over the 2-year period, using Pearson's linear correlation coefficient according to standard methodology in the Statistical Package for the Social Sciences software (IBM, USA).

## RESULTS

Based on the inclusion and exclusion criteria, 63 patients aged 18 to 44 years were enrolled in the study; the mean age of the study population was 25.98 ± 6.69 years. The frequency of syncope and episodes of SCD was assessed over a 2-year period from the first syncopal episode. To determine personalised SCD risk and to evaluate the sensitivity of the EGSYS score for this specific nosological spectrum, all patients were divided into several groups.

The first group (12 patients) consisted of individuals with channelopathies (mean age 21.84 ± 4.37 years): long QT syndrome type 1 with a mutation in the KCNQ1 gene (3 patients), long QT syndrome type 2 with a mutation in the KCNH2 gene (5 patients), one patient with Jervell-Lange-Nielsen syndrome (KCNQ1 genotype), two patients with Brugada syndrome, and one patient with a diagnosed early repolarisation syndrome. The second group (16 patients; mean age 25.84 ± 6.56 years) included patients with symptomatic sinus node dysfunction. The third group comprised patients with atrioventricular block (15 patients; mean age 26.71 ± 7.13 years): 9 patients with complete AV block and 6 patients with second-degree AV block, Mobitz type II.The fourth group included patients with paroxysmal ventricular tachycardia (15 patients; mean age 25.74 ± 7.79 years), including 11 patients with monomorphic VT and 4 patients with polymorphic VT and/or documented ventricular fibrillation. The fifth group (5 patients; mean age 25.64 ± 3.05 years) consisted of patients with syncope in the setting of Wolff-Parkinson-White syndrome.

In patients with channelopathies, the mean EGSYS score was 5.84, corresponding to a probability of cardiogenic syncope of 77% and a probability of SCD of 21%. In reality, the mean frequency of syncope over the 2-year period in this group was 7.84, and the frequency of SCD was 0.38. The correlation coefficient between the EGSYS score and syncope frequency was $r = 0.58$ ($p = 0.01$), and between the EGSYS score and SCD frequency $r = 0.55$ ($p = 0.02$).

In the group of patients with sinus node dysfunction, the mean EGSYS score was 1.54, with a probability of cardiogenic syncope of 2% and a probability of SCD of 2%. Over the 2-year period, the frequency of syncope was 4.43,

while the frequency of SCD (SCA) was 0. Thus, in this patient group, the SCD risk according to the EGSYS score did not exceed the average population risk. No clear association was observed between the EGSYS score and syncope frequency (correlation coefficient r = 0.12, p = 0.3).

In patients with atrioventricular block, the mean EGSYS score was 3.13, corresponding to a probability of cardiogenic syncope of 13% and a probability of SCD of 21%. The mean syncope frequency during the observation period was 3.1, and the frequency of SCD was 0.21. The correlation between the EGSYS score and syncope frequency was weak (r = 0.21, p = 0.2), whereas a moderate correlation with SCD frequency was observed (r = 0.54, p = 0.02).

In the VT group, the mean EGSYS score was 4.4, with a probability of cardiogenic syncope of 33% and a probability of SCD of 21%. The mean syncope frequency over the 2-year period was 4.2, and the frequency of SCD was 0.33. A significant correlation was observed between the EGSYS score and syncope frequency (r = 0.73, p = 0.002), as well as between the EGSYS score and SCD episode frequency (r = 0.52, p = 0.02).

In patients with Wolff-Parkinson-White syndrome, the mean EGSYS score was 3.4, corresponding to a probability of cardiogenic syncope of 13% and a probability of SCD of 21%. During follow-up, the mean syncope frequency over the 2-year period was 3.4, and the frequency of SCD was 0.2. The correlation coefficient between the EGSYS score and syncope frequency was r = 0.32 (p = 0.29), and between the EGSYS score and SCD episode frequency r = 0.32 (p = 0.12).

## DISCUSSION

A retrospective risk stratification of syncope recurrence and SCD (SCA) was performed in young patients with arrhythmogenic syncope using the EGSYS score, along with an assessment of the actual frequency of syncope and SCD episodes over a 2-year period from the first syncopal event. It was found that in 23 patients included in the study (36.5%), the EGSYS score exceeded 5 (very high), corresponding to a 2-year SCD risk of 21% and a syncope recurrence risk of 77%. These findings are comparable with data from the Framingham Study, which demonstrated that one-year mortality in patients with cardiogenic syncope was higher (up to 33%) than in patients with non-cardiogenic causes of syncope (up to 12%) or syncope of unknown origin (up to 6%) [37].

According to the developer of the EGSYS score, a score ≥3 identifies recurrent cardiogenic syncope with a sensitivity of 92-95%. During long-term follow-up (614 days), mortality among patients with a score ≥3 was significantly higher than among those with a score <3 (17% vs 3%, p < 0.001). These data were also confirmed by external studies. Thus, a study conducted by Hamid Kariman and colleagues from Iran demonstrated high sensitivity of the EGSYS score in predicting syncope recurrence in patients with scores ≥3, with reported sensitivity reaching 91% [38]. A study by a Portuguese research group demonstrated a statistically significantly higher EGSYS score in patients with cardiogenic syncope compared with syncope of other aetiologies (1.85 ± 2.3 vs 0.64 ± 2.0, p = 0.005) [39]. Another study reported that death occurred in 9.2% of patients with recurrent syncope over a 2-year period, and deceased patients had significantly higher EGSYS scores (p < 0.001) [40].

Given that young patients with cardiogenic syncope represent a heterogeneous population, determination of personalised risk of syncope recurrence and SCD is of substantial clinical importance. According to our data, the highest EGSYS scores were observed in patients with channelopathies (mean score 5.84), which was associated with the highest frequency of syncope and SCD episodes requiring cardiopulmonary resuscitation over a 2-year period, demonstrating a correlation of moderate strength.

According to various authors, the annual incidence of SCD in untreated patients with long QT syndrome ranges from 0.33% to 0.9%, whereas the annual risk of syncope is estimated at approximately 5% [23, 26]. In patients with Brugada syndrome, cardiogenic events were observed in 7.7% of cases over one year, and 86% of patients with implanted cardioverter defibrillators experienced shocks. Convincing data on other channelopathies are lacking in the international literature due to their rarity and diagnostic challenges. Moreover, underdiagnosis among patients with channelopathies remains a significant issue, making it extremely difficult to establish accurate mortality rates in this patient group at present [1, 23, 25-27].

The 2-year risk of SCD in the group of patients with sinus node dysfunction did not exceed the average population risk (less than 2%), which was consistent with the absence of SCD episodes. Mortality from asystole has been reported at 15-20%; however, definitive data regarding the isolated contribution of sinus node dysfunction are currently lacking. Adverse outcomes have been described in patients with progressive involvement of the cardiac conduction system, as well as in those with combined binodal disease (sinus node dysfunction and atrioventricular block) [1, 2, 5, 7, 9, 11].

Considering the heterogeneity of high-risk patients with cardiogenic syncope and the variability in personalised risk of syncope recurrence and SCD, the question arises regarding the clinical setting in which the EGSYS score demonstrates the greatest sensitivity. Such studies are currently scarcely represented in the international literature. The strongest correlation between the EGSYS score and syncope frequency over the 2-year period was observed in patients with ventricular tachycardia (r = 0.73, p = 0.002). According to contemporary studies, ventricular arrhythmias account for 85% of all causes of SCD. Although numerous studies have demonstrated a high risk of SCD in patients with ventricular arrhythmias in the presence of structural heart disease, risk stratification for idiopathic ventricular tachycardia has not yet been established [8]. The frequency of syncope in patients with atrioventricular block was lower compared with other groups, likely due to more timely diagnosis.

**Study limitations**

This study has a single-centre design and a retrospective nature, which may limit the strength of the obtained results. The study included a cohort of young patients aged 18 to 44 years; children, adolescents, and older individuals

were not included, despite the fact that high-risk syncope and episodes of SCD may also occur in these age groups in the absence of structural heart disease. This may represent a potential source of selection bias. On the other hand, young patients without structural heart disease may more accurately reflect the true clinical profile of patients with arrhythmogenic syncope associated with primary electrical heart diseases. The sample size (63 patients) was determined by the single-centre nature of the study, as well as by the extremely low prevalence of certain nosological entities.

## CONCLUSION

Already at the first syncopal episode, it is possible to determine a personalised risk of syncope recurrence and SCD using the EGSYS score. According to the study findings, the highest sensitivity of the score was observed in patients with VT, which allows the EGSYS score to be considered a basis for the development of a prognostic model for stratifying the risk of SCD in young patients without structural heart disease presenting with cardiogenic syncope.

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# NON-FLUOROSCOPIC ABLATION OF TYPICAL ATRIAL FLUTTER: EFFECTIVENESS AND SAFETY

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**Aim.** To evaluate the effectiveness and safety of catheter treatment of typical atrial flutter (AFl) using exclusively intracardiac echocardiography (ICE) compared to the fluoroscopic method.

**Material and methods.** There were 176 patients with typical AFl (88 patients in each group). The study group consisted of patients who underwent radiofrequency ablation (RFA) with intracardiac ultrasound visualization only (ZF - Zero Fluoro). The comparison group included patients who underwent RFA of the AFl using minimal fluoroscopy time and ICE (MF - Minimal Fluoro). The follow-up period was 12 months.

**Results.** Intraoperative success rate was 100% in both groups. The absence of recurrence of AFl during the follow-up period was comparable (94.3% vs. 96.6%, p=0.4703). No acute or delayed complications were reported. Fluoroscopy was used in none patient who underwent the procedure under intracardiac ultrasound guidance ($p < 0.001$). Surgery time and overall RF-ablation time did not differ statistically (69.4 min vs. 63.9 min, p=0.1030; 9.1 min vs. 8.3 min, p=0.1606, respectively) in the MF- and ZF-group.

**Conclusion.** Catheter RFA of a typical AFl with ICE-visualization is feasible without the use of fluoroscopy, with comparable efficiency and safety results.

**Key words:** atrial flutter; cavo-tricuspid isthmus; ablation; nonfluoroscopic; intracardiac ultrasound; intracardiac echocardiography

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Typical atrial flutter (AFL) is one of the most common cardiac arrhythmias. The incidence of this arrhythmia is estimated at 88 cases per 100,000 person-years, increasing to 317 cases per 100,000 person-years among individuals older than 50 years [1]. A prolonged course of AFL is associated with the development and progression of chronic heart failure, thromboembolic complications, increased rates of hospitalisation, and higher mortality [2-4]. Studies have shown that catheter ablation of AFL reduces the frequency of repeat hospitalisations and atrial fibrillation (AF) recurrences, improves quality of life, and leads to a more favourable clinical course of chronic heart failure by reducing arrhythmia burden compared with cardioversion and pharmacological rhythm control strategies [5-7].

Catheter treatment of typical AFL, in which the tachycardia wavefront circulates around the tricuspid valve annulus, consists in creating a continuous conduction block across the cavotricuspid isthmus (CTI). The long-term efficacy of CTI radiofrequency ablation (RFA) exceeds 90% when bidirectional isthmus block is used as the procedural endpoint [8, 9].

The conventional approach to CTI RFA is based on fluoroscopy as the primary method of catheter visualisation, which is inevitably associated with significant radiation exposure for both patients and medical staff. According to published data, radiation doses during this procedure range from 6.7 to 13.1 Gy/cm² [10, 11]. The introduction of intracardiac echocardiography (ICE) into clinical practice as an adjunctive imaging modality has made it possible to reduce reliance on fluoroscopy during many electrophysiological procedures [12-17]. The first use of a rotational ultrasound catheter for ablation in the right atrium was reported in 1994

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by E. Chu et al. [18]. In 2003, Joseph B. Morton et al. were the first to apply a phased-array ICE catheter during CTI RFA. As additional advantages of this technique, the authors highlighted continuous visualisation of isthmus anatomy along its entire length and real-time assessment of ablation catheter-endocardial contact [19].

In 2023, Blerim Luani et al. published the first experience with a completely non-fluoroscopic approach to catheter treatment of AFL, based exclusively on intracardiac ultrasound as the sole imaging modality. The study described CTI RFA in 30 patients with typical AFL. The authors reported that all procedural steps could be performed without fluoroscopy and that no intraprocedural complications were observed [20]. To date, there are no published data on the long-term efficacy of AFL RFA performed under exclusive intracardiac ultrasound guidance.

The aim of the present study was to compare intraoperative and long-term efficacy and safety outcomes of a non-fluoroscopic approach to catheter treatment of typical AFL using ICE as the imaging modality with those of the conventional fluoroscopy-guided method.

## MATHERILAS AND METHODS

A retrospective single-centre study was conducted at the Laboratory of Surgical and Interventional (X-ray-guided) Methods for the Treatment of Cardiac Arrhythmias, E.I. Chazov National Medical Research Centre of Cardiology, Ministry of Health of the Russian Federation, between 2019 and 2024. The study included 176 patients with typical AFL.

Inclusion criteria were a documented diagnosis of paroxysmal or persistent AFL. Exclusion criteria comprised a history of cardiac surgery or prior catheter-based treatment of cardiac arrhythmias, as these conditions implied a potential risk of incisional (post-surgical) AFL. If sinus rhythm was present at baseline, an electrophysiological study with programmed stimulation was performed to induce tachycardia. In cases where intraoperative tachycardia could not be induced, empirical cavotricuspid isthmus (CTI) RFA was performed until bidirectional conduction block was achieved; such patients were excluded from the study. Patients in whom a non-typical AFL arrhythmia was induced received appropriate treatment but were also excluded from the analysis.

The study group consisted of patients who underwent CTI RFA using ICE as the sole imaging modality (ZF, zero fluoroscopy). The comparison group included patients who underwent CTI RFA with the use of minimal fluoroscopy in combination with intracardiac ultrasound (MF, minimal fluoroscopy). Follow-up Holter monitoring was performed at 3, 6, and 12 months after the procedure. The total duration of follow-up for each patient was 12 months.

In the MF group, fluoroscopy and ICE were used for visualisation. Diagnostic 20-pole and 10-pole catheters were positioned under fluoroscopic guidance along the lateral wall of the right atrium (RA) and within the coronary sinus, respectively. The ablation catheter was placed in the CTI region

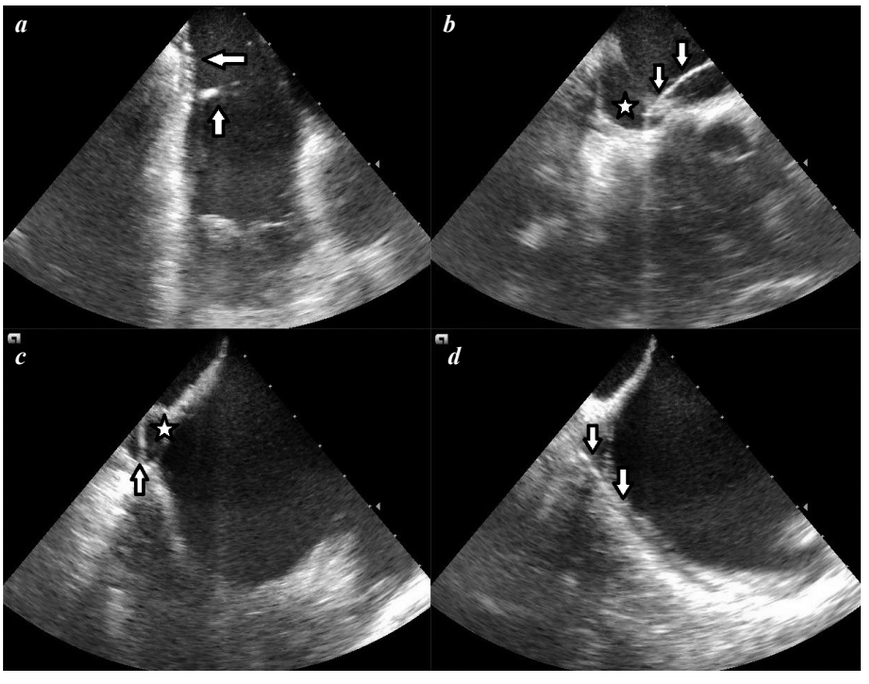


***Figure 1. Catheter positioning under intracardiac echocardiography (ICE) guidance: (a) the ablation catheter (horizontal arrow) positioned at the central portion of the cavotricuspid isthmus (CTI); the pronounced length of the isthmus is notable; (b-d) placement of the diagnostic 10-pole catheter (vertical arrows) into the coronary sinus; the asterisk indicates the coronary sinus ostium.***

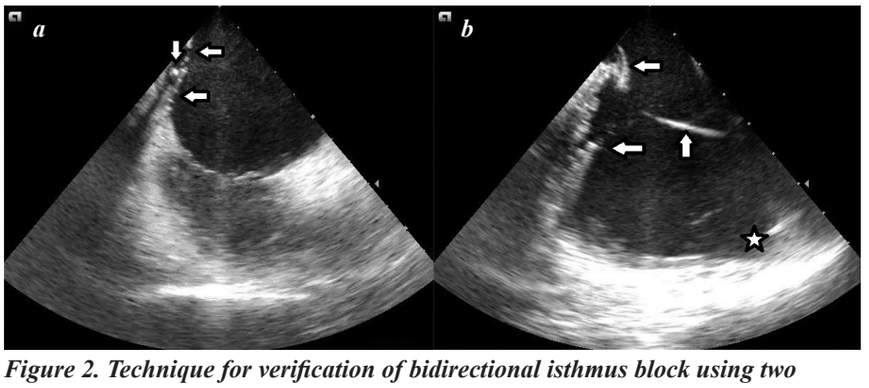


***Figure 2. Technique for verification of bidirectional isthmus block using two catheters: (a) the ablation catheter (horizontal arrows) positioned on the lateral aspect of the CTI; (b) the ablation catheter positioned on the right atrial free wall. The vertical arrow indicates the diagnostic 10-pole catheter positioned in the coronary sinus; the asterisk marks the right atrial appendage.***

under ICE guidance. After confirmation of typical AFL, continuous linear CTI ablation from the tricuspid valve annulus to the inferior vena cava (IVC) orifice was performed with constant assessment of catheter-endocardial contact, using the following parameters: power 35 W and irrigation rate 30 mL/min. Energy delivery at each target point was continued until a change in the morphology of the local electrogram recorded on the distal electrode pair of the ablation catheter was observed (Fig. 1a). Ablation was continued until bidirectional CTI conduction block was achieved, as determined by changes in activation patterns on the diagnostic catheters.

In the ZF group, catheter positioning at all stages of the procedure was performed exclusively under ICE guidance. To assess intracardiac electrograms, an ablation catheter positioned in the CTI region and a single diagnostic 10-pole catheter were used instead of two diagnostic catheters. A 20-pole catheter was not employed due to the technical difficulty of positioning it along the lateral RA wall without fluoroscopy (Fig. 1b-d). The diagnosis of typical AFL was confirmed using the entrainment technique during pacing from the CTI region. Under ICE guidance, linear CTI ablation from the tricuspid annulus to the IVC orifice was performed using parameters identical to those applied in the MF group. The presence of CTI block was assessed during pacing from the proximal electrodes of the 10-pole catheter positioned at the coronary sinus ostium. The interval from the pacing stimulus to the signal recorded on the ablation catheter electrodes was evaluated with the catheter positioned at two sites: immediately lateral to the radiofrequency lesion line and at the lateral RA wall. In the presence of CTI conduction block, the stimulus-signal interval shortened as the ablation catheter was moved further away from the ablation line. A similar assessment of the stimulus-signal interval was performed during pacing from the ablation catheter itself (Fig. 2). In this manner, bidirectional isthmus block was confirmed. This methodology was originally described by D.G. Katritsis et al. [21].

ICE was performed using the AcuNav intracardiac ultrasound catheter (Siemens, Germany). Radiofrequency energy was delivered using an irrigated 4-mm non-navigational ablation catheter (Blazer Open Irrigated, Boston Scientific, USA), introduced via a steerable intracardiac sheath, which ensured optimal and stable catheter-endocardial contact. In cases of residual conduction across the isthmus, mapping with the ablation catheter was performed to identify the presumed breakthrough site, followed by additional radiofrequency applications. If necessary, linear ablation of the lateral portion of the CTI was carried out (Fig. 2). Acute procedural success was defined as persistence of CTI conduction block during a 20-minute waiting period.

The primary endpoints were freedom from AFL recurrence during the follow-up period and the absence of complications. Secondary endpoints included total procedure duration (from the first vascular puncture to removal of the final instrument), fluoroscopy time, length of postoperative hospital stay, and the number of deaths during the follow-up period.

***Table 1.***

***Clinical and demographic characteristics of patients***

| | MF (n=88) | ZF (n=88) | p |
|---|---|---|---|
| Male sex, % | 64.8 | 76.1 | 0.0995 |
| Age, years | 61.5±10.4 | 61.2±10.6 | 0.841 |
| BMI, kg/m$^2$ | 30.2±5.3 | 30.3±4.9 | 0.886 |
| AH, n (%) | 63 (71.6) | 70 (79.5) | 0.2208 |
| CAD, n (%) | 20 (22.7) | 25 (28.4) | 0.3890 |
| CHF, n (%) | 24 (27.3) | 34 (38.6) | 0.1098 |
| DM, n (%) | 13 (14.8) | 21 (23.9) | 0.1277 |
| PH, n (%) | 4 (4.5) | 4 (4.5) | 1.0 |
| CIED, n (%) | 6 (6.8) | 9 (10.2) | 0.4193 |
| RA size, cm | 19.4±4.9 | 20.8±5.1 | 0.0650 |
| Paroxysmal AFL, % | 39.8 | 52.3 | 0.0971 |
| Persistent AFL, % | 60.2 | 47.7 | |
| AF, n (%) | 41 (46.6) | 30 (34) | 0.0919 |
| Class IC AAD, n | 20 (Allapinin 40%, Propafenone 60%) | 13 (Allapinin - 54%, Propafenone - 46%) | 0.3464 |
| Class II AAD, n | 42 (Bisoprolol 67%, Metoprolol 33%) | 42 (Bisoprolol - 79%, Metoprolol - 21%) | 1.0 |
| Class III AAD, n | 17 (Sotalol - 59%; Amiodarone - 41%) | 25 (Sotalol - 52%, Amiodarone - 48%) | 0.1583 |
| Class IV AAD, n | 5 (Verapamil - 100%) | 2 (Verapamil - 100%) | 0.2486 |
| Digoxin, n | 3 | 3 | 1.0 |
| CombAADT, n | 14 | 18 | 0.4357 |
| No AADT, n | 15 | 20 | 0.3464 |

Notes: hereinafter, MF - minimal fluoro; ZF - zero fluoro; BMI - body mass index; AH - arterial hypertension; CAD - coronary artery disease; CHF - chronic heart failure; DM - diabetes mellitus; PH - pulmonary hypertension; CIED - implanted cardiac electronic device; RA - right atrium; parAFL and persAFL - paroxysmal and persistent atrial flutter; AF - atrial fibrillation; AAD - antiarrhythmic drug; combAADT - combination antiarrhythmic drug therapy (AADT).

Statistical analysis of the study data was performed using SPSS Statistics, MedCalc, and Microsoft Excel software. Descriptive statistics for continuous variables are presented as the mean and standard deviation. Inferential statistical analysis was conducted using Student's t-test for comparisons of quantitative variables and the Pearson $\chi^2$ test for categorical variables. Freedom from arrhythmia recurrence during long-term follow-up was assessed using the Kaplan-Meier method. Differences were considered statistically significant at $p < 0.05$.

## RESULTS

A total of 176 patients were included in the analysis: 88 in the MF group and 88 in the ZF group. The compared groups were comparable in terms of the main clinical and demographic characteristics. A trend toward a larger RA size was observed in the ZF group (19.4 cm vs 20.9 cm, p = 0.0611, respectively); however, this difference did not reach statistical significance (Table 1).

Intraoperative success was achieved in 100% of cases. The duration of the procedure did not differ significantly between the groups. In the non-fluoroscopic group, 100% of procedures were performed without the use of X-ray radiation. No clinically significant complications were recorded in either group. The length of postoperative hospital stay also did not differ between the groups (Table 2).

During the follow-up period, death occurred in 4 patients (2 in the MF group and 2 in the ZF group, p = 1.0): in 2 cases due to pre-existing pulmonary hypertension, in 1 case due to acute pulmonary embolism, and in 1 case as a consequence of myocardial infarction. Among the 172 patients who completed the follow-up period, long-term efficacy was comparable between groups and amounted to 94.2% and 96.5% over one year in the MF and ZF groups, respectively (p = 0.4703). The incidence of atrial fibrillation did not differ between groups and was 30.7% and 22.7% in the MF and ZF cohorts, respectively (p = 0.2343) (Table 3). Kaplan-Meier curves were used to assess freedom from typical AFL recurrence during follow-up (Fig. 3).

## DISCUSSION

Fluoroscopy is considered the universally accepted imaging modality for performing CTI RFA. However, the development and clinical implementation of new technologies, such as three-dimensional electroanatomical mapping and ICE, have made it possible to reduce the need for X-ray radiation to a minimum. Several studies published in the international literature have evaluated approaches that minimize (MF) or completely eliminate (ZF) the need for fluoroscopy during CTI RFA, based on the use of electroanatomical mapping systems or ICE (Tables 4 and 5) [10, 11, 20, 22-26]. According to published data, the use of intracardiac ultrasound as an additional imaging modality in catheter treatment of typical AFL is associated with

***Table 2.***

***Comparison of in-hospital and intraoperative parameters between MF and ZF approaches***

| | MF | ZF | p |
|---|---|---|---|
| Intraoperative success, % | 100 | 100 | |
| Procedure duration, min | 69.4±23.7 | 63.9±20.6 | 0.1030 |
| Fluoroscopy time, min | 6.5±4.9 | 0 | <0.001 |
| RF application time, min | 9.1±4.1 | 8.3±3.4 | 0.1606 |
| Complications | 0 | 0 | 1.0 |
| PHP, days | 4.6±1.7 | 4.3±2.4 | 0.302 |

Note: RF - radiofrequency; PHP - postoperative hospital period.

***Table 3.***

***Comparison of long-term outcomes (12-month follow-up) between MF and ZF approaches***

| | MF | ZF | p |
|---|---|---|---|
| Freedom from recurrence, % | 94.2 | 96.5 | 0.4703 |
| Mortality, n (%) | 2 (2.8) | 2 (2.8) | 1.0 |
| AF*, n (%) | 27 (30.7) | 20 (22.7) | 0.2343 |

Note: * - during the follow-up period

***Table 4.***

***Comparison of MF-approach outcomes across different studies***

| | This study | Hindricks 2009 [23] | Bencsik 2012 [11] | Herman 2017 [10] | Turcsan 2023 [22] | Debreceni 2023 [24] |
|---|---|---|---|---|---|---|
| AVT | ВС-ЭхоКГ | ЭАН | ВС-ЭхоКГ | ВС-ЭхоКГ | ВС-ЭхоКГ | ВС-ЭхоКГ |
| Number of procedures, n | 88 | 105 | 50 | 40 | 219 | 40 |
| Acute success, % | 100 | 94 | 100 | 100 | 100 | 100 |
| Long-term success, % | 94.3 | 93.3 | 99 | - | - | - |
| Complications, % | 0 | 0 | 0 | 0 | 0 | 0 |
| Procedure time, min | 69.4±23.7 | 99±57 | 68.1±15.1 | 82.0±20.8 | 70 [52; 90] | 55.5 [46.5; 66.8] |
| RF application time, min | 9.1±4.1 | - | 8±8.9 | 10±6.3 | 10.9 [6.9; 16.4] | 9.9 [7.5; 15.1] |
| Fluoroscopy time, min | 6.5±4.9 | 7.7±7.3 | 5.54±3.77 | 3.29±2.60 | 15 [9.4; 19.6] | 0.9 [0.6; 1.5] |

Note: hereinafter, AVT - additional visualization tool; ICE - intracardiac echocardiography; EAM - electroanatomical mapping.

a significant reduction in fluoroscopy time and radiation dose while achieving efficacy and safety outcomes comparable to those of the conventional fluoroscopic approach [10, 11, 22]. At the same time, in 5-13% of cases, intracardiac ultrasound had to be used in addition to fluoroscopy to achieve intraoperative success because anatomical features prevented the creation of a durable ablation line. Such characteristics as CTI length, concave configuration, trabeculation, and a prominent Eustachian ridge are the main factors that hinder the creation of a durable isthmus block [27, 28]. During ablation, direct visualization of anatomical structures becomes crucial, which is not achievable with fluoroscopy or electroanatomical mapping alone.

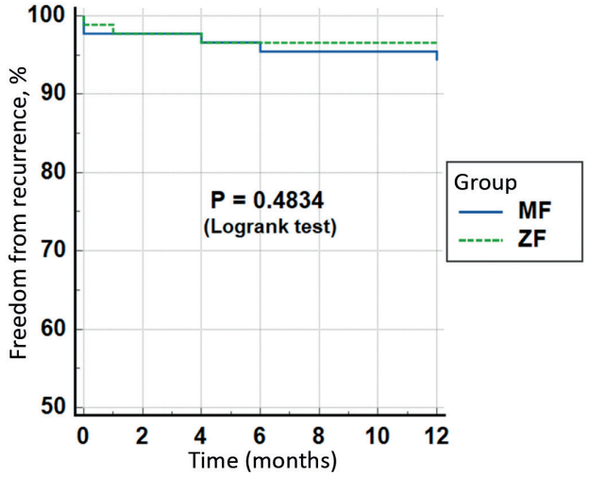


***Figure 3. Kaplan-Meier curve for atrial flutter recurrence. MF - minimal fluoro; ZF - zero fluoro.***

In the present study, a prominent Eustachian ridge was identified as the key factor preventing the achievement of a durable isthmus block with the first ablation line. Under these conditions, adequate endocardial contact near the IVC ostium could only be achieved by maximal deflection of the steerable sheath and ablation catheter under direct intracardiac ultrasound guidance (Figure 4a). In this study, the above-described maneuver was required in 36 of 176 patients (20.4%) to achieve a durable isthmus block. In some cases, conduction block was facilitated by additional ablation of the Eustachian ridge itself (Fig. 4b).

Overall, 8 patients with pulmonary hypertension (PH) were included in the study, accounting for 4.5% of the total cohort. It is well known that the manifestation of arrhythmias in patients with PH is associated with right ventricular failure, deterioration of clinical status, and increased mortality. At the same time, recent studies suggest that strategies aimed at restoring and maintaining sinus rhythm are associated with better clinical outcomes in this population [29]. In 4 of the 8 patients with PH (2 in the MF group and 2 in the ZF group), intraoperative ICE revealed thinning of the myocardium in the CTI region. For safety reasons, ablation under these conditions was performed with particular caution and with reduced power settings, not exceeding 30 W. Overall, 25% (2 of 8) of patients with PH died from causes unrelated to AFL recurrence. Among the remaining patients, 33.3% (2 of 6) experienced AFL recurrence during follow-up, which is comparable to data from recent studies [30]. It remains debatable whether the relatively high

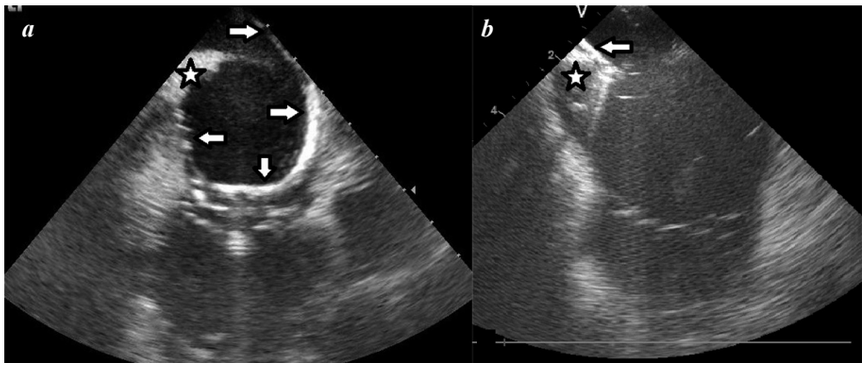


***Figure 4. Ablation in the presence of a prominent Eustachian ridge (asterisks): (a) maximal deflection of the steerable sheath and ablation catheter (arrows) to achieve adequate endocardial contact near the inferior vena cava ostium; (b) ablation of the Eustachian ridge itself from the inferior vena cava side.***

***Table 5.***

***Comparison of zero-fluoroscopy (zf) approach outcomes across different studies***

| | This study | Alvarez 2011 [25] | Fernandez-Gomez 2014 [26] | Debreceni 2023 [24] | Luani 2023 [20] |
|---|---|---|---|---|---|
| Visualization modality | ICE | EAM | ICE | ICE | ICE |
| Number of procedures | 88 | 83 | 153 | 40 | 30 |
| Acute success, % | 100 | 98.8 | 99.3 | 100 | 100 |
| Fluoroscopy required, % | 0 | 9.6 | 5.9 | 2.5 | 0 |
| Long-term success, % | 96.6 | 96.25 | 100 | - | - |
| Complications, % | 0 | 1.2 | 0 | 0 | 0 |
| Procedure time, min | 63.9±20.6 | 141±47 | 102.3±52.9 | 51.5 [44.0; 65.5] | 41.4±19.9 |
| RF application time, min | 8.3±3.4) | 15±13 | 7.8±11.3 | 7.2 [4.3; 12.5] | 6±3.1 |
| Fluoroscopy time, min | 0 | 1.8±7.2 | - | - | 0 |

recurrence rate is directly related to the course of PH itself or to the reduced ablation power settings used in the setting of a thinned myocardium, given that a durable isthmus block was achieved in all cases. Further studies with larger sample sizes are required to clarify the mechanisms underlying AFL recurrence after catheter ablation in patients with PH.

The incidence of atrial fibrillation during the follow-up period did not differ between the groups. Overall, atrial fibrillation episodes were documented in 47 of 176 patients (26.7%). The incidence was 42% among patients with a prior history of atrial fibrillation and 16% among those without such a history. These findings are consistent with the results of a large meta-analysis by F.J. Pérez et al. [8].

No differences between the two groups were identified with respect to the key efficacy and safety parameters (Tables 2 and 3). All procedures in the ZF group were performed exclusively under intracardiac ultrasound guidance, without the need for fluoroscopy at any stage, while demonstrating comparable procedure duration and radiofrequency application time. Thus, the feasibility of ICE as a standalone imaging modality for catheter treatment of typical AFL was demonstrated.

When compared with data from international studies, the present results were comparable in terms of key outcomes, including intraoperative and long-term efficacy, safety, and procedure duration (Tables 4 and 5). This study represents the first investigation to assess the long-term efficacy of a non-fluoroscopic approach to catheter treatment of typical AFL based exclusively on the use of ICE as the imaging modality, in comparison with the conventional fluoroscopic approach.

## CONCLUSION

The development of catheter-based treatments for cardiac arrhythmias that rely on non-fluoroscopic imaging modalities represents one of the most relevant directions in modern interventional electrophysiology. ICE is widely used as an adjunctive imaging tool in most electrophysiological procedures, allowing for a substantial reduction in radiation exposure. The present study describes a radiation-free approach to catheter treatment of typical AFL, based on the use of intracardiac ultrasound as the sole imaging modality. The absence of significant differences in procedural efficacy demonstrates that ICE is capable of replacing fluoroscopy at all stages of CTI radiofrequency ablation, in some cases providing more detailed visualization. The proposed technique enables the complete elimination of X-ray radiation during catheter treatment of typical AFL without compromising procedural efficacy or safety.

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# INTRAOPERATIVE ESOPHAGEAL TEMPERATURE MONITORING DURING CRYOBALLOON ABLATION IN PATIENTS WITH ATRIAL FIBRILLATION

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**Aim.** To study the frequency of a significant decrease in the esophageal temperature during the standard and "extended" cryoballoon ablation (CBA) procedure in patients with paroxysmal and persistent atrial fibrillation (AF).

**Methods.** The study included 160 patients (median age 66 [57;70] years, 90 [56.3%] male) with symptomatic paroxysmal and persistent AF. 139 (80.0%) patients with paroxysmal AF underwent pulmonary vein (PV) CBA, and 21 (20.0%) patients with persistent AF underwent "extended" PV CBA in combination with cryoablation of the left atrial posterior wall. At all stages of CBA exposure, esophageal temperature was assessed using the Astrocard Esosafety multichannel esophageal temperature monitoring system (MTP) (Astrocard, JSC Meditek). The criterion for stopping the CBA was considered to be a decrease in temperature below 20 °C.

**Results.** Electrical isolation of PV was achieved in all 160 patients with CBA. In the group of standard CBA PV (n=139), the temperature <20 °C in MTP was determined in 22 (16%) patients, with an average value of 17.23±1.74 °C. In 13 of 22 (59%) patients the temperature <20 °C in MTP was recorded with CBA of the left lower PV. In the group of "extended" CBA (n=21), the temperature <20 °C in MTP was determined in 18 (86%) patients, with an average value of 17.1±0.6 °C. When evaluating the fluoroscopic options for the location of the MTP sensor in the esophagus relative to PV, the esophagus of "central localization" was determined in 105 (76%) patients, "left localization" in 21 (15%) patients, and "right localization" in 13 (9%) patients. In patients with a "left-sided" esophagus a decrease in temperature < 20 °C was observed significantly more often than in patients with a "central" esophagus (81% vs. 5.7%, p<0.05 according to the Fisher exact test). No serious complications were observed during the follow-up period after CBA.

**Conclusion.** Temperature monitoring using the "Astrocard Esosafety" system allows us to assess the dynamics of temperature changes in the esophagus during standard and "extended" CBA of the LA, providing important information for selecting ablation strategies and parameters that potentially reduce the risk of thermal damage to the esophagus.

**Key words:** atrial fibrillation; cryoballoon ablation; pulmonary veins; extended cryoballoon ablation; esophageal temperature monitoring; left atrium

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At present, catheter ablation is a highly effective method for the treatment of atrial fibrillation (AF). Radiofrequency catheter ablation (RFA) and cryoballoon ablation (CBA) of the pulmonary veins (PVs) have a high level of recommendation for the treatment of symptomatic paroxysmal and persistent AF in cases of ineffective antiarrhythmic drug therapy. In patients with paroxysmal AF, catheter ablation is considered a first-line treatment option [1, 2].

RFA and CBA are classified as so-called "thermal" tissue ablation technologies, although this definition is fully applicable only to cryothermal ablation during CBA. Both energy modalities are capable of causing injury to adjacent anatomical structures. Due to the close anatomical relationship between the esophagus and the posterior wall of the left atrium (LA) and/or the PVs, cryothermal energy delivery during CBA may result in cold-induced injury of the esophageal wall, leading to necrosis, as well as bronchial injury and phrenic nerve palsy [3-5].

The most rare yet life-threatening complication of catheter ablation is the development of an atrioesophageal fistula (AEF). According to published data, mortality associated with AEF reaches 66-90%, and favorable outcomes

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are largely dependent on timely diagnosis and early surgical intervention. Diagnostic difficulty is primarily related to the delayed onset of symptoms, typically occurring 2-4 weeks after hospital discharge, which are often nonspecific and may include sepsis, cerebrovascular events, and gastrointestinal bleeding. According to the international POTTER-AF registry, among 553,729 AF ablation procedures, 138 cases (0.025%) of AEF were identified, with an overall mortality of 65.8% [6]. Registry authors reported that the incidence of fistula formation was 25-fold higher after RFA compared with CBA (0.038% vs. 0.0015%) [6].

Less severe esophageal injuries during catheter ablation occur more frequently and are often underestimated. These include esophageal mucosal erythema, erosions and ulcerations, esophageal and gastric motility disorders, and gastroesophageal reflux [7-9].

Current strategies aimed at reducing the risk of esophageal injury include shortening cryoapplication duration in the region of the posterior wall of the left atrium (PWLA), assessment of esophageal proximity to the LA using multislice computed tomography (MSCT), and continuous luminal esophageal temperature monitoring (ETM). Since 2017, the consensus document on catheter and surgical ablation of AF has recommended the use of luminal ETM systems to guide LA energy delivery in order to reduce the risk of esophageal injury [10].

Thus, real-time intraoperative monitoring of intraluminal esophageal temperature may potentially reduce the likelihood of esophageal injury during CBA procedures. The present study demonstrates the use of the Astrocard Esosafety temperature monitoring system for the prevention of possible esophageal injury during both standard and "extended" CBA procedures.

The aim of this study was to evaluate the incidence of clinically significant esophageal temperature reduction during standard and extended CBA procedures in patients with paroxysmal and persistent AF.

## MATERIALS AND METHODS

The study included patients ≥18 years of age with symptomatic paroxysmal or persistent AF who met the indications for CBA according to national guidelines. Exclusion criteria were any contraindications to interventional procedures, LA appendage thrombosis, uncorrected thyroid dysfunction, mitral valve disease, and long-standing persistent AF lasting more than 1 year.

Prior to the procedure, all patients underwent a comprehensive clinical evaluation, including complete blood count and biochemical analysis, thyroid hormone assessment, 12-lead electrocardiography (ECG), 24-hour Holter ECG monitoring, and transthoracic echocardiography. In addition, esophagogastroduodenoscopy was performed in all patients before the intervention to exclude erosive or ulcerative lesions of the esophagus and stomach.

All CBA procedures were performed under combined endotracheal general anesthesia. Venous access was obtained via puncture of the right femoral vein using the Seldinger technique. A steerable multipolar catheter (EP-XT, Boston Scientific, USA) was positioned in the coronary sinus for atrial signal recording and pacing. Prior to transseptal puncture, transesophageal echocardiography was performed in all patients to exclude atrial and left atrial appendage thrombosis and to guide transseptal access. Intravenous heparin was administered to maintain an activated clotting time of 300-350 ms.

CBA was performed using a 28-mm Arctic Front Advance Pro balloon catheter (Medtronic, USA). A 20-mm Achieve circular mapping catheter (Medtronic, USA) was used for PV potential recording and balloon positioning. A single cryoapplication lasting 240 seconds was delivered at the antral portion of each PV, targeting temperatures between -40 °C and -60 °C. If the time to isolation (TTI) was ≤40 seconds, the cryoapplication duration was reduced to 180 seconds. In the absence of antral isolation within 60 seconds in the inferior PVs, a pulldown maneuver was performed to improve balloon contact with the inferior PV wall.

In 21 patients with persistent AF (duration up to 12 months), an "extended" CBA protocol was applied, which included, in addition to PV antral isolation, a series of cryoapplications targeting the PWLA. The extended protocol was performed according to the methodology described by A. Aryana et al. [11].

Prior to ablation, a baseline left atrial voltage map was created using the Abbott EnSite Precision system (Abbott, USA) with a high-density multipolar HD Grid mapping catheter (Abbott, USA). Areas with bipolar signal amplitude >0.5 mV were classified as normal voltage, amplitudes 0.1-0.5 mV as low voltage, and amplitudes <0.1 mV as very low voltage areas.

After PV isolation, PWLA isolation was performed segmentally, with stepwise fixation of the circular catheter within each PV. A total of 10-14 cryoapplications were delivered to the PWLA, each lasting 120-180 seconds. The effectiveness of PWLA isolation was assessed using repeat electroanatomical mapping. In cases of incomplete PWLA

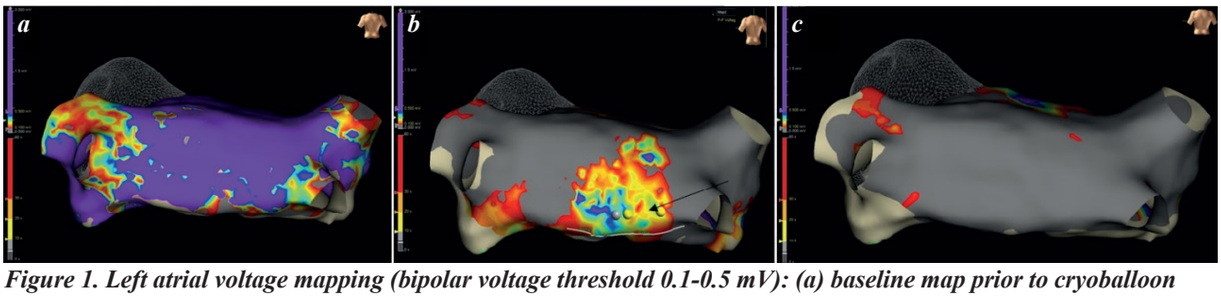


***Figure 1. Left atrial voltage mapping (bipolar voltage threshold 0.1-0.5 mV): (a) baseline map prior to cryoballoon ablation (CBA); (b) after pulmonary vein (PV) and posterior wall of the left atrium (PWLA) CBA (the arrow indicates an area of incomplete isolation of the mid-PWLA segment and the sites of additional radiofrequency applications); (c) final left atrial voltage map confirming complete isolation of the PVs and PWLA.***

isolation, additional irrigated radiofrequency ablation (30-35 W, 60 seconds) was applied to sites of residual atrial activity using a FlexAbility catheter (Abbott, USA). Complete PWLA isolation was confirmed by repeat voltage mapping (Fig. 1).

Prior to cryoballoon applications, the ETM probe was positioned within the esophagus under fluoroscopic guidance in the anteroposterior projection. The study utilized the KT-7 ASTROCARD probe (Fig. 2) and the Astrocard Esosafety temperature monitoring system, which enables real-time ETM across seven independent temperature channels, covering a range from 0 °C to +70 °C.

ETM was performed during all CBA applications and adjunctive RFA procedures. The position of the ETM probe was fluoroscopically adjusted relative to the cryoballoon before each cryoapplication. Termination of energy delivery was mandated when esophageal temperature decreased below +20 °C, as additional temperature reduction of up to 5 °C may occur within 60 seconds after cessation of cryoablation during the balloon thawing phase [12, 13]. The minimum esophageal temperature was defined as the lowest value recorded either during cryoapplication or during balloon thawing on any sensor of the ETM probe.

In patients with previously documented typical atrial flutter, RFA of the cavotricuspid isthmus (CTI) was performed as a second stage of the procedure. To assess bidirectional intra-atrial conduction across the CTI before and after RFA, a 20-pole Halo XP catheter (Biosense Webster, USA) positioned around the tricuspid annulus and a multipolar EP-XT catheter (Boston Scientific, USA) positioned in the coronary sinus were used. CTI RFA was performed using an irrigated FlexAbility catheter (Abbott, USA) via mid-septal, septal, or lateral approaches. The criterion for effective anatomically guided linear ablation between the tricuspid valve and the inferior vena cava was the achievement of bidirectional CTI conduction block [14, 15].

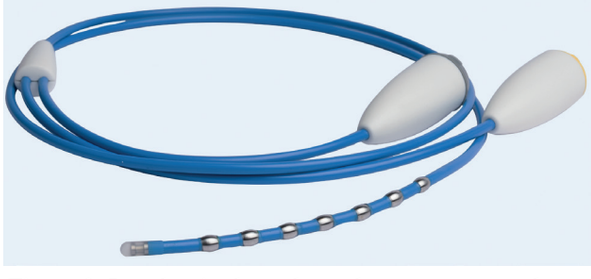

***Figure 2. Intraluminal esophageal temperature probe KT-7 (Astrocard).***

All patients, regardless of the extent of the intervention, were prescribed oral anticoagulant therapy for at least 2-3 months, with further continuation determined by the $CHA_2DS_2$-VASc score and individual thromboembolic risk. In addition, following CBA, all patients received antiarrhythmic therapy with class IC or class III agents (excluding amiodarone) or beta-blockers for a 3-month blanking period. Proton pump inhibitors were prescribed for 1 month after the procedure.

**Statistical analysis**

Statistical analysis was performed using Statistica 12.0 (StatSoft Inc., Tulsa, OK, USA) and Microsoft Office XP (Microsoft, USA). Data normality was assessed using the Shapiro-Wilk test. For quantitative variables with non-normal distribution, data are presented as median with lower and upper quartiles (lq; uq). Categorical dichotomous variables are presented as frequencies and percentages. Comparisons between independent groups for dichotomous variables were performed using Fisher's exact test. Differences were considered statistically significant at $p < 0.05$.

## RESULTS

A total of 160 patients with paroxysmal (n = 139, 87%) and persistent (n = 21, 13%) AF were included in the study. Among the enrolled patients, 90 (56.3%) were male, and the median age was 66 [57; 70] years. According to echocardiographic assessment, the mean LA volume was 70 ± 15.5 mL (95% CI: 65-74), and the LA volume index was 34.78 ± 7.6 mL/m² (95% CI: 32.4-35.8). When thromboembolic risk was assessed using the $CHA_2DS_2$-VASc score, the majority of patients (n = 94, 58.8%) had a score of ≥2 points. Among comorbid conditions, arterial hypertension predominated (n = 124, 77.5%). Detailed clinical and instrumental characteristics of the patients are presented in Table 1.

***Table 1.***

***Baseline clinical characteristics of the patients***

| Paremeter | Value |
|---|---|
| Age, years | 66.0 [57; 70] |
| Male sex, n (%) | 90 (56.3) |
| Body mass index, kg/m$^2$ | 27.8±4.4 (95% ДИ: 26.3-29.3) |
| Paroxysmal atrial fibrillation, n (%) | 139 (87.0) |
| $CHA_2DS_2$-VASc score, points | 3 [2; 4] |
| Arterial hypertension, n (%) | 124 (77.5) |
| Diabetes mellitus, n (%) | 31 (19.4) |
| Stroke / TIA, n (%) | 12 (7.5) |
| Coronary artery disease, n (%) | 15 (9.4) |
| Left atrial volume, mL | 70±15.5 (95% ДИ: 65.2-74.1) |
| Left atrial volume index, mL/m$^2$ | 34.78±7.6 (95% ДИ: 32.4-35.8) |

Note: TIA - transient ischemic attack.

During CBA, electrical isolation of the PVs was achieved in all 160 (100%) patients with paroxysmal and persistent AF. Contrast-enhanced left atrial angiography revealed a common PV collectorin 10 (6.3%) patients, which did not prevent successful cryoisolation. In 21 (13%) patients with persistent AF, PWLA cryoablation was performed; the median number of cryoapplications to the PWLA was 11 [IQR: 10-11.4]. Radiofrequency ablation of the CTI was performed in 11 (6.8%) patientswith previously documented concomitant typical atrial flutter.

According to ETM data, among 139 patients who underwent PVs-only CBA, 22 (16%) patients exhibited a decrease in esophageal temperature below 20 °C, necessitating termination of cryoenergy delivery. The mean minimum esophageal temperature recorded

was 17.23 ± 1.74 °C, with a median cryoablation duration of 104 [74; 126] seconds until temperature reduction occurred. In 4 of these 22 patients, the temperature dropped below 20 °C within the first 60 seconds of cryoablation.

Critical esophageal temperature reduction most frequently occurred during left inferior pulmonary vein (LIPV) ablation, observed in 13 of 22 (59%) patients. In 5 (23%) cases, temperature reduction occurred during right superior PV ablation; in 2 (9%) cases, during left superior PV ablation; and in 2 (9%) cases, during right inferior PV ablation (Fig. 3 and 4). To achieve isolation of the inferior PVs, the "pulldown" maneuver during CBA of the LIPV was performed in 88 of 139 (65%) patients, and during CBA of the RIPV in 25 of 139 (18%) patients. Among patients in whom ETM detected a temperature decrease below 20 °C, the pulldown maneuver during LIPV ablation resulted in a significantly higher incidence of esophageal temperature reduction <20 °C compared with its use during RIPV ablation (68% vs 12%, $p < 0.05$, Fisher's exact test).

In 18 of 21 (86%) patients undergoing extended cryoablation with PWLA applications, a decrease in esophageal temperature below 20 °C was observed. The mean minimum esophageal temperature was 17.1 ± 0.6 °C, with a median cryoablation duration of 128 [112; 162] seconds until temperature decrease. Comparison of minimum esophageal temperatures during PV CBA and PWLA CBA revealed no significant difference ($p = 0.834$).

In 139 patients, fluoroscopic assessment in the anteroposterior projection was used to evaluate esophageal probe position relative to the left and right PVs. In the majority of cases (n = 105, 76%), a central esophageal position was identified; a left-sided position was observed in 21 (15%) patients, and a right-sided position in 13 (9%) patients (Figure 5).

According to ETM results during CBA, with left-sided esophageal positioning, a temperature decrease below 20 °C was registered in 17 of 21 (81%) patients; with right-sided positioning, in 3 of 13 (23%) patients; and with central positioning, in 6 of 105 (5.7%) patients. Esophageal temperature reduction below 20 °C occurred significantly more frequently with left-sided positioning compared with the central variant (81% vs 5.7%, $p < 0.05$, Fisher's exact test).

No major complications (death, cardiac tamponade/hemopericardium, atrioesophageal fistula, or major bleeding) were observed in this study cohort. Transient phrenic nerve palsy occurred in 7 (5%) patients during CBA and resolved during hospitalization. Venous thrombosis at the puncture site was detected in 11 (8%) patients and resolved with anticoagulant therapy within 1 month.

## DISCUSSION

According to the international POTTER-AF registry, AEF is a rare but highly lethal complication of CBA for AF. However, in routine clinical practice, the true incidence of AEF and other types of esophageal injury following cryoablation remains insufficiently studied. According to the Russian Cryoablation Registry (2017-2019), which included 976 patients with AF, AEF was identified in 2 (3.8%) patients among clinically significant complications of CBA (n = 53). Notably, ETM during pulmonary vein CBA was used in only 16 (1.6%) procedures.

Currently, several techniques and technologies may potentially reduce the risk of esophageal injury during CBA:

1. CT or MRI visualization of esophageal anatomy with integration into electroanatomical mapping systems;
2. esophageal deviation maneuvers during the procedure;
3. breathing pattern modification techniques;
4. use of devices that increase esophageal temperature;
5. dosing and limitation of cryoenergy delivery;
6. ETM with multisensor probes and immediate termination of energy delivery upon reaching critical temperature thresholds.

ETM represents the most accessible intraoperative method for real-time assessment of temperature changes

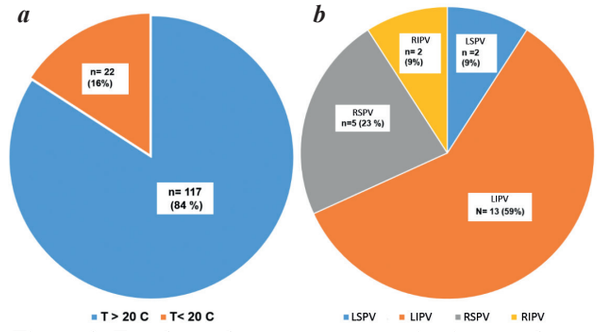


***Figure 3. Esophageal temperature monitoring results during cryoablation limited to pulmonary vein isolation: (a) distribution of temperature values >20 °C and <20 °C; (b) anatomical sites of temperature reduction below 20 °C (RSPV, RIPV, LSPV, and LIPV - right superior, right inferior, left superior, and left inferior pulmonary veins, respectively).***

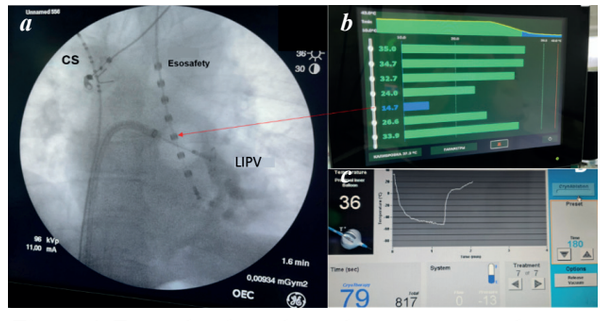


***Figure 4. Example of esophageal temperature reduction to 14.7 °C recorded by the esophageal temperature monitoring (ETM) probe at 79 seconds of cryoapplication with a balloon temperature of -52 °C in the antral region of the left inferior pulmonary vein (LIPV): (a) fluoroscopy in the anteroposterior projection showing the cryoballoon position at the LIPV, the ETM probe located in the mid-esophagus (arrow), and the diagnostic coronary sinus (CS) catheter positioned in the superior vena cava for phrenic nerve pacing; (b) real-time temperature monitoring from all seven sensor poles during LIPV cryoablation; (c) temperature trend graph during CBA displayed on the cryoconsole monitor (CS - coronary sinus; LIPV - left inferior pulmonary vein; arrow indicates the ETM sensor pole recording the minimum intraluminal esophageal temperature).***

to identify potential thermal injury risk. According to the HRS consensus document on catheter and surgical ablation of AF, esophageal monitoring is recommended to guide energy delivery during both radiofrequency ablation (RFA) and cryoballoon ablation.

Large randomized trials have demonstrated that CBA is comparable to RFA in terms of efficacy, reduction in hospitalization rates, repeat ablation procedures, and recurrence of atrial tachyarrhythmias. With respect to esophageal injury risk, several studies suggest a potential safety advantage of cryoablation over RFA.

During CBA (as with RFA), intramural atrial myocardial injury occurs. Rapid formation of intracellular and interstitial ice crystals initiates apoptotic processes, leading to cell death followed by fibrotic remodeling. The zone of cryothermal injury may extend to adjacent organs, particularly the esophagus, which lies in close proximity to the PWLA and/or PVs, potentially causing esophageal vascular necrosis and wall injury.

The anatomical relationship between the esophagus and the LA/PVs is highly variable, which must be considered when assessing the risk of esophageal injury. In a CT-based study by K. Lemola et al. (2004) involving 50 patients, the esophagus was found to be in direct contact with the PWLA in nearly all cases, with a mean contact length of approximately 19 mm, most commonly positioned closer to the left pulmonary veins. In addition to proximity, LA myocardial thickness, pericardial fat, and connective tissue layers may influence esophageal cooling during CBA, factors that are not always adequately assessed preoperatively.

Use of multisensor esophageal temperature probes has been associated with a lower incidence of esophageal injury detected by post-ablation esophagogastroduodenoscopy, compared with single-sensor probes (2.3% vs 6.8%; p = 0.016). In the study by A. Fürnkranz et al. (2015), termination of CBA when esophageal temperature dropped below 15 °C during ETM significantly reduced the risk of esophageal injury (to ~1.5%), while achieving PV isolation in all cases.

In the present study, the use of a multielectrode ETM probe allowed temperature recording across a wide range via multiple independent channels, enabling timely termination of cryoenergy delivery. Our results demonstrate that during standard CBA, critical esophageal temperature reduction was observed in 16% of cases within 1-2 minutes of cryoapplication. Temperature reduction occurred most frequently during ablation of the left inferior pulmonary vein (LIPV) (Fig. 2). Because ablation of inferior PVs often requires additional maneuvers to achieve complete venous occlusion (the "pull-down" maneuver), the resulting increased balloon pressure on the atrial wall may elevate the risk of rapid excessive esophageal cooling, underscoring the need for continuous temperature monitoring to prevent collateral injury. In our study, use of the pull-down maneuver during LIPV CBA was associated with a significantly higher incidence of esophageal temperature reduction below 20 °C compared with its use during right inferior pulmonary vein ablation.

In the present study, we demonstrate for the first time that the use of an "extended" CBA protocol is associated with a higher risk of esophageal temperature reduction, making ETM mandatory in all such cases. When comparing the minimum esophageal temperatures recorded during pulmonary vein CBA and (PWLA) ablation, no significant differences in ETM values were observed.

It was noted that the position of the esophagus may significantly influence the probability of excessive temperature reduction during CBA. In the most common "central" esophageal position, the risk was relatively low (5.7%), but increased to 23% with right-sided esophageal positioning. The highest risk of excessive temperature reduction was observed in the left-sided esophageal position, reaching 81% during CBA.

Another important approach to improving the safety of CBA is the use of the time-to-isolation (TTI) protocol for cryoenergy dosing. According to this protocol, investigators propose limiting the duration of cryoablation to the time required to achieve PV isolation plus one additional minute. This strategy allows durable pulmonary vein isolation while reducing the risk of esophageal injury. However, this approach has certain limitations, as even with modern balloon catheter designs, electrical activity of the PVs cannot always be recorded during cryoablation due to anatomical factors. Moreover, the use of the TTI protocol does not eliminate the need for ETM, as confirmed by our findings, where critical esophageal temperature reduction occurred within the first minute of ablation in 16% of cases.

Importantly, shortening cryoablation duration based on ETM data did not negatively affect procedural efficacy. In our study, termination of cryoenergy delivery upon reaching critically low esophageal temperatures did not prevent PV isolation, did not result in reconnection of previously isolated veins, and did not compromise achievement of PWLA isolation criteria in any case.

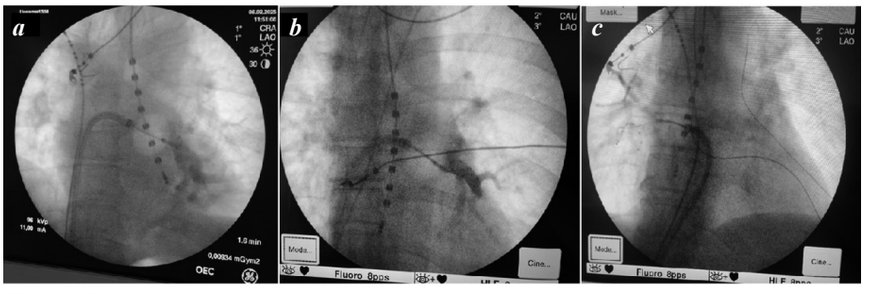


***Figure 5. Variants of esophageal probe positioning during pulmonary vein contrast injection in CBA: (a) left-sided; (b) central; (c) right-sided localization.***

**Study limitations**

The main limitations of this study include the absence of post-procedural endoscopic assessment of potential subclinical esophageal mucosal injury associated with CBA. Given the very low incidence of AEF after CBA (0.0015% according to the POTTER-AF registry) and the limited sample size of our single-center study, it is not possible to

reliably assess the risk of clinically significant esophageal injury following CBA. The temperatures recorded during ETM reflect values in the esophageal segment closest to the balloon at the time of cryoapplication. In addition, in our study, the fluoroscopically determined position of the ETM probe was considered an additional risk factor for excessive esophageal cooling, rather than a true representation of esophageal anatomical variants relative to the left atrium and pulmonary veins.

## CONCLUSION

Esophageal temperature monitoring using the Astrocard Esosafety system enables real-time assessment of esophageal temperature dynamics during both standard and extended PV CBA. This provides clinically relevant information for selecting ablation strategies and parameters that may reduce the risk of esophageal thermal injury.

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# CLINICAL BENEFITS OF SWITCHING FROM RIGHT VENTRICULAR APICAL PACING TO LEFT BUNDLE BRANCH AREA PACING IN PATIENTS WITH COMPLETE ATRIOVENTRICULAR BLOCK: ACUTE RESULTS

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**Aim.** To evaluate the impact of upgrading from right ventricular apical pacing (RVAP) to left bundle branch area pacing (LBBAP) on the clinical and functional status of patients with complete atrioventricular block (AVB) in the acute period.

**Methods.** The study included 30 patients with complete AVB and previously implanted pacemakers. All patients underwent elective pacemaker replacement with repositioning of the ventricular lead from the apical site to the LBBAP area. Clinical and instrumental assessments were performed before surgery and on postoperative day 5, including electrocardiography, echocardiography, a 6-minute walk test and quality of life evaluation using the EQ-5D questionnaire.

**Results.** After conversion to LBBAP, QRS duration decreased (from 158.5±25.5 ms to 111.2±13.8 ms, $p < 0.05$), interventricular and intraventricular dyssynchrony indices (interventricular mechanical delay and time to peak systolic velocity) were reduced, and the degree of mitral regurgitation decreased. The 6-minute walk test distance increased from 368.7±87.06 m to 466.15±127.2 m, and patients reported improved quality of life according to the EQ-5D questionnaire.

**Conclusion.** Conversion from RVAP to LBBAP leads to improved electrical and mechanical synchrony of cardiac function, which is associated with increased exercise tolerance and enhanced quality of life. LBBAP demonstrates potential as a more physiological and effective alternative to conventional apical pacing.

**Key words:** cardiac pacing; conduction system pacing; left bundle branch pacing; atrioventricular block; myocardial dyssynchrony

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Implantation of a permanent pacemaker significantly improves survival and quality of life in patients with complete atrioventricular block (AVB) and remains the cornerstone of treatment for bradyarrhythmias [1]. Recent studies have demonstrated that long-term right ventricular apical pacing induces myocardial dyssynchrony due to abnormal mechanical and electrical ventricular activation. This has a detrimental effect on left ventricular (LV) contractile function and subsequently leads to impaired myocardial perfusion, an increased risk of atrial fibrillation, a higher incidence and progression of heart failure (HF), and increased cardiovascular mortality [2]. Consequently, over the past decade, there has been an active search for alternative pacing sites capable of providing more physiological electromechanical ventricular activation. Currently, physiological conduction system pacing (CSP) is recommended in patients with a high percentage of ventricular pacing in order to reduce the risk of adverse outcomes [3].

CSP is a relatively new field of cardiac pacing that continues to gain popularity as a more physiological alternative to conventional right ventricular pacing (RVP) and as a potential substitute for biventricular cardiac resynchronization therapy (CRT) in patients with sinus rhythm and conduction disturbances [4]. One form of CSP is left bundle branch area pacing (LBBAP), which was first described as an alternative to LV resynchronization by Huang et al. in 2017. This pacing modality achieves direct activation of the left bundle branch (LBB) by positioning the pacing lead within the subendocardial region of the interventricular septum [5]. Compared with His bundle pacing (HBP), LBBAP is characterized by easier implantation and lower, more stable pacing thresholds. This pacing strategy has been associated with en-

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couraging clinical outcomes, preservation of myocardial contractile function, improved exercise tolerance, and enhanced quality of life [6].

In 2022 the results of the MELOS registry were published, including 14 European centers and 2,533 patients. The study demonstrated a procedural success rate of 92.4% in patients with bradycardia. Complications related to transventricular lead implantation occurred in 8.3% of cases, while the rate of long-term complications was low and comparable to that observed with conventional right ventricular pacing [7].

Several studies have also shown the efficacy and safety of switching to LBBAP in the treatment of pacing-induced cardiomyopathy caused by prolonged RVP [8]. Transition to LBBAP may also serve as a rescue strategy for patients who do not respond to CRT, resulting in significant improvements in cardiac function and clinical outcomes [9].

The aim of our study was to assess the immediate impact of changing the pacing site from the RVP to LBBAP on the clinical and functional status of patients with complete AVB.

## MATHERIALS AND METHODS

The study included 30 patients with previously implanted permanent pacemakers (PM) for complete AVB. The inclusion criteria were age ≥18 years, preserved left ventricular ejection fraction (LVEF ≥50%), and a ventricular pacing burden ≥80%. Patients with atrial fibrillation were not included. All patients were electively admitted to the Department of Surgical Treatment of Complex Cardiac Arrhythmias and Cardiac Pacing at the Republican Cardiology Dispensary (Cheboksary) for planned pacemaker replacement due to battery depletion. The mean pacemaker service life was 7.3 ± 0.8 years. The mean ventricular pacing percentage was 96.5 ± 2.7% (Table 1).

The mean age of the patients (Table 1) was 70.8 ± 8.7 years; 16 patients were male (53.33%) and 14 were female (46.67%). All patients had a high comorbidity burden, which is typical for this age group. Arterial hypertension was present in 29 patients (96.7%). Half of the study population (15 patients) had coronary artery disease; among them, 4 patients (13.3%) had a history of myocardial infarction, and 6 patients (20%) had previously undergone percutaneous coronary intervention. All patients had at least two concomitant diseases. HF was diagnosed in all patients: 17 patients (56.67%) had New York Heart Association (NYHA) functional class III HF, 12 patients (40%) had NYHA class II, and 1 patient (3.33%) had NYHA class I.

All patients were offered surgical intervention consisting of pacemaker reimplantation with relocation of the ventricular pacing lead from the right ventricular apical position to LBBAP. Written informed consent was obtained from all participants. The study complied with ethical standards based on the Declaration of Helsinki of the World Medical Association ("Ethical Principles for Medical Research Involving Human Subjects"), including the 2000 revision, and the "Rules of Good Clinical Practice in the Russian Federation," approved by Order No. 200n of the Ministry of Health of the Russian Federation dated April 1, 2016.

Before and after the surgical intervention (on the fifth postoperative day), all patients underwent 12-lead electrocardiography (ECG), transthoracic echocardiography with

***Table 1.***

***Patient characteristics***

| Parameter | Значение |
|---|---|
| Age, years | 70.8±8.7 |
| Male, n (%) | 16 (53.3) |
| Female, n (%) | 14 (46.7) |
| Pacemaker mode DDDR | 30 (100) |
| Pacemaker service life, years | 7.3±0.8 |
| Ventricular pacing percentage, % | 96.5±2.7 |
| CAD, n (%) | 15 (50) |
| PCI, n (%) | 6 (20) |
| Post-MI cardiosclerosis, n (%) | 4 (13.3) |
| Arterial hypertension, n (%) | 29 (96.67) |
| Stroke, n (%) | 2 (6.67) |
| BCA atherosclerosis, n (%) | 12 (40) |
| Diabetes mellitus, n (%) | 10 (33.3) |
| HF pre-stage, n (%) | 2 (6.67) |
| HF stage I, n (%) | 27 (90 ) |
| HF stage II, n (%) | 1 (3.33) |
| NYHA class I HF, n (%) | 1 (3.33) |
| NYHA class II HF, n (%) | 12 (40) |
| NYHA class III HF, n (%) | 17 (56.67) |

Note: PM - permanent pacemaker; PCI - percutaneous coronary intervention; CVA - cerebrovascular accident; BCA - brachiocephalic arteries; HF - heart failure; FC - functional class.

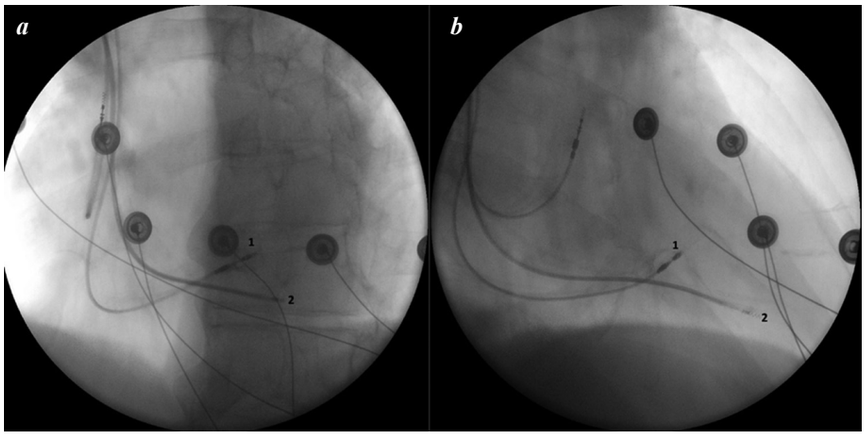


***Figure 1. Intraoperative fluoroscopy in the left (a) and right (b) oblique projections, where 1 indicates the ventricular lead positioned in the left bundle branch area and 2 indicates the previous ventricular lead in the apical position.***

additional assessment of myocardial dyssynchrony parameters, a six-minute walk test, and quality-of-life evaluation using the EQ-5D questionnaire.

During the procedure a modified stylet with two curves was used to position the pacing lead in the mid-septal region of the interventricular septum: a larger curve directed toward the right ventricle and a smaller curve to achieve maximum of perpendicular orientation of the lead relative to the interventricular septum. Lead position was confirmed using fluoroscopy in right and left anterior oblique projections at 30 degrees (Fig. 1). After meeting the criteria for left bundle branch capture during unipolar pacing, the effectiveness of pacing in bipolar mode was also assessed. If left bundle branch capture was not achieved in bipolar mode, additional rotations of the lead were performed to advance it deeper into the septum (Fig. 2). Once the final lead position was achieved, the stylet was removed and the lead was secured to the soft tissues.

**Statistical analysis**

Statistical analysis of the obtained data was performed using Statistica 10.0 software. Quantitative variables were assessed for normality using the Shapiro-Wilk test. Quantitative data were expressed as mean (M) ± standard deviation (SD) in the case of a normal distribution, and as median (Me) with lower and upper quartiles (Q1-Q3) when the distribution was non-normal.


***Figure 2. Changes in QRS morphology during stepwise advancement of the pacing lead within the interventricular septum on standard 12-lead ECG recordings: (a) native QRS complex without pacing; (b) left ventricular septal pacing (V6 RWPT = 78 ms, interpeak interval in leads V6-V1 = 47 ms); (c) non-selective left bundle branch pacing (V6 RWPT = 76 ms, interpeak interval in leads V6-V1 = 40 ms); (d) selective left bundle branch pacing (V6 RWPT = 60 ms, interpeak interval in leads V6-V1 = 54 ms).***

Comparisons between variables were performed using parametric statistical methods, specifically the Student's t-test for comparison of two independent samples. Differences were considered statistically significant at $p < 0.05$.

## RESULTS

After changing the ventricular pacing site from the apical position to LBBAP, we observed a number of changes in both electrocardiographic and echocardiographic parameters (Table 2). The mean QRS duration decreased significantly from 158.5 ± 25.5 ms before the procedure to 111.2 ± 13.8 ms after implantation ($p < 0.05$).

In all patients, myocardial dyssynchrony was reduced after the procedure, as reflected by a decrease in interventricular mechanical delay (IVMD) from 33.3 ± 24.2 ms to 15.8 ± 13.4 ms, and a reduction in septal-to-lateral delay measured as time to peak systolic velocity (Ts TDI) from 49.3 ± 34.2 ms to 21.4 ± 17.4 ms, indicating improved intraventricular synchrony. In addition, the severity of functional mitral regurgitation decreased from 17.05 ± 10.01% to 11.53 ± 9.24% ($p < 0.05$).

No statistically significant differences were observed in LVEF, cardiac chamber dimensions, or global longitudinal strain (GLS) before and after the procedure, most likely due to the early timing of follow-up echocardiography performed on postoperative day 5. It is evident that a longer follow-up period is required to assess dynamic changes in these parameters.

All patients underwent a six-minute walk test after the procedure. With LBBAP, the walking distance increased to 466.15 ± 127.2 m, compared with 368.7 ± 87.1 m during apical pacing ($p < 0.05$), representing an improvement of more than 25%. According to the EQ-5D quality-of-life questionnaire, the health status score increased from 61.2 ± 13.2% at baseline to 71.8 ± 14.9% after the procedure ($p < 0.05$).

## DISCUSSION

We identified clear advantages of transitioning from RVP to LBBAP, reflecting its greater physiology and potential effectiveness in providing optimal electrical and mechanical myocardial synchrony. Similar findings have been reported in several contemporary studies. For example, G. Dell'Era et al. demonstrated early echocardiographic changes in 50 patients following initiation of LBBAP, showing improvement in both interventricular and intraventricular dyssynchrony. This was achieved through a reduction in the time-to-peak strain standard deviation derived from the interventricular septum and the left ventricular lateral wall from 38.2 (13.6-53.9) ms to 15.1 (8.3-31.5) ms ($p < 0.001$), as well as between the interventricular septum and the right ventricular free wall from 27.9 (10.2-41.5) ms to 13.9 (4.3-28.7) ms ($p = 0.001$) [11].

Our findings are consistent with the results reported by W. Y. Yang et al., who also demonstrated favorable electrocardiographic

and echocardiographic effects following transition to LBBAP [12]. Their study included 40 patients and evaluated QRS duration, LVEF, septal-to-posterior wall motion delay, IVMD, and the maximal difference in time to peak systolic strain among 18 left ventricular segments (TDmax). According to their results, IVMD was significantly shorter in the LBBAP group (-5.38 ± 9.31 ms) compared with both RVP (44.8 ± 16.4 ms) and septal pacing (25.3 ± 21.4 ms). Septal-to-posterior wall motion delay was also markedly lower in the LBBAP group (28.7 ± 21.9 ms) than in the apical and septal pacing groups, where values were approximately threefold higher (99.1 ± 46.6 ms and 91.5 ± 26.7 ms, respectively). TDmax was longest in the RVP group (189.8 ± 91.9 ms) and significantly shorter with LBBAP (87.6 ± 56.0 ms), confirming the association of LBBAP with reduced myocardial dyssynchrony.

It should be noted that our study was limited to the early postoperative period (day of re-implantation and postoperative day 5), which precluded assessment of long-term clinical outcomes. However, data from a large registry by P. S. Sharma et al., including 703 patients (LBBAP: 321; RVP: 382) with a mean follow-up of 583 ± 274 days, demonstrated a clear long-term advantage of LBBAP over apical pacing. All-cause mortality was significantly higher in the RVP group (23.3% vs 10% with LBBAP). Moreover, analysis stratified by ventricular pacing burden revealed a significant mortality difference among patients with >40% ventricular pacing: 8.6% (19/220) in the LBBAP group versus 27.6% (53/192) in the RVP group ($p < 0.001$). During follow-up, a total of 52 heart failure decompensation events requiring hospitalization were recorded, with 3.7% (12/332) occurring in the LBBAP group and 10.5% (40/382) in the RVP group [13].

According to several smaller observational studies, a longer follow-up period is required to adequately assess myocardial remodeling and changes in functional capacity. In the study by Y. Shan et al., a 12-month follow-up of patients with pacing-induced cardiomyopathy due to RVP showed that upgrading to LBBAP resulted in a significant increase in LVEF from 36.6 ± 7.2% to 51.3 ± 8.7% ($p < 0.001$) and a reduction in left ventricular end-diastolic diameter from 61.5 ± 6.4 mm to 55.2 ± 6.5 mm ($p < 0.001$) [14]. A meta-analysis of eight observational studies involving 217 patients (mean baseline LVEF 38.4 ± 8.8%) demonstrated that transition to conduction system pacing not only improved LVEF but also reduced NYHA functional class and, consequently, improved patients' quality of life [15].

Ongoing large international trials evaluating the efficacy and safety of conduction system pacing (PROTECT-HF, OptimPacing, Protect-Sync, LEAP-Block, PHYSPAVB) may substantially influence future guideline recommendations for the management of patients with conduction disorders and promote wider adoption of conduction system pacing in clinical practice across diverse patient populations.

## CONCLUSION

1. Conversion from RVP to LBBAP in patients with preserved baseline left ventricular systolic function results in a more physiological pattern of ventricular activation, as evidenced by a reduction in QRS duration. This transition is associated with decreased electrical and mechanical myocardial dyssynchrony, leading to improved intracardiac hemodynamics. As a result, patients demonstrate increased exercise tolerance and, consequently, improved quality of life.
2. In the long-term perspective, LBBAP may promote reverse myocardial remodeling with improvement in left ventricular contractile function, which is expected to translate into a reduction in heart failure symptoms, fewer heart failure-related hospitalizations, and a decreased burden on the healthcare system.

***Table 2.***

***Electrocardiographic and echocardiographic data, quality-of-life indicators, and six-minute walk test results in patients before and after surgery***

| Parameter | Before surgery | After surgery | p |
|---|---|---|---|
| QRSduration, ms | 158.5±25.5 | 111.2±13.8 | <0.05 |
| IVMD, ms | 33.3±24.2 | 15.8±13.4 | <0.05 |
| Ts TDI, ms | 49.3±34.2 | 21.4±17.4 | <0.05 |
| AV-dyssynchrony | 51±3.6 | 53.1±2.8 | 0.179 |
| GLS | -14.4±2.7 | -15.2±2.4 | 0.483 |
| LVEF, % | 59.7±5.1 | 61.4±4.2 | 0.12 |
| LVEDD, cm | 5.04±0.44 | 5.02±0.42 | 0.448 |
| LVESD, cm | 3.38±0.31 | 3.37±0.29 | 0.402 |
| LVEDV, mL | 121.01±26.62 | 119.0±25.3 | 0.143 |
| LVESV, mL | 47.09±18.74 | 46.17±18.55 | 0.140 |
| MR, % | 17.05±10.01 | 11.53±9.24 | <0.05 |
| mPAP, mmHg | 30.8±9.5 | 29.3±10 | 0.622 |
| 6MWT, m | 368.7±87.06 | 466.15±127.2 | <0.05 |
| EQ-5D*, % | 61.2±13.2 | 71.8±14.9 | <0.05 |

Note: LVEF - left ventricular ejection fraction; LV - left ventricle; LVEDD - left ventricular end-diastolic diameter; LVESD - left ventricular end-systolic diameter; LVEDV and LVESV - left ventricular end-diastolic and end-systolic volumes; MR - mitral regurgitation; mPAP - mean pulmonary artery pressure; IVMD - interventricular mechanical delay; Ts TDI - time to peak systolic velocity (septal-to-lateral delay); GLS - global longitudinal strain; 6MWT - six-minute walk test; * - health status scale.

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# ALTERNATION OF THE QRS COMPLEX - NEW OR WELL-FORGOTTEN OLD? CLINICAL OBSERVATIONS

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*Three cases of registration of a rare electrocardiographic (ECG) phenomenon - alternation of the QRS complex (AQRS) are presented. AQRS was detected in two girls aged 6 and 16 with third variant of long QT syndrome (LQT3) and in an asymptomatic patient aged 13 with a family history of sudden death at a young age. AQRS was recorded in combination with macroscopic alternans of the T wave during Holter monitoring and bicycle ergometry. A definition of AQRS is given and possible mechanisms and clinical significance of the detected ECG phenomenon are discussed.*

**Key words:** QRS alternans; long QT syndrome; LQT3; sudden cardiac death; mechanical and electrical cardiac alternans; Holter monitoring; bicycle ergometry

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Risk stratification for the development of life-threatening cardiac arrhythmias is a mandatory component of the assessment of patients from high-risk groups and is often based on electrocardiographic (ECG) markers of myocardial electrical instability [1-4]. Visible, so-called macroscopic T-wave alternans (MTWA) represents one of these validated ECG markers across different patient populations [5-8]. MTWA, in turn, is part of the broader concept of cardiac alternans, which encompasses not only cyclical changes in the T wave but also alternation of other ECG components [9].

In the present report, we describe three cases of a rare form of cardiac alternans manifested as QRS complex alternans (QRSA) during sinus rhythm and discuss its potential mechanisms and clinical significance.

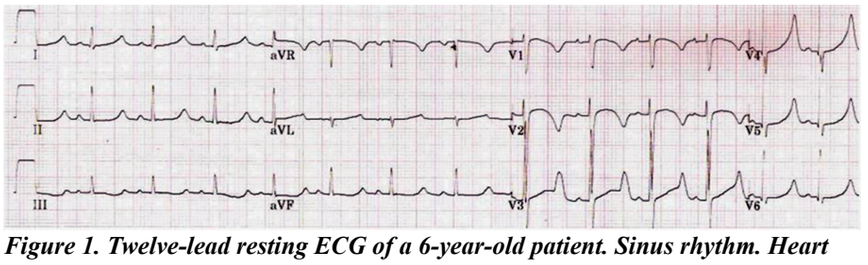


***Figure 1. Twelve-lead resting ECG of a 6-year-old patient. Sinus rhythm. Heart rate 94 bpm (R-R interval 638 ms), electrical axis 68°, PR interval 134 ms, QRS duration 78 ms, QT interval 454 ms. Corrected QT interval calculated using Bazett's formula was 568 ms. T-wave (QT interval) morphology in lead II is characterized by a prolonged isoelectric ST segment.***

Three patients (girls aged 6, 13, and 16 years) with ECG-documented QRSA identified between 2024 and 2025 were examined. All patients underwent comprehensive clinical and cardiological evaluation, including physical examination, detailed family history with emphasis on sudden cardiac death, complete blood count and urinalysis, biochemical blood tests with electrolyte assessment, resting 12-lead ECG, high-resolution ECG, transthoracic echocardiography (TTE), exercise testing (bicycle ergometry or treadmill test), and 24-hour Holter monitoring. To exclude Brugada syndrome, ECG recordings in high parasternal (precordial) leads were performed [10].

***Patient 1***

*A 6-year-old girl. During a routine pre-school ECG screening, prolongation of the corrected QT interval (QTc) up to 568 ms was identified on a resting 12-lead ECG (Fig. 1). The QT interval configuration in lead II was characterized by a prolonged isoelectric ST segment and delayed onset of the T wave. No ventricular late potentials were recorded, and there were no ECG findings suggestive of Brugada syndrome.*

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*The patient was asymptomatic, received no medical therapy, and had no history of syncope. The mother denied any family history of sudden cardiac death. Physical examination was unremarkable. TTE showed no abnormalities. Complete blood count, urinalysis, biochemical blood tests, serum electrolytes, and thyroid hormone levels were within normal limits. ECGs of both parents and two siblings showed no QT interval prolongation. Holter monitoring revealed no clinically significant arrhythmias.*

*Molecular genetic testing identified a de novo mutation in the SCN5A gene, classified as pathogenic (class V). A heterozygous variant NM_000335:c.1231G>A (p.Val411Met) was detected in exon 10 of the SCN5A gene and was considered potentially related to the observed phenotype. Pathogenicity classification was assigned in accordance with current recommendations [11].*

*A diagnosis of long QT syndrome (LQTS), molecular-genetic variant 3 (LQT3) was established. During nocturnal sleep, intermittent episodes of QRSA were recorded in combination with MTWA, manifested as beat-to-beat cyclical changes in QRS complex amplitude and T-wave morphology, without evidence of premature beats (Fig. 2).*

*Exercise testing (treadmill) revealed no rhythm disturbances, ischemic changes, or alternans phenomena. The patient's ECG findings had been previously described by us prior to molecular genetic testing and initiation of therapy [12,13].*

*Treatment with atenolol (1 mg/kg/day in two divided doses) was initiated, followed by the addition of flecainide (2 mg/kg/day in two divided doses). Given the identified genetic variant, persistence of QTc prolongation >500 ms despite therapy, and the presence of MTWA, implantation of an implantable cardioverter-defibrillator (ICD) was recommended.*

***Patient 2***

*A 16-year-old girl with a history of syncopal episodes and a family history of sudden cardiac death. Resting 12-lead ECG demonstrated QTc prolongation up to 522 ms (Fig. 3). The QT interval configuration in lead II was characterized by a prolonged isoelectric ST segment and delayed onset of the T wave. Structural heart disease, cardiomyopathies, inflammatory conditions, and electrolyte disturbances were excluded. The patient was not receiving any medical therapy.*

*No ventricular late potentials were recorded, and there were no ECG findings suggestive of Brugada syndrome. Molecular genetic testing revealed a known pathogenic mutation in the SCN5A gene (pathogenicity class V), identified both in the patient and her mother, in contrast to Patient 1. A heterozygous pathogenic variant NM_001099404.2:c.5350G>A (p.Glu1784Lys) was detected in exon 28 of the SCN5A gene and was considered potentially related to the observed phenotype. Pathogenicity classification was assigned in accordance with current recommendations [11].*

*A diagnosis of long QT syndrome (LQTS), molecular-genetic variant 3 (LQT3) was established. During 24-hour Holter monitoring, episodes of QRSA in combina-*

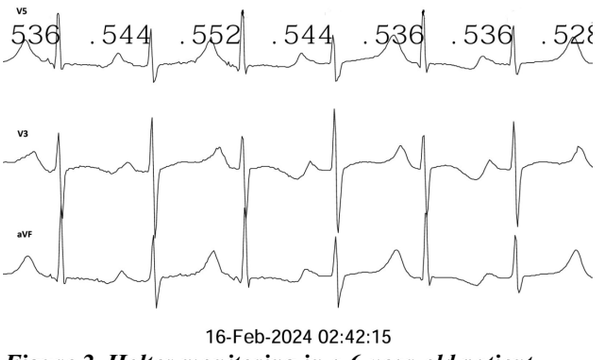


***Figure 2. Holter monitoring in a 6-year-old patient. T-wave alternans (cyclical alternation of T-wave morphology) and QRS alternans (cyclical alternation of QRS complex amplitude from the second to the fifth beat) recorded in all leads during nocturnal sleep (03:54) in a patient with long QT syndrome (LQT3). R-R intervals (ms) are indicated in lead V5.***

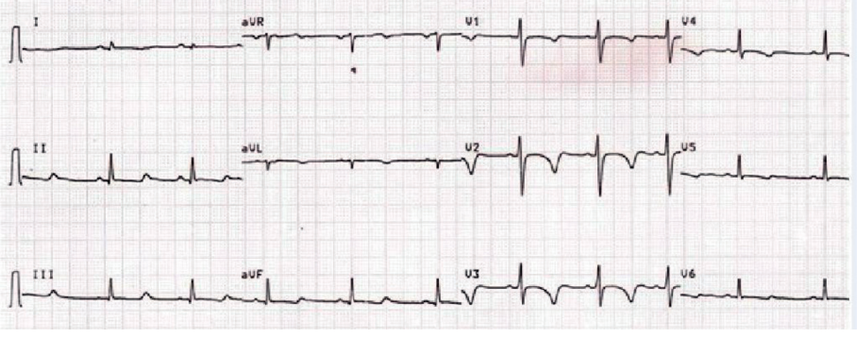


***Figure 3. Resting 12-lead ECG of a 16-year-old patient with long QT syndrome (LQT3). Sinus rhythm. Heart rate 66 bpm, QTc = 522 ms. The QT interval demonstrates a prolonged ST segment with delayed onset of the T wave.***

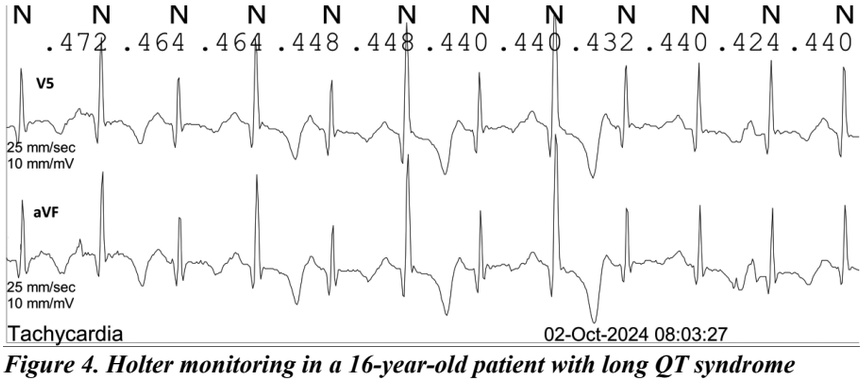


***Figure 4. Holter monitoring in a 16-year-old patient with long QT syndrome (LQT3). Sinus rhythm, heart rate 134 bpm. QRS alternans (cyclical alternation of QRS complex amplitude) and T-wave alternans recorded in modified Holter leads V5 and V3. R-R intervals (ms) are shown in lead V5.***

*tion with MTWA were recorded in modified Holter leads (Fig. 4). Periods of QRSA and MTWA were observed both during nighttime and daytime hours.*

*During bicycle ergometry testing, no arrhythmias or ischemic changes were detected. However, at the first workload stage, within a heart rate range of 120-130 beats per minute, QRSA was observed in leads II, aVL, aVR, V1, V2, and V3, associated with MTWA (Fig. 5). The electrical axis of the heart measured 94° during non-alternating beats and 105° during alternating beats. QRSA resolved at heart rates exceeding 130 beats per minute.*

*Therapy with atenolol (1 mg/kg/day in two divided doses) was initiated, followed by the addition of flecainide (2 mg/kg/day in two divided doses). Given the identified genetic variant, persistence of QTc prolongation >500 ms despite therapy, presence of MTWA and a history of syncope, implantation of an ICD was recommended. The case had been previously reported by our group prior to initiation of therapy [14].*

***Patient 3***

*A 13-year-old girl, a competitive athlete (softball), was referred for evaluation after suspicion of a coronary artery anomaly was raised during routine periodic in-depth medical screening of athletes. TTE revealed features suggestive of a retroaortic anomalous coronary artery course (RAC sign). The patient was asymptomatic, denied syncope, and was not receiving any medical therapy.*

*Family history was notable for sudden death of a brother at the age of 18 years (cause undetermined) and death of the maternal grandfather at the age of 60 years (reported by the patient's mother as a "heart attack"). Physical examination was unremarkable. Complete blood count, urinalysis, biochemical blood tests, serum electrolytes, and thyroid hormone levels were within normal ranges. Ventricular late potentials were not detected, and there were no ECG findings suggestive of Brugada syndrome.*

*Resting ECG demonstrated a heart rate of 71 beats per minute with normal PR and QT intervals (QTc 435 ms). Holter monitoring did not reveal any pathological findings. According to multislice computed tomography of the heart and coronary angiography, the presence of right coronary artery hypoplasia could not be excluded. A small pericardial effusion was also noted. Stress myocardial perfusion scintigraphy did not demonstrate significant perfusion defects or stress-induced myocardial ischemia.*

*During bicycle ergometry testing, no arrhythmias or ischemic changes were recorded. However, at the first workload stage, within a heart rate range of 110-130 beats per minute, QRSA was observed in leads aVR and V1, associated with MTWA (Fig. 6). QRSA resolved at higher heart rate values. The electrical axis of the heart was 93° during non-alternating cycles and 87° during alternating cycles.*

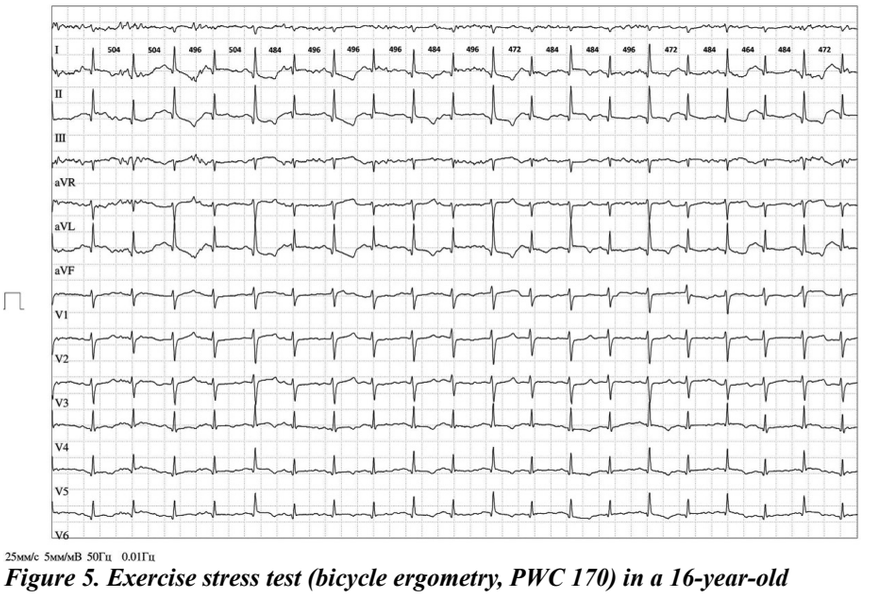


***Figure 5. Exercise stress test (bicycle ergometry, PWC 170) in a 16-year-old patient with long QT syndrome (LQT3) at the first workload stage. Sinus rhythm. Heart rate 115 bpm. Combined QRS complex alternans and macroscopic T-wave alternans observed in leads II, III, aVR, aVL, aVF, V2, and V3. R-R intervals (ms) are indicated in lead II.***

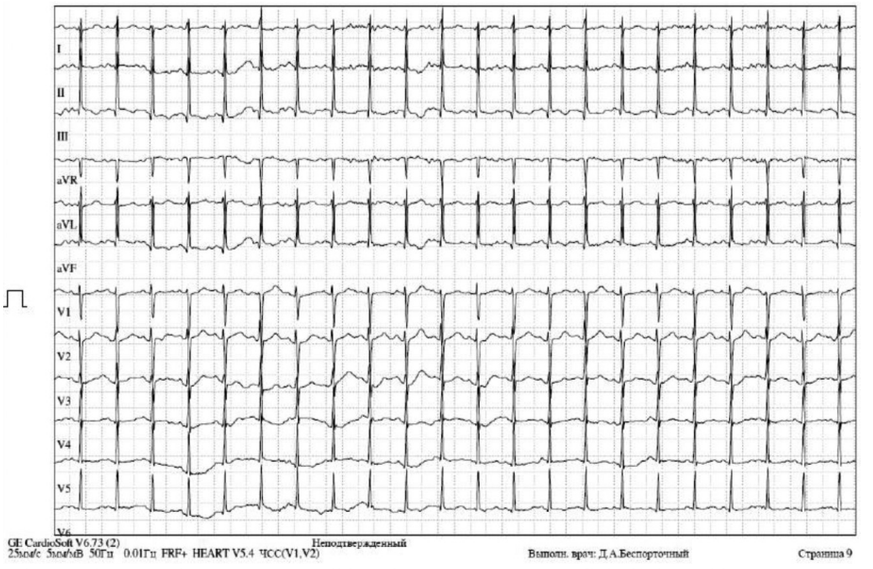


***Figure 6. Exercise stress test (bicycle ergometry, PWC 170) in a 13-year-old patient at the first workload stage. Sinus rhythm. Heart rate 115 bpm. Combined QRS complex alternans and macroscopic T-wave alternans observed in leads aVR and V1.***

*Given the absence of symptoms, lack of confirmed pathological coronary artery anomalies, absence of myocardial ischemia, and absence of clinically significant arrhythmias, no treatment was initiated. Considering the family history, molecular genetic testing was recommended to exclude arrhythmogenic channelopathies and cardiomyopathies, in accordance with protocols for evaluation of family members in whom unexplained sudden death at a young age has been documented [15].*

In all examined patients, RR interval variation during alternating cycles ranged from 8% to 13%, QRS complex width varied by no more than 10%, and the electrical axis of the heart during stress testing deviated rightward/downward by 10% in the 16-year-old patient (Patient 2) and leftward/upward by 6% in the 13-year-old patient (Patient 3).

Based on analysis of all recorded episodes of QRSA in the three patients, we propose the following definition of electrical QRS alternans on sinus rhythm:

Electrical QRS alternans on sinus rhythm is defined as a beat-to-beat cyclical change in QRS complex amplitude with minimal variation in QRS duration and RR intervals in alternating consecutive sinus cycles, lasting for at least six consecutive RR intervals and recorded in at least two ECG leads, by analogy with the definition of macroscopic T-wave alternans, in patients without cardiac diseases associated with pericardial effusion [5].

## DISCUSSION

The study of cardiac alternans has a long history. As early as 1872, L. Traube published observations of beat-to-beat changes in pulse intensity (pulsus alternans) in a patient with cardiomyopathy and heart failure who died suddenly two months later [16]. In 1909, H. Hering documented QRSA and MTWA in animal experiments, while T. Lewis was the first to describe cardiac alternans in patients during psycho-emotional stress [17, 18]. In contemporary literature, QRSA is regarded as part of the broader concept of cardiac alternans [9].

B. Surawicz distinguished between mechanical and electrical QRSA [9]. Mechanical QRSA is associated with conditions accompanied by pericardial effusion, cardiac tamponade, and exudative pericarditis, in which the phenomenon of a “swinging heart” occurs. In such cases, the electrical axis of the heart changes from beat to beat due to cardiac motion within the pericardial fluid, and QRSA resolves after drainage of the effusion [19].

The mechanism of electrical QRSA is linked to delayed conduction or conduction block within the His-Purkinje system or ventricular myocardium, typically observed in patients with paroxysmal supraventricular or ventricular tachycardias [20]. In 1978, H. Klein et al. reported a case of QRSA on sinus rhythm caused by intermittent incomplete left anterior fascicular block occurring every second beat during procainamide therapy [21]. The authors concluded that when QRSA on sinus rhythm is not related to a large pericardial effusion, it should be classified as pseudo-electrical alternans. According to their interpretation, such alternans may result from cyclical changes in QRS amplitude due to alternating conduction within the His-Purkinje system without changes in the physical orientation of the heart, or may be related to ventricular bigeminy in which late premature beats are synchronized with normal QRS complexes, causing axis deviation every other beat.

A. Bayés de Luna described QRSA occurring in patients without cardiac tamponade or paroxysmal tachyarrhythmias as false alternans, often related to respiratory motion during ECG recording in precordial leads. This category includes observations reported by E. Schulze-Bahr, such as transient Wolff-Parkinson-White syndrome, bigeminy with long pre-ectopic intervals, and related phenomena [22-24].

There are, however, isolated reports of QRSA on sinus rhythm that do not fit these definitions, as they occur in the absence of pericardial effusion, drugs affecting intraventricular conduction, or conditions associated with so-called false alternans, and are not accompanied by overt arrhythmogenic events [21, 22, 25]. In such cases, the mechanism of QRSA remains hypothetical and its clinical significance uncertain. These atypical variants of QRSA were observed in our patients.

In the 6-year-old girl (Patient 1), QRSA was recorded during nighttime hours, corresponding to a period of maximal arrhythmogenic vulnerability in LQT3 [26]. In the patient with a more severe LQT3 phenotype (Patient 2), combined QRSA and MTWA were also observed during daytime hours and during exercise testing. MTWA is a well-established arrhythmogenic trigger in patients with long QT syndrome; therefore, the coexistence of QRSA and MTWA in these patients suggests that QRSA may represent a highly probable proarrhythmic marker of myocardial electrical instability [1, 5].

This hypothesis is supported by the experimental study by M. Chinushi et al., who demonstrated in a canine LQT3 model that periods of combined QRSA and MTWA arise due to delayed conduction in mid-myocardial layers (as opposed to epicardium or endocardium) and serve as precursors or triggers of torsade de pointes ventricular tachycardia, which developed even in the absence of a triggering ventricular premature beat [27].

In the 13-year-old patient (Patient 3), no overt cardiac disease was identified. A clinically significant coronary artery anomaly was not definitively confirmed, no ischemic changes were detected, known channelopathies were excluded, and the small pericardial effusion was insufficient to cause a “swinging heart” phenomenon and mechanical QRSA. Nevertheless, the adverse family history, including sudden death at a young age (brother aged 18 years), cannot be ignored and warrants further evaluation [15].

In the treatment of our two patients with long QT syndrome, standard beta-blocker therapy was employed, with the addition of the sodium channel blocker flecainide, a drug approved in the Russian Federation that shortens the QT interval specifically in patients with the LQT3 molecular-genetic subtype [28, 29].

## CONCLUSION

At present, accurate risk stratification in patients with QRS complex alternans on sinus rhythm in the absence of pericardial effusion remains unclear. It is highly likely that the electrophysiological mechanisms underlying this ECG phenomenon increase the risk of cardiac events in patients with an arrhythmogenic myocardial substrate (including

channelopathies, cardiomyopathies, and myocardial ischemia). This uncertainty underscores the need for long-term follow-up and further accumulation of clinical and electrophysiological data.

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# A CLINICAL CASE OF REFRACTORY VENTRICULAR TACHYCARDIA TREATMENT: FROM SIMPLE TO COMPLEX AND BACK AGAIN

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*The article presents a clinical case of a patient with recurrent refractory ventricular tachycardia (VT) on the background of postinfarction cardiosclerosis. Despite optimal drug therapy and several catheter ablation procedures using modern navigation technologies, episodes of VT persisted. The key factor of ineffectiveness of the endocardial approach turned out to be the intramural location of arrhythmogenic zones. Therefore, a decision was made to perform surgical intervention with cryoablation of scar tissues. After the surgery, a stable remission was achieved, which was confirmed by the data of regular checks of the implantable cardioverter-defibrillator. The presented case emphasizes the importance of individualized and multidisciplinary approach in the choice of treatment tactics for patients with refractory VT.*

**Key words:** ventricular tachycardia; catheter ablation; cryoablation; implantable cardioverter-defibrillator; ischemic heart disease

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Cardiovascular diseases remain the leading cause of mortality worldwide, with sudden cardiac death (SCD) accounting for 40-45% of such cases. More than 70% of SCD episodes are associated with ventricular tachycardia (VT), and survival after its occurrence remains extremely low, at only 3-5% [1, 2]. Despite advances in the treatment of patients with chronic heart failure (CHF) and reduced left ventricular ejection fraction (LVEF), the residual risk of SCD remains high. The main method of SCD prevention in patients with reduced LVEF, in addition to optimal medical therapy, is the use of implantable cardioverter-defibrillators (ICDs) - devices capable of recognising and terminating life-threatening arrhythmias. However, even with a comprehensive treatment approach, many patients experience appropriate ICD therapies, which negatively affect patients' psycho-emotional state and prognosis [3].

Advances in catheter treatment of VT in patients with structural heart disease make it possible to significantly reduce arrhythmia burden and improve prognosis and represent the treatment of choice for recurrent arrhythmias resistant to medical therapy [4, 5]. Nevertheless, in some patients endocardial ablation does not produce the desired effect, which is associated with an intramural and/or epicardial localisation of the arrhythmogenic substrate. In such cases, consideration may be given to cardiac surgical treatment, including resection of scar tissue. We present a demonstration of cardiac surgical treatment in a patient with VT recurrent despite prior endocardial radiofrequency ablation (RFA).

*A 64-year-old man presented to the centre's clinic with complaints of recurrent episodes of dizziness and loss of consciousness occurring during attacks of rapid heartbeat lasting up to several minutes and terminating with ICD activation. According to the medical history, at the age of 49 years (2009) the patient sustained a myocardial infarction in the territory of the left anterior descending artery (LAD), followed by stent implantation. In 2016, 2019, and 2023, repeat endovascular revascularisation of the LAD territory was performed due to restenosis.*

*In October 2023 (at the age of 63 years), following a long-haul flight, the first episode of VT accompanied by dizziness was documented. During the patient's stay in the intensive care unit, the episodes recurred, requiring electrical cardioversion. Amiodarone was initiated as antiarrhythmic therapy, followed by implantation of a dual-chamber ICD. Device interrogations revealed episodes of VT with ineffective antitachycardia pacing (ATP) requiring shock therapy. During hospitalisations for these events, no reversible causes were identified. In October 2023, an endocardial electrophysiological study was performed, during which sustained VT was not inducible and ablation was not performed.*

*Subsequently, ICD therapies continued to occur, and in November 2023 RFA of arrhythmogenic areas along the anterior wall of the right ventricle was performed. During the control endocardial electrophysiological study, VT with a QRS morphology different from the clinical VT was induced. At that time, a decision was made to refrain*

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*from further continuation of the procedure. During the same hospitalisation, coronary angiography was also performed, which revealed a haemodynamically significant LAD stenosis; percutaneous coronary intervention with implantation of a drug-eluting stent was carried out.*

*The patient continued to experience episodes of palpitations accompanied by device therapies. ICD interrogation documented episodes of fast VT with a cycle length (CL) of 280-330 ms, occasionally terminated by shock delivery due to ineffective ATP (Fig. 1).*

*According to transthoracic echocardiography, the LVEF was 31%, with a left ventricular apical aneurysm measuring 52 × 38 mm, an end-diastolic volume of 150 mL, and an end-systolic volume of 93 mL. These findings were also confirmed by cardiac magnetic resonance imaging. Laboratory test results were within normal limits. A decision was made to proceed with repeat catheter-based treatment.*

*The procedure was performed under combined anaesthesia with invasive haemodynamic monitoring. Left ventricular mapping was carried out via antegrade and retrograde approaches using the Abbott EnSite X system (Abbott Laboratories, USA) and the Advisor™ HD Grid diagnostic catheter (Abbott Laboratories, USA). Vascular access and transseptal puncture were performed under ultrasound guidance. Intracardiac echocardiography (ICE) revealed pronounced spontaneous echo contrast localised within the apical aneurysm, characterised by markedly thinned walls.*

*Using programmed ventricular stimulation according to a standard protocol, the clinical VT with a CL of 315 ms was repeatedly induced. Attempts to terminate VT using ATP resulted in a change in arrhythmia morphology followed by rhythm acceleration (CL 307 ms) and subsequent transformation into ventricular fibrillation during repeated attempts at termination with burst pacing, which necessitated electrical cardioversion (Fig. 2).*

*Given the haemodynamic instability, ventricular substrate mapping was performed during the patient's intrinsic rhythm using both antegrade and retrograde pacing. According to the activation map, a zone of late myocardial activation was identified within the post-infarction aneurysm, closer to the interventricular septum (Fig. 3a). At the first stage, a strategy aimed at eliminating excitation entry channels into the late activation zones was selected. Analysis of the activation pattern revealed the presence of two channels (Fig. 3a). However, frequency analysis of the recorded electrograms demonstrated that only one channel had a true endocardial localisation.*

*Pacing from the zone of late activation resulted in a match between the paced QRS morphology and that of the clinical VT. However, entrainment mapping could not be performed due to the development of haemodynamically unstable VT. Elimination of the endocardial channel was therefore performed as the first stage (Fig. 3b, c). At the second stage, homogenisation of the scar tissue within the apical aneurysm was carried out. The total ablation time was 20 minutes at a power of 40 W, irrigation flow of 25 mL/min, and contact force exceeding 8 g at each point.*

*It should be noted that RFA was performed under intracardiac echocardiography guidance, which provided the necessary visualisation of anatomical structures during the intervention. During the procedure, it was*

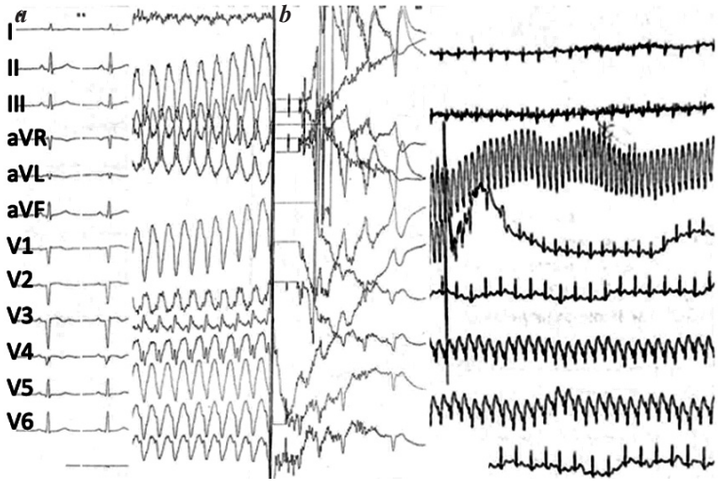


***Fig. 1. Data from 24-hour ECG monitoring: (a) an episode of fast monomorphic VT with a CL of 250 ms, terminated by shock therapy delivery (analysis of QRS morphology during VT suggests localisation of the arrhythmogenic zone within the apical aneurysm with exit to the inferior wall of the left ventricle); (b) multiple episodes of VT with ineffective antitachycardia pacing (ATP) and termination by shock therapy.***

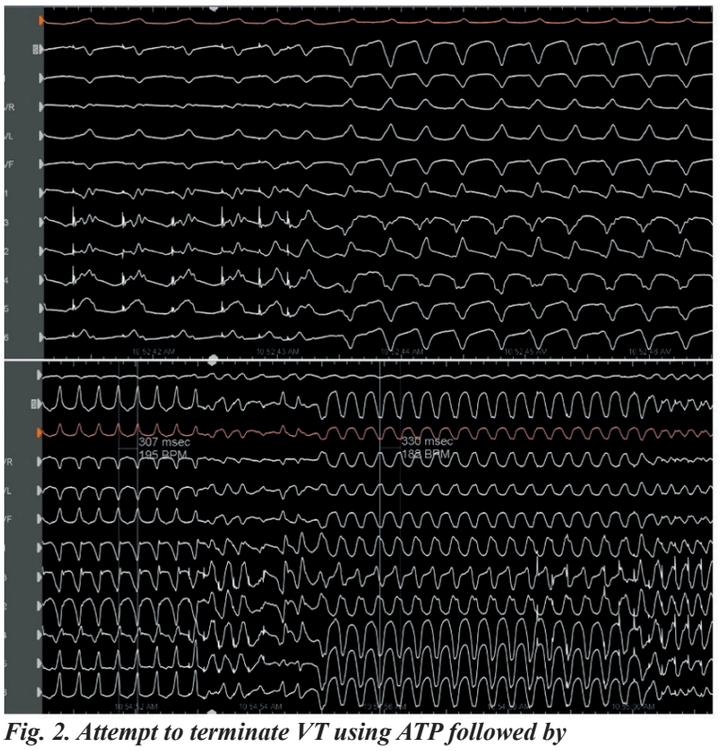


***Fig. 2. Attempt to terminate VT using ATP followed by transformation into ventricular fibrillation.***

*found that areas of interest with significant myocardial thickness were localised in the region of the anterior interventricular groove, where ablation lesions had previously been delivered by colleagues from the right-sided, septal aspect. Epicardial access in this region was limited by the close proximity of a coronary artery and a pronounced epicardial fat layer, which restricted the feasibility of this approach.*

*After RFA in the region of late potential recording, myocardial capture during pacing from the scar tissue was absent. During repeat induction testing, VT was not induced, which led to termination of the procedure. On the second postoperative day, a recurrence of VT with a CL of 315 ms was recorded and terminated by shock therapy. Subsequently, VT episodes again acquired a recurrent pattern (Fig. 4).*

*Due to the ineffectiveness of repeated endocardial ablation procedures, a decision was made to perform aneurysm resection with left ventricular reconstruction and cryoablation of the border zones. Upon opening the left ventricular cavity, a pronounced layer of epicardial fat located along the perimeter of the left ventricular aneurysm was noted, which had also been previously identified by intracardiac echocardiography. Along the scar tissue of the anterior wall, a fresh mural thrombus measuring 2 × 3 cm was visualised. In the demarcation zone, circumferential cryoablation of the endocardium and epicardium was performed: applications were delivered along the perimeter of the resection area, forming a continuous ring of necrosis. The objective of cryoablation was to isolate potential arrhythmogenic foci within the transition zone between viable myocardium and scar tissue, as well as to prevent recurrent ventricular arrhythmias. Subsequently, the left ventricle was reconstructed using a double-layer continuous suture with Teflon pledgets (Fig. 5). During one year of follow-up after cardiac surgery, no recurrence of cardiac rhythm disturbances was recorded, and the patient continued to receive optimal medical therapy.*

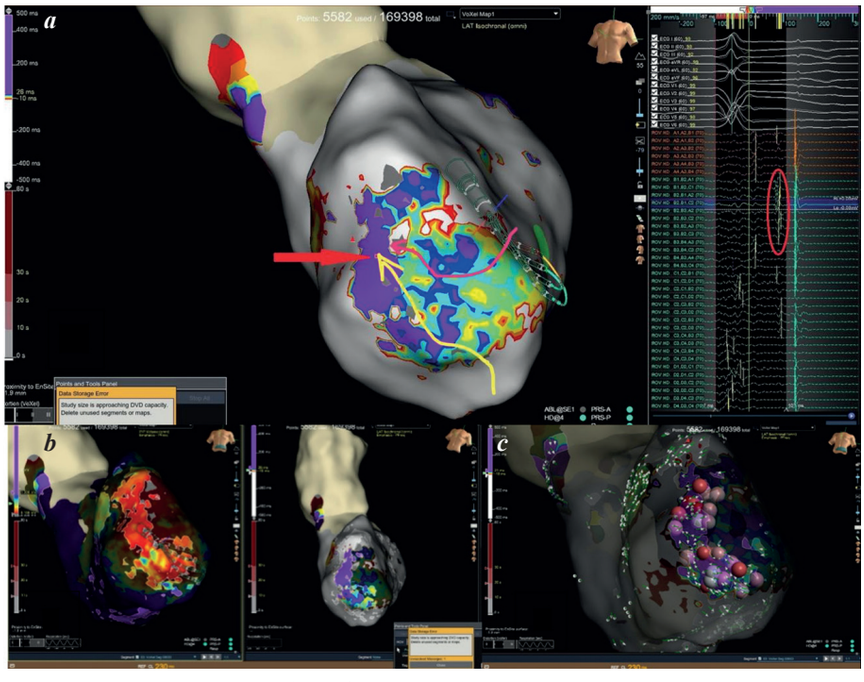


***Fig. 3. Substrate mapping data: (a) area of late left ventricular myocardial activation within the post-infarction aneurysm; (b) area of late myocardial activation in the apical region displayed in frequency-domain signal analysis mode (window 250-1000 Hz); notably, only part of the scar zone demonstrates far-field signals, indicating an intramural/epicardial localisation of a proportion of the conduction channels; (c) radiofrequency ablation of the channel within the scar region.***

## DISCUSSION

One of the main methods of SCD prevention is implantation of an implantable cardioverter-defibrillator (ICD); however, these devices do not address the problem of recurrent cardiac arrhythmias, and each delivery of shock therapy is associated with a worsening of prognosis [6]. Endocardial ablation is the gold standard for the treatment of therapy-refractory sustained VT in patients with structural myocardial disease leading to ICD therapies [7]. One of the pioneers in the study of VT in patients with structural heart disease was Mark Josephson, who confirmed the presence of critical zones within the border area between scar tissue and intact myocardium, which became the starting point for subsequent research and led to the development of electrophysiological techniques and navigation systems [8, 9]. Since then, catheter ablation of VT has been increasingly performed worldwide and has demonstrated favourable outcomes.

Thus, the randomised controlled trial PARTITA demonstrated a significant reduction in the risk of death or hospitalisation due to decompensated CHF from 42% in the control group to 4% in the ablation group (HR 0.11; 95% CI 0.01-0.85; p = 0.034) in patients after the first appropriate ICD therapy [10]. The most pronounced benefit of interventional therapy has been observed in patients with post-infarction cardiosclerosis, which is attributable to the extensive clinical experience in treating this population and the presence of scar-related substrates responsible for VT maintenance.

According to a meta-analysis of five randomised controlled trials including 635 patients with post-infarction cardiosclerosis, catheter ablation was associated with a 51% reduction in the likelihood of ICD shock therapy (HR 0.49; 95% CI 0.28-0.87). In addition, the risks of electrical storm and hospitalisation were reduced by 36% (HR 0.64; 95% CI 0.43-0.95) and 33% (HR 0.67; 95% CI 0.46-0.97), respectively [11]. In the VANISH2 randomised controlled trial, which included 416 patients with ischaemic cardiomyopathy and clinically significant VT, catheter

ablation was shown to be superior to antiarrhythmic drug therapy as a first-line strategy: over a median follow-up of 4.3 years, the composite primary endpoint (all-cause mortality or clinically significant ventricular tachyarrhythmia) occurred in 50.7% of patients in the ablation group and in 60.6% of those receiving medical therapy (HR 0.75; 95% CI 0.58-0.97; p = 0.03) [4]. In addition, the catheter ablation group demonstrated a lower incidence of treatment-related adverse events (12.3% vs 22.1%) as well as a lower rate of therapy-related mortality.

The study findings once again confirm the appropriateness of catheter ablation as the preferred first-line therapy in patients with VT of ischaemic origin, aimed at improving quality of life and reducing the risk of adverse outcomes. However, the efficacy of endocardial ablation does not reach 100%, which is attributable to multiple factors, including the presence of numerous arrhythmogenic zones, their de novo formation, and the "non-subendocardial" localisation of conduction channels, which limits the effective delivery of radiofrequency energy into deeper myocardial layers. At the same time, aggressive catheter ablation is associated with an increased risk of myocardial perforation in areas of post-infarction aneurysms with thinned walls.

In cases of ineffective repeated endocardial ablation, epicardial and/or cardiac surgical interventions with excision of scar tissue and ablation of border zones represent the treatment of choice. These techniques have a long historical background, beginning with Charles Bailey's report of successful elimination of recurrent VT in a patient with post-infarction cardiosclerosis through aneurysm resection, which marked a turning point in the development of surgical treatment strategies for this patient population and led to the introduction of a new technique-subendocardial resection of arrhythmogenic zones, known as the "Pennsylvania peel" method [12].

Several important factors merit attention in the present clinical case. First, the large size of the apical left ventricular scar with markedly thinned walls limited the feasibility of aggressive ablation. Second, the presence of an intramural component responsible for VT maintenance was identified. As demonstrated in a number of studies, analysis of the frequency characteristics of electrograms correlates with near-field signal components [13]. The use of algorithms designed to identify regions with target frequency characteristics allows prediction of the effectiveness of endocardial ablation [14]. Returning to the mapping results (Fig. 4), only a portion of the signals within the scar region demonstrated a true subendocardial origin. Despite homogenisation of the scar tissue, VT recurrence was observed. In such cases, the only viable option is a combined epi-endocardial approach. In the present case, taking into account all myocardial characteristics, a decision was made to proceed with additional cardiac surgical intervention; however, given the small left ventricular volumes, complete resection of the aneurysmal tissue was abandoned in favour of circumferential cryoablation along the perimeter of the aneurysm using both epicardial and endocardial approaches.

## CONCLUSION

Modern arrhythmology and cardiac surgery have demonstrated substantial progress in the development of minimally invasive methods for the treatment of VT since the early decades of the twentieth century. These advances have made it possible to significantly reduce the recurrence rate of arrhythmias, minimise intraoperative complications, improve patients' quality of life, and increase survival. However, as clinical practice shows, including the case presented herein, in certain situations there remains a need for individualised arrhythmological strategies, including those involving the use of radical treatment approaches. Such cases require particularly thorough analysis of clinical data and a personalised approach to selecting the optimal management strategy, which was implemented in the present clinical case.

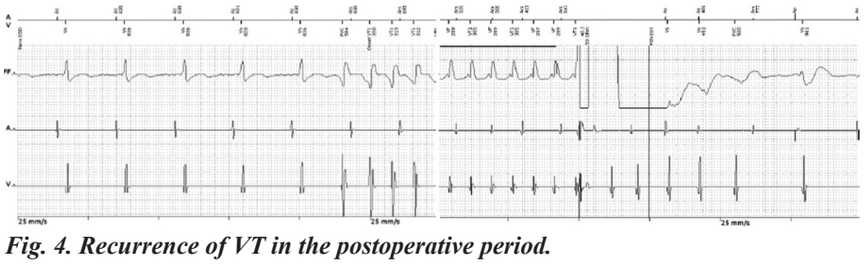

***Fig. 4. Recurrence of VT in the postoperative period.***

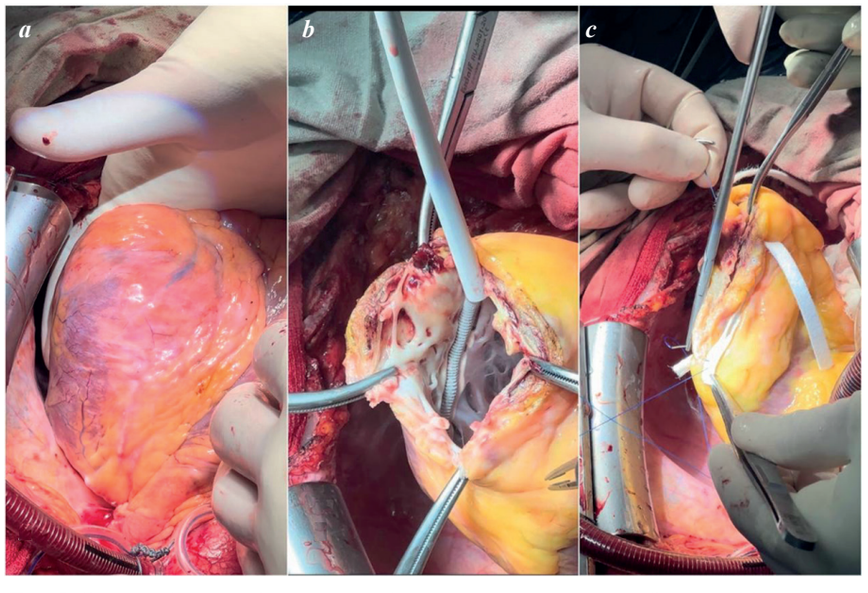


***Fig. 5. Stages of surgical treatment: (a) prior to intervention; (b) cryoablation of the border zones; (c) left ventricular reconstruction.***

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# PSEUDO-ATRIOVENTRICULAR BLOCK

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*A fragment of Holter ECG recording is presented, demonstrating a pseudo-second-degree atrioventricular block type II pattern, diagnosed by the presence of a non-conducted sinus P wave following a ventricular ectopic complex.*

**Key words:** ventricular arrhythmias; atrioventricular block; Holter monitoring; conduction disturbance; ventriculoatrial conduction

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In recent years, discussion of various electrocardiographic (ECG) phenomena has largely shifted to various groups and chats on the Internet. A frequent subject of discussions is the interpretation of non-conducted P waves following ventricular ectopic complexes (VECs). Incorrect interpretation of this ECG pattern as second-degree atrioventricular (AV) block type II (Mobitz II) can lead to unjustified referral of patients for pacemaker implantation [1-5].

We present a corresponding fragment from Holter ECG monitoring (Fig. 1). Among the sinus rhythm complexes, two VECs with identical coupling intervals are registered. Following the first VEC, a narrow, negative in the inferior leads P wave, retrogradely conducted through the AV node, is clearly visible. After the second VEC, there is no retrograde conduction of the impulse to the atria; however, a sinus P wave is recorded which is not conducted to the ventricles. This is due to the refractoriness of the AV junction induced by the VEC.

Interpreting this ECG pattern as second-degree AV block type II is incorrect. We should keep in mind that, according to the ACC/AHA/HRS 2018 guidelines, a mandatory condition for diagnosing second-degree AV block is P waves proceeding in a constant rhythm at a rate of less than 100 per minute.

The scheme presented in the lower part of Figure 1 demonstrates that premature ventricular contractions are capable of causing refractoriness of the AV node regardless of the presence or absence of retrograde conduction to the atria. In the latter case, the subsequent sinus P wave fails to conduct to the ventricles precisely due to refractoriness of the AV node induced by the premature ventricular contractions, rather than due to second-degree AV block. The prolongation of the next post-extrasystolic sinus cycle is usually interpreted as a consequence of a vagal reflex that occurs upon stimulation of aortic and carotid receptors at the moment of premature ventricular systole (ventriculophasic effect).

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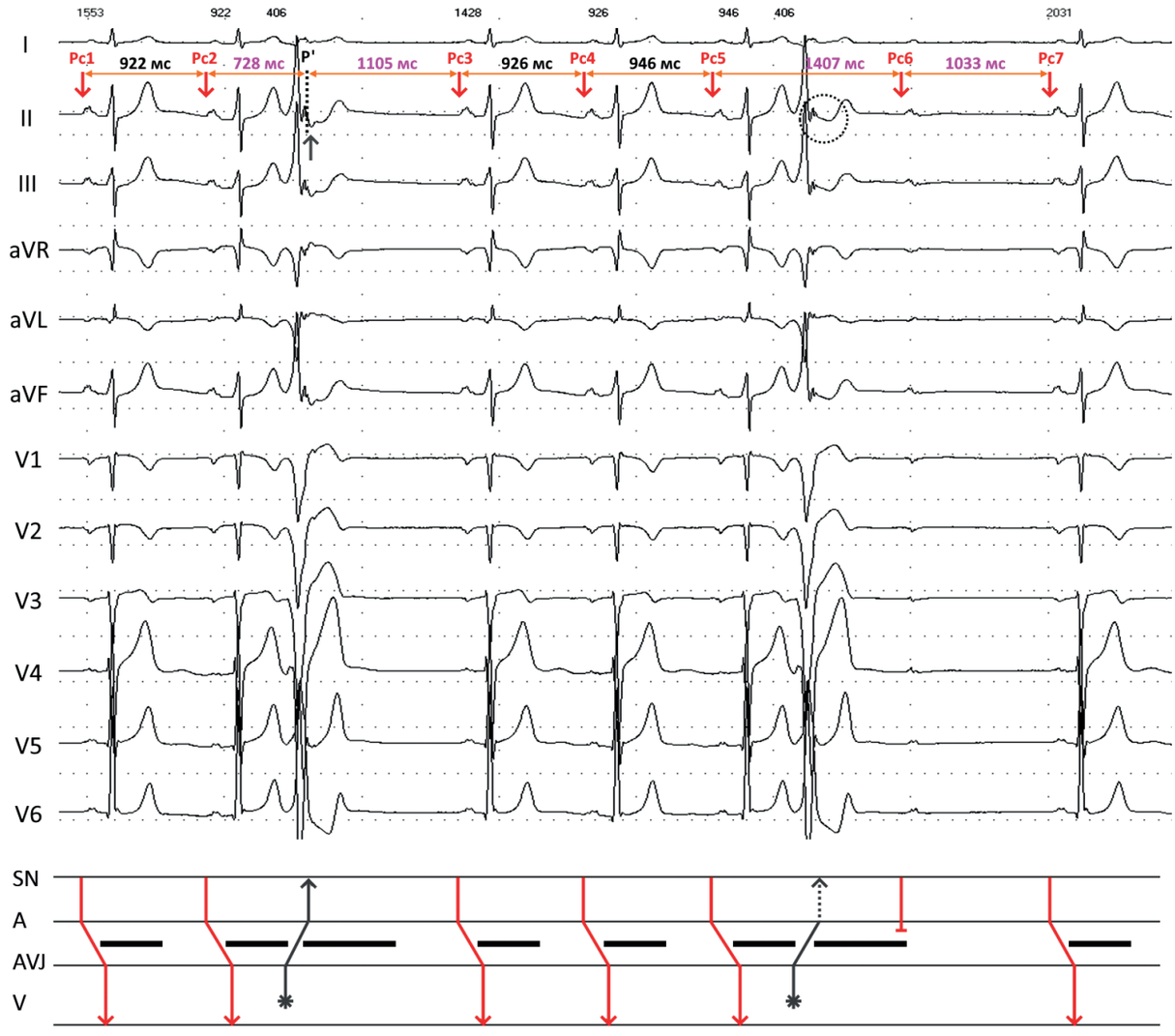


***Figure 1. A fragment of Holter ECG recording, the black arrow indicates a retrograde P wave; red arrows - sinus P waves; dashed circle - absence of a retrograde P wave; Pc - sinus P wave; P' - retrograde P wave; SN - sinus node; A - atria; AVJ - atrioventricular junction; V - ventricles; black horizontal lines - presumed AVJ refractory periods.***