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Almazov National Medical Research Centre, 2. Akkuratova str., 197341 St. Petersburg
NP «St. Petersburg Cardiology Society», 2. Akkuratova str., 197341 St. Petersburg
NAO «Institute of Cardiology Technic», 22A Vyborgskoye shosse, 194214 St. Petersburg

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RUSSIAN REGISTRY OF CRYOBALLON ABLATION OF ATRIAL FIBRILLATION: CHARACTERISTICS OF THE PROCEDURE AND FEATURES OF PATIENT'S MANAGEMENT

L.E.Korobchenko[1], T.A.Lyubimtseva[1], K.V.Davtyan[2], A.G.Topchyan[2], G.Yu.Simonyan[2], S.E.Serduk[2], S.V.Korolev[3], A.Ya.Kosonogov[4], K.A.Kosonogov[4], E.S.Tarasyuk[5], K.A.Lubenkov[5], A.S.Shulga[5], E.A.Artyukhina[6], A.Sh.Revishvili[6], D.V.Kryzhanovskii[7], R.E.Batalov[8], S.Yu.Usenkov[8], D.N.Khomutinin[9], G.V.Kolunin[9], V.E.Kharats[9], A.A.Nechepurenko[10], I.Sh.Sagitov[11], N.I.Grachev[12], N.L.Sharikov[13], S.Yu.Chetverikov[13], D.I.Perchatkin[14], Yu.V.Virstyuk[15], F.G.Rzaev[16], D.S.Lebedev[1], E.N.Mikhaylov[1]

[1]FSBI "Almazov NMRC" of the MH RF, 2nd Akkuratova str., Saint Petersburg, Russia; [2]FSBI "NMRC for Therapy and Preventive Medicine" of the MH RF, 10th Petroverigsky Lane, Moscow, Russia; [3]FSBI "Federal Scientific and Clinical Center for Specialized Types of Medical Care and Medical Technologies of the FMBA", Russia, Moscow, 28th Orekhovy Boulevard; [4]State budgetary medical centre "City Clinical Hospital N5" of the Nizhny Novgorod district of Nizhny Novgorod, Russia, Nizhny Novgorod, 34th Nesterova str.; [5]Federal state budgetary educational institution of higher education "Amur State Medical Academy" of the MH RF, Russia, Blagoveshchensk, 95th Gorky str.; [6]FSBI " Vishnevsky NMRC for Surgery" of the MH RF, Russia, Moscow, 27th Bolshaya Serpukhovskaya str.; [7]State budgetary medical centre "City Hospital N26" of St. Petersburg, Russia, St. Petersburg, 2nd Kostiusko str.; [8]Scientific Research Institute of Cardiology - branch of the FSBI "Tomsk National Research Medical Center of the RAS", Russia, Tomsk, 111-A Kievskaya str.; [9]State budgetary medical centre "Regional Clinical Hospital N1" of Tyumen region, Russia, Tyumen, 55th Kotovsky str.; [10]FSBI "Federal Center of Cardiovascular Surgery" of the MH RF, Astrakhan, 4th Pokrovskaya Grove str., [11]State budgetary medical centre "Republican Center of Cardiology" of the Republic of Bashkortostan, Russia, Ufa, 96th Stepan Kuvykin str.; [12]Primorsky Regional Clinical Hospital N1, Vladivostok, 53th Aleutskaya str., Russia; [13]Budgetary Institution "District Clinical Hospital" of Khanty-Mansiysk Autonomous Okrug-Yugra, Russia, Khanty-Mansiysk, Kalinina str., 40; [14]State budgetary medical centre "City Pokrovskaya Hospital" of Saint Petersburg, Russia, St. Petersburg, 85thBolshoy pr. VI; [15]Commercial Institution of Healyh "Russian Railway Company-medicine", Russia, Moscow, 2c4 Budayskaya str.,; [16]State budgetary medical centre "I.V.Davydovsky City Hospital", Russia, Moscow, 11th Yauzskaya str.

Aim. To study the characteristics of the atrial fibrillation (AF) cryoballoon ablation (CBA) procedure and features of patient's management in real clinical practice in Russia.

Methods. "Prospective Atrial Fibrillation Cryoablation Registry" is an observational prospective national multi-center study. It was conducted from 01.2017 to 12.2019 in centers of Russian Federation. The registry included patients over the age of 18 who were agreed to participate this study and had indications for CBA of AF. The study protocol did not provide for significant restrictions on inclusion criteria, procedure technique and postoperative follow-up. The data was collected prior to the CBA of AF, during hospitalization for CBA and on the 12-month follow-up.

Results. Participating centers enroll 980 patients according to inclusion criteria. CBA of AF was performed in 976 (99.6%) (mean age 59.7±9.2 years, 545 (55.8%) men) primary procedure - 840 (86.1%), re-ablation - 136 (13.9%). Paroxysmal AF occurred in 828 (84.8%) patients and persistent AF (mean time of persistence 4.4±3.7 months) - in 145 (15.1%) patients. The average procedure time was 108.1±33.3 minutes and mean fluoroscopy time was 24.9±13.6 min. Most of the procedures were performed under general anesthesia. Complications after AF CBA occurred in 53 (5.4%) patients. The most common complication was paresis of the phrenic nerve - 20 (37.7%) cases which were associated with lower temperatures of CBA application of the right pulmonary veins (τ=0.08; $p<0.05$). The features of antiarrhythmic and anticoagulant therapy were evaluated. A group of patients without adequate anticoagulant therapy in the postoperative period was identified. Due to COVID-19 restrictions only 374 (38.3%) patients completed 12-month follow-up. The recurrence of arrhythmia was occurred in 85 (22.7%) patients. Multivariate regression analysis revealed the following predictors of arrhythmia recurrence: the first procedure (OR 3.96; p=0.023), male sex (OR 1.77; p=0.014), duration of the procedure (min) (OR 1.01; p=0.007).

Conclusion. CBA is an effective and relatively safe procedure for the treatment of paroxysmal and persistent AF. Data from real clinical practice show a low proportion of serious complications of AF CBA. Data on the dynamics of drug therapy, including anticoagulant and antiarrhythmic therapy, were obtained. The attention of specialists performing AF catheter ablation and patient monitoring is required, since errors in patient management have been identified.

Keywords: atrial fibrillation; cryoballoon ablation; registry

Conflict of interest: none.

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Corresponding author: Lev E. Korobchenko, E-mail: lev.korobchenko@gmail.com

L.E.Korobchenko - ORCID ID 0000-0001-7185-0983, T.A.Lyubimtseva - ORCID ID 000-0002-8651-7777, K.V.Davtyan - ORCID ID 0000-0003-3788-3997, A.G.Topchyan - ORCID ID 0000-0001-7605-6316, G.Yu.Simonyan ORCID ID 0000-0002-1118-5376, S.E.Serduk - ORCID ID 0000-0003-4479-6963, S.V.Korolev - ORCID ID 0000-0001-5513-2332, A.Ya.Kosonogov - ORCID ID 0000-0002-0961-3546, K.A.Kosonogov - ORCID ID 0000-0001-7482-4983, E.S.Tarasyuk - ORCID ID 0000-0002-8353-7510, K.A.Lubenkov - ORCID ID 0000-0002-6506-2646, A.S.Shulga - ORCID ID 0000-0003-0854-2990, E.A.Artyukhina - ORCID ID 0000-0001-7065-0250, A.Sh.Revishvili - ORCID ID 0000-0003-2855-303X, D.V.Kryzhanovskii - ORCID ID 0000-0002-5021-9129, R.E.Batalov - ORCID ID 0000-0003-1415-3932, S.Yu.Usenkov - ORCID ID 0000-0001-9553-9647, D.N.Khomutinin - ORCID ID 0000-0003-4006-9339, G.V.Kolunin - ORCID ID 0000-0002-9376-897X, V.E.Kharats - ORCID ID 0000-0002-6297-7859, A.A.Nechepurenko - ORCID ID 0000-0001-5722-9883, I.Sh.Sagitov - ORCID ID 0000-0002-5830-5056, N.I.Grachev - ORCID ID 0000-0001-6100-3625, N.L.Sharikov - ORCID ID 0000-0002-4517-1642, S.Yu.Chetverikov- ORCID ID 0000-0001-8377-202X, D.I.Perchatkin - ORCID ID 0000-0003-2865-7760, Yu.V.Virstyuk - ORCID ID - 0009-0006-7632-5620, F.G.Rzaev - ORCID ID 0000-0002-4094-7771, D.S.Lebedev- ORCID ID 0000-0002-2334-1663, E.N.Mikhaylov- ORCID ID 0000-0002-6553-9141

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Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. The estimated prevalence of AF was 50 million people in the general population in 2020. Furthermore, the number of newly diagnosed cases continues to increase each year [1]. AF is associated with the development of adverse cardiovascular events, with the risks of stroke, myocardial infarction, and heart failure increasing by 2.4, 1.5, and 5 times, respectively [2, 3].

Currently, there is accumulating evidence regarding the positive impact of a sinus rhythm control strategy on the prognosis of patients with AF. This has strengthened the position of clinical guidelines on sinus rhythm control. Today, interventional catheter-based procedures have firmly established themselves in the armamentarium for treating patients with AF, with electrical isolation of the pulmonary veins (PVI) being the endpoint of catheter ablation [4, 5].

Cryoballoon Ablation (CBA) is one of the methods of PVI that has shown superiority over antiarrhythmic therapy (AAT) in the STOP-AF and CRYO-FIRST studies as a first-line treatment for AF. Furthermore, its efficacy and safety were found to be equivalent to radiofrequency (RF) ablation in several studies [6-9]. Technically, CBA uses a balloon catheter positioned at the PV orifice and cooled to negative temperatures by filling the internal balloon lumen with cryorefrigerant (nitric oxide). Cooling the myocardium to -40°C causes the intracellular formation of ice crystals, leading to cardiomyocyte damage and the subsequent development of reactive inflammation and replacement fibrosis, isolating the PV [10].

To study the efficacy and safety of CBA of AF in real clinical practice, the "Prospective Registry of Cryoablation for Atrial Fibrillation" was initiated in 2016, starting in January 2017. The registry is an observational, prospective, national, multicenter study conducted in medical institutions in the Russian Federation. The project is registered in the international clinical research system ClinicalTrials.gov, identification number NCT 03040037. The goal of the study was to investigate the clinical characteristics of patients referred for CBA, procedural parameters, and its efficacy in the early and long-term postoperative periods.

METHODS

Design

Patients were enrolled in the registry from January 2017 to December 2019. The inclusion criteria for the study were: (1) an indication for performing CBA of AF in patients aged over 18 years, (2) signed informed voluntary consent. Within the study, CBA of AF was performed both as a primary procedure and as a repeat procedure in patients with paroxysmal (PAF) and persistent (PeAF) forms of AF.

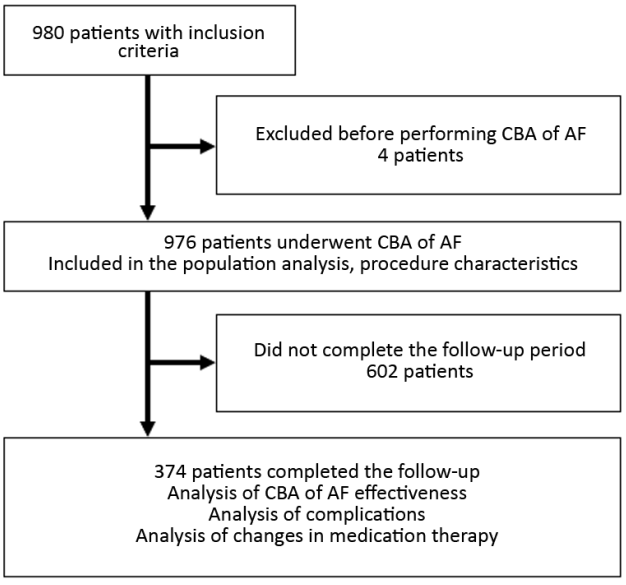

Fig. 1. Study diagram, where CBA is Cryoballoon Ablation, AF is Atrial Fibrillation.

Data collection and storage were carried out using the «Univers MDM» software (LLC «Univers Data,» St. Petersburg). The specifics of collecting clinical and demographic information were described previously [11]. All patients who participated in the study signed voluntary informed consent. Local ethical committees of each participating center approved the study protocol. The study was conducted in accordance with the Helsinki Declaration and the legislation of the Russian Federation.

Aim and endpoints

The aim of this registry was to study the characteristics of the CBA procedure of AF and the management of patients in real clinical practice in Russia. The primary endpoint was to describe the clinical and demographic characteristics of patients referred for CBA of AF.

Secondary endpoints included: (1) evaluation of the effectiveness and safety of the procedure in centers with different levels of experience in treating atrial fibrillation, (2) description of the technical aspects of performing the procedure, (3) acute and chronic complications of CBA, (4) identification of predictors of AF recurrence during the follow-up period.

Characteristics of the procedure

It should be noted that during data collection from the participating centers, preoperative preparation, anesthesia protocols, and the performance of CBA of AF were not strictly standardized. Patient management was carried out based on clinical guidelines and internal protocols of the participating institutions. The study included operators with varying levels of experience in interventional AF treatment (less than 100 procedures per year and more than 100 procedures per year) and CBA (less than 50 procedures per year and more than 50 procedures per year).

Table 1.

Clinical characteristics of patients participating in the study

	General population, n=976	Recurrent arrhythmias, n=134
Age, M±SD (min-max)	59.7±9.2 (27-80)	59.6±9.1 (29-72)
Women, n (%)	545 (55.8)	53 (39.6)
BMI <25 kg/m², n (%)	143 (14.7)	14 (10.4)
BMI 25-30 kg/m², n (%)	380 (38.9)	79 (59.0)
BMI ≥30 kg/m², n (%)	395 (40.5)	41 (30.6)
No BMI data	58 (5.9)	-
Paroxysmal AF, n (%)	828 (84.8)	116 (86.6)
Persistent AF, n (%)	145 (15.1)	15 (11.2)
No data on AF type, n (%)	3 (0.01)	3 (2.2)
Primary AF ablation, n (%)	840 (86.1)	124 (92.5)
Repeat AF ablation, n (%)	136 (13.9)	10 (7.5)
Hypertension, n (%)	744 (76.2)	101 (75.4)
Coronary artery disease, n (%)	183 (18.8)	28 (20.9)
Diabetes, n (%)	81 (8.3)	16 (11.9)
Stenting history, n (%)	59 (6.0)	7 (5.2)
CVA/TIA, n (%)	53 (5.4)	9 (6.7)
COPD, n (%)	44 (4.5)	7 (5.2)
Acute myocardial infarction, n (%)	34 (3.5)	5 (3.7)
Cardiomyopathy, n (%)	20 (2)	3 (2.2)
CHF I-II FC (NYHA), n (%)	188 (19.3)	25 (18.7)
CHF III-IV FC (NYHA), n (%)	4 (0.4)	-
LVEF ≤40%, n (%)	4 (0.4)	-
LVEF 41-49%, n (%)	28 (2.9)	4 (3.0)
LVEF ≥50%, n (%)	870 (89.1)	126 (94.0)
No data on LVEF, n (%)	74 (7.6)	4 (3.0)
LA ≤40 mm, n (%)	319 (32.3)	35 (26.1)
LA 41-50 mm, n (%)	403 (41.3)	69 (51.5)
LA >50 mm, n (%)	86 (8.8)	4 (3.0)
No data on LA size, n (%)	168 (17.2)	26 (19.4)

Note: BMI - body mass index; AF - atrial fibrillation; CVA - cerebrovascular accident; TIA - transient ischemic attack; COPD - chronic obstructive pulmonary disease; CHF - chronic heart failure; FC - functional class; LVEF - left ventricular ejection fraction; LA - left atrium.

Observation period

The observation period was 12 months, and the end of this period served as the main endpoint for postoperative follow-up. Patients underwent the follow-up either through in-person visits or using remote technologies. Recurrence of arrhythmia was defined as any supraventricular tachycardia lasting more than 30 seconds, detected through a 12-lead ECG, ECG monitor, telephone monitoring, or implanted loop recorders, identified after a 90-day blanking period. Due to restrictions related to the COVID-19 pandemic, a significant portion of patients could not complete the follow-up and was excluded from the assessment of long-term procedure efficacy, medication dynamics, and identification of arrhythmia recurrence predictors. However, the data from these patients were included in the characteristics of the overall population and CBA of AF procedure.

Statistical analysis

Descriptive statistics for variables are presented as the mean ± standard deviation, except for categorical variables, which are shown as percentages. To test for Gaussian distribution, the Kolmogorov-Smirnov test was used. For comparisons of variables with a Gaussian

distribution, the Student's t-test was applied; for variables with non-Gaussian distribution, the Wilcoxon test was used. Categorical variables were compared using the $\chi 2$ test. The Kendall test was applied to identify associations between variables. Logistic regression analysis was employed to identify predictors of arrhythmia recurrence. The analysis of arrhythmia recurrences was performed using the Kaplan-Meier method, and the standard error was calculated using Greenwood's formula. A p-value of <0.05 was considered statistically significant. Calculations were performed using RStudio software with the R programming language (©2023 Posit Software, PBC formerly RStudio, PBC).

RESULTS

A total of 33 medical institutions in the Russian Federation, where Cryoballoon Ablation of Atrial Fibrillation was technically possible in 2017, were invited to participate in the registry. 15 (46%) institutions participated in the registry. The registry included 980 patients, of whom 976 (99.6%) underwent CBA of AF, and 4 patients were excluded from the analysis. The 12-month follow-up point was completed by 374 (38.3%) patients. The study design is shown in Figure 1. The average number of patients included by each institution was 65.3±83.2 patients. The primary procedure of pulmonary vein isolation (PVI) was performed in 840 (86.1%) patients, and repeat AF ablation occurred in 136 (13.9%) cases.

The clinical characteristics of the patients are presented in Table 1. The study group included 545 (55.8%) women. PAF was present in 828 (84.8%) patients, and PeAF (mean duration 4.4±3.7 months) was present in 145 (15.1%) patients, with data missing for 3 (0.1%) patients. The majority of patients had obesity (395, 40.5%) and overweight (380, 38.9%). The most common comorbidity was arterial hypertension (AH), present in 744 (76.2%) patients. Most of the patients had a preserved left ventricular ejection fraction (LVEF), 870 (89.1%).

Characteristics of the procedure

The characteristics of the CBA of AF procedure are presented in Tables 2 and 3. The majority of CBA of AF procedures were performed by experienced operators: those with experience in AF ablation >100 procedures per year - 754 (77.3%) patients, and those with experience in CBA of AF >50 procedures per year - 804 (82.4%) patients. General anesthesia was used in 448 (45.9%) cases, and 185 (19.0%) procedures were performed under local anesthesia and sedation. Preoperative imaging (multi-slice computed tomography or magnetic resonance imaging) was conducted in 196 (20.1%) cases.

Most of the procedures, 778 (79.7%), were performed without the use of electroanatomical mapping systems. However, in 134 (14%) cases, transesophageal echocardiography was used for navigation, and in 479 (49%) cases, intracardiac echocardiography was utilized. Phrenic nerve function monitoring via stimulation mapping was performed in 889 (91.1%) patients, and esophageal temperature monitoring with a special sensor was done in 16 (1.6%) patients. The average procedure time was 108.1±33.3 minutes (Figure 2). However, no significant correlation was found between procedure duration and operator experience.

Left superior pulmonary vein (LSPV) ablation was performed in 955 (97.8%) patients, with one patient having previously undergone LSPV isolation. Intraoperative isolation was achieved in 952 (99.7%) patients, with 743 (77.8%) cases requiring one application, 178 (18.6%) requiring two, and 34 (3.6%) requiring three applications. The average temperature reached during LSPV ablation was -47.5±10.0°C.

Left inferior pulmonary vein (LIPV) ablation was performed in 947 (97.0%) patients, with 4 patients having previously undergone isolation of this vein and 8 patients not receiving treatment in this vein. One application was performed in 772 (81.4%) patients, two in 147 (15.6%), and three in 28 (3.0%) patients. Pulmonary vein isolation was successfully achieved in 933 (98.5%) patients. The

Table 2.

CBA of AF Characteristics

	GP, n=976
Procedure duration, min.	108.1±33.3
Fluoroscopy duration, min.	24.9±13.6
Application duration	
180 seconds, n (%)	332 (34.0)
240 seconds, n (%)	601 (61.6)
Individualized, n (%)	43 (4.4)
Anesthesia	
Sedation, n (%)	330 (33.1)
Local anesthesia, n (%)	185 (19.0)
General anesthesia, n (%)	448 (45.9)
No data, n (%)	13 (1.3)
Navigation	
Carto, n (%)	2
NavX, n (%)	3
Astrocard, n (%)	22 (2.3)
Other NS, n (%)	28 (2.9)
No NS used, n (%)	778 (79.7)
No data, n (%)	143 (14.7)

Note: GP - general population; NS - navigation system.

Table 3.

Pulmonary vein isolation, n (%)

	LSPV	LIPV	RSPV	RIPV
Total	955 (97.8)	947 (97.0)	951 (97.4)	941(96.4)
1 application	743 (77.8)	772 (81.4)	807(84.9)	791 (84.1)
2 applications	178 (18.6)	147 (15.6)	119 (12.5)	123 (13.1)
3 applications	34 (3.6)	28(3.0)	25 (2.6)	27 (2.8)
IOI	952 (99.7)	933 (98.5)	935(98.3)	917(97.4)

Note: LSLV, LILV, RSLV, and RILV - left and right, upper and lower pulmonary veins, respectively; IOI - intraoperative isolation..

average temperature during LIPV ablation was -44.8±9.3 °C. Right superior pulmonary vein (RSPV) ablation was performed in 951 (97.4%) patients and was successful in 935 (98.3%) cases. Additionally, 4 patients had previously undergone RSPV isolation, and 1 patient did not undergo treatment in this vein. One application was performed in 807 (84.9%) patients, two in 119 (12.5%), and three in 25 (2.6%). The average temperature during RSPV CBA was -48.4±9.5°C.

Right inferior pulmonary vein (RIPV) ablation was performed in 941 (96.4%) cases, with RIPV isolation achieved in 917 (97.4%) patients. Four patients had previously undergone RIPV isolation, and one patient did not undergo ablation. One, two, and three applications were performed in 791 (84.1%), 123 (13.1%), and 27 (2.8%) patients, respectively. The average temperature during RIPV CBA was -41.9±8.9°C.

In 8 cases, there was a common ostium of the left pulmonary veins, and in 2 cases, a single ostium of the right pulmonary veins.

The majority of procedures were performed using traditional CBA of AF protocols (application time 240 or 180 seconds), and only in 4% of cases were individualized protocols used with the «time-to-isolation» approach for pulmonary vein isolation. Additional radiofrequency (RF) energy to achieve pulmonary vein isolation was applied in 9 (0.9%) cases.

Complications

Complications after CBA of AF occurred in 53 (5.4%) patients (Table 4). The most common complication, observed in 20 (37.7%) cases, was transient phrenic nerve paresis, which was associated with lower temperatures during CBA of the right pulmonary veins (τ=0.08; p<0.05). No cases of persistent diaphragm paralysis were registered. Three patients died within 30 days after the procedure, but the cause of death was not specified.

Pneumothorax is an atypical complication of CBA of AF. However, based on the registry data, it was not possible to determine the exact cause of its development in one patient. The registry did not account for surgical access variations, and in this patient, it is possible that subclavian vein puncture was performed for the placement of a central venous catheter or additional electrodes.

Antiarrhythmic therapy

Preoperative AAT was administered to 880 (90.1%) patients (Table 5). The most commonly used drug group was beta-blockers, prescribed to 213 (21.8%) patients. Combined AAT, including a beta-blocker and a Class Ic or III drug, was used in 210 (21.5%) patients, while Class III drugs (sotalol – 189 (19.4%), amiodarone – 132 (13.5%)) were also frequently used. The least commonly used drug group was sodium channel blockers (Class Ic; at the time of registry enrollment, propafenone, lapacontine hydrobromide, and diethylamino propionyl ethoxycarbonylaminophenothiazine hydrochloride were available in Russia) – a total of 136 (13.9%) patients. Among the 321 patients who received Class III drugs, there were no contraindications for prescribing Class Ic in 153 patients.

In 96 (9.8%) patients, CBA of AF was chosen as first-line treatment (no AAT was administered prior to CBA of AF). The average age of this subgroup was 58.1±10.8 years. The majority of patients in this group had PAF – 67 (69.8%) compared to 6 (6.3%) with PeAF. The following comorbidities were reported in this subgroup: AH – 54 (56.3%); other comorbidities included a history of myocardial infarction in 2 patients, chronic heart failure (LVEF

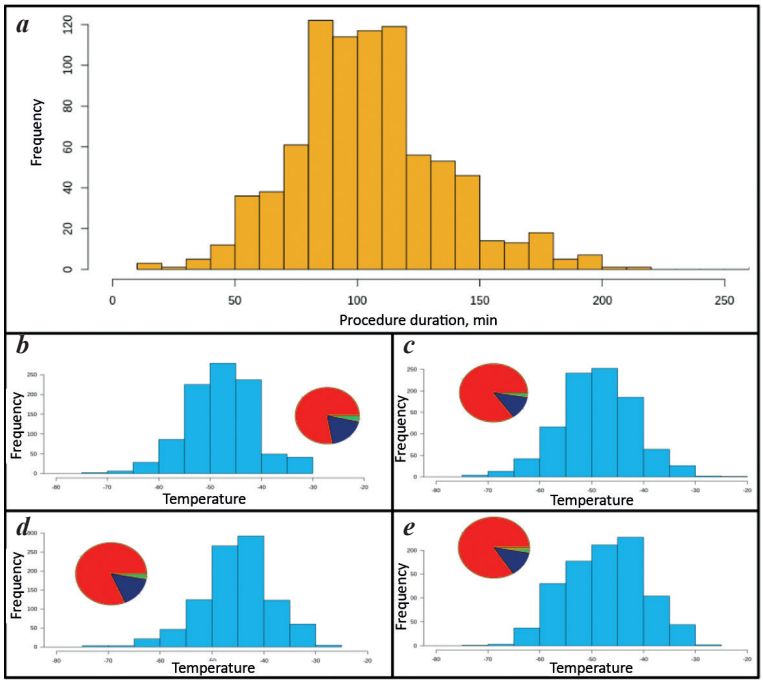

Fig. 2. Characteristics of pulmonary vein CBA: a - histogram of procedure time distribution; b-d - histograms of temperature distribution and pie charts of the number of applications (red - 1 application, blue - 2 applications, green - 3 applications) for CBA of LSLV, RSLV, LILV, and LILV, respectively.

Table 4.

CBA of AF complications

Transient phrenic nerve paresis, n (%)	20 (37.8)
Hematoma, n (%)	12 (22.6)
Hemopericardium, n (%)	5 (9.4)
Arteriovenous fistula, n (%)	3 (5.7)
Death within 30 days, n (%)	3 (5.7)
Femoral artery pseudoaneurysm, n (%)	2 (3.8)
Hemoptysis, n (%)	2 (3.8)
Atrial-esophageal fistula, n (%)	2 (3.8)
Pneumothorax, n (%)	1 (1.9)
Hemothorax, n (%)	1 (1.9)
Cardiac tamponade	1 (1.9)
Transient ischemic attack, n (%)	1 (1.9)
Total	53 (100)

- 54%) in 2 patients, and peripheral vascular diseases in 8 patients. The average left atrial diameter in this subgroup was 40.7±7.3 mm.

Anticoagulant therapy (ACT)

Before the CBA of AF, ACT was administered to 831 (85.1%) patients, while 145 (14.9%) patients did not receive ACT. Among the patients not receiving ACT, 41 (28.3%) were at high risk, 43 (29.7%) were at intermediate risk, and 61 (42.1%) were at low risk. In 399 (40.9%) cases, ablation was performed while continuing therapy with novel oral anticoagulants (NOACs), in 51 (5.2%) patients, therapy with warfarin was continued with target INR levels achieved, and in 330 (33.8%) cases, bridge therapy with low-molecular-weight heparin (LMWH) was used. In 196 (20.1%) cases, no data on the perioperative ACT regimen were available.

At the 12-month follow-up, 171 (45.7%) patients continued receiving ACT, while 203 (54.3%) patients had discontinued ACT. Among the patients who did not receive ACT, 201 (99%) were at intermediate or high risk of thromboembolic events (79 patients at high risk, 122 patients at intermediate risk).

Arrhythmia recurrences

The 12-month follow-up was completed by 374 (38.3%) patients. Among them, a documented recurrence of arrhythmia occurred in 85 (22.7%) patients (Fig. 3). Additionally, there were 16 early recorded episodes of arrhythmia that occurred during the blind period, which were not included in the evaluation of long-term effectiveness. No data on subsequent recurrences were available for this group of patients.

A trend towards more stable maintenance of sinus rhythm was observed in patients with PAF compared to PeAF: 78.1±2.3% (95% CI: 73.7-82.7%) vs 72.0±6.4% (95% CI: 60.6-85.6%), respectively. However, statistical significance was not reached, p=0.32. «Bonus applications» (additional CBA application after achieving PVI from the first application) were more common in the arrhythmia recurrence group (47.0% vs 40.5%), but no statistical significance was found (p=0.152).

The association with arrhythmia recurrence was examined for all parameters entered into the database. After constructing the correlation matrix of factors, pairs that correlated were excluded from the analysis. Univariate analysis revealed three factors with statistically significant correlations to arrhythmia recurrence: primary ablation, male sex, and procedure duration. Multivariate regression analysis showed that all three factors were independently associated with arrhythmia recurrence, though the odds ratio was minimal for procedure duration (Table 6).

DISCUSSION

The Prospective Registry of Cryoablation for Atrial Fibrillation is a national, prospective study on the effectiveness and safety of CBA for AF in real clinical practice. When characterizing the registry sample, it is notable that the majority of patients had no significant structural heart pathology, preserved LEVF, and minimal left atrial dilation, with a predominance of PAF (84.8%) and primary ablation procedures (86.1%), which aligns with similar studies [12, 13].

The low representation of PeAF in the registry is likely due to the perception of reduced effectiveness of CBA for AF in this form of arrhythmia, as CBA for AF was initially studied in patients with PAF [7-9] (and also approved by the FDA for the treatment of PAF [14]). However, it is also known that pulmonary vein isolation (PVI) has shown a positive impact on prognosis in patients with PeAF, leading to the STOP Persistent AF trial [15], which demonstrated the safety of using CBA for AF in PersAF with a sinus rhythm maintenance rate of around 55% over 12 months, which was further supported by registry studies [16]. The higher efficacy of sinus rhythm maintenance in the national registry is likely related to insufficient control and the small number of PeAF patients in the final observation group (15 patients). When deciding on interventional treatment for PeAF, it should be remembered that CBA for AF is an effective and safe method, comparable to radiofrequency ablation (RFA), and may be considered for this category of patients [17].

Interestingly, a small proportion of patients (96, 9.8%) underwent CBA as first-line therapy (i.e., without previous AAT). According to the Cryo AF Global Registry, the number of such patients in global practice approaches

Table 5.

Antiarrhythmic therapy

	At the time of inclusion (n=976)	Observation 12 months (n=374)
Lappaconitine hydrobromide, n (%)	47 (4.8)	7 (1.9)
Propafenone, n (%)	82 (8.4)	13 (3.5)
DAPEKA, n (%)	7 (0.7)	3 (0.8)
Beta-blockers, n (%)	213 (21.8)	139 (37.2)
Amiodarone, n (%)	132 (13.5)	16 (4.3)
Sotalol, n (%)	189 (19.4)	44 (11.7)
Combination AAT, n (%)	210 (21.5)	24 (6.4)
Without AAT, n (%)	96 (9.8)	128 (34.2)

Note: DAPEKA - diethylaminopropionylmethoxycarbonylaminophenothiazine; AAT - antiarrhythmic therapy

Table 6.

Anticoagulant therapy

	At the time of inclusion (n=976)	Observation 12 months (n=374)
Received ACT, n (%)	830 (85.0)	171 (45.7)
Apixaban, n (%)	143 (14.7)	34 (9.1)
Rivaroxaban, n (%)	406 (41.6)	75 (20.1)
Dabigatran etexilate, n (%)	150 (15.4)	30 (8.0)
Warfarin, n (%)	131 (13.4)	32 (8.6)
Did not receive ACT, n (%)	145 (14.9)	203 (54.3)

Note: ACT - anticoagulant therapy.

half of all CBA procedures for AF (42%) [13]. It is known that early rhythm control reduces the frequency of cardiovascular events, and early catheter ablation has higher efficacy, slowing disease progression [4, 18]. Early referral for catheter ablation can improve prognosis and quality of life for patients.

Nearly half (45.9%) of all procedures in the registry were performed under general anesthesia. Some studies have shown the advantage of performing the procedure under sedation due to reduced anesthetic time. However, there is currently no consensus regarding anesthetic management during catheter ablation for AF and the choice between general anesthesia and sedation. This largely depends on the experience and internal protocols of each specific institution, as reflected in the literature [6, 19].

Preoperative imaging (multislice computed tomography or magnetic resonance imaging) was performed in 196 (20.1%) patients. The vast majority of procedures were performed without using electroanatomical mapping systems, though transesophageal echocardiography or intracardiac echocardiography was used for additional imaging in over half of the cases.

Considering the study's limitations, the effectiveness of CBA for AF at 12 months was 78.1% for PAF and 72.0% for PeAF, which also aligns with the results of other registry studies. When analyzing these data, one should take into account the large number of patients lost to follow-up, the significant bias towards PAF, and specific treatment centers performing a high number of these procedures [12, 13].

According to the registry, operators most commonly use one application for PVI lasting 240 seconds, though the «bonus application» strategy (additional CBA application after achieving PVI from the first application) is used in 15-20% of cases. The dosing of cryoapplications is also nuanced. Technically, CBA for AF is considered a single-shot procedure, where one application should be sufficient for PVI. However, in clinical practice, a «bonus application» strategy is sometimes used after PVI is achieved. This strategy was introduced in foundational studies with first-generation cryoballoons. However, with the advent of second-generation cryoballoons, studies have emerged focusing on reducing the dose of cryoapplication. It is now known that routine use of the «bonus» strategy does not lead to better ablation outcomes. Subsequent comparisons of different cryoapplication durations (180 and 240 seconds) also showed no difference in PVI and sinus rhythm maintenance. The most relevant strategy today is the individualized approach, selecting the application time based on the «time to isolation» parameter. Individualized approaches reduce the duration of the procedure without affecting its effectiveness, but according to the registry, individualized approaches were relatively rare, requiring attention from operators [20-24].

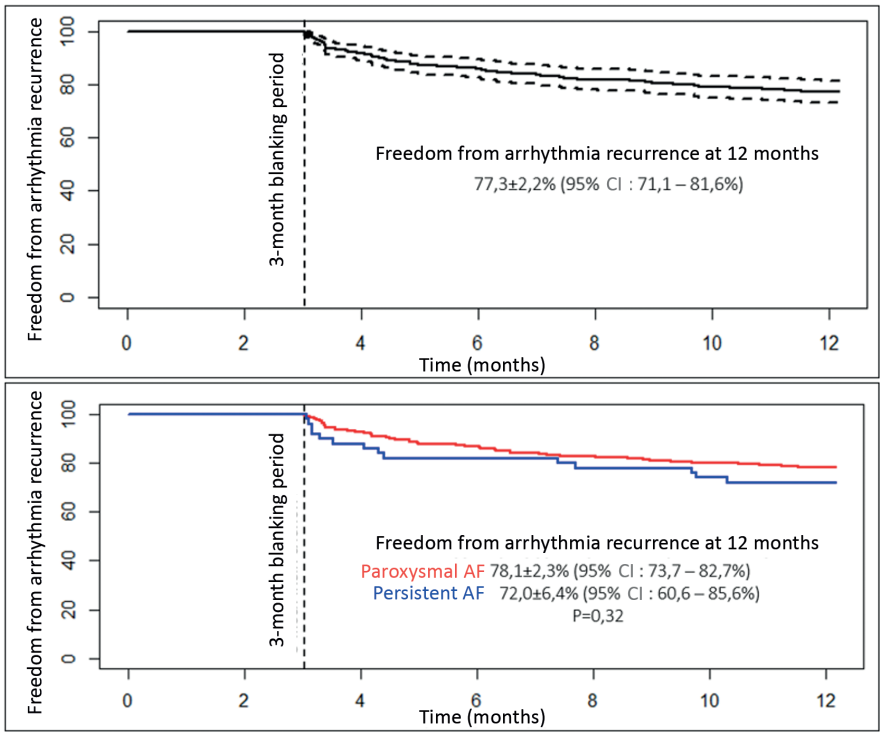

Fig. 3. Sinus rhythm maintenance curves.

The low complication rate for CBA for AF speaks to its safety. The most common complication, as expected, was transient phrenic nerve palsy, which was associated with lower temperatures during the ablation of the right pulmonary veins.

Regarding AAT, the registry data show a traditional predominance of beta-blockers and class III antiarrhythmic drugs [25]. Beta-blockers were the most common AADs in the patients included in the registry. Specific indications for beta-blocker use (antihypertensive, antianginal, chronic heart failure therapy) cannot be determined within the scope of the study. However, it should be remembered that, for AF therapy, beta-blockers are not intended for long-term sinus rhythm control (exception: when

Table 7.

Predictors of arrhythmia recurrence

Factor	OR	CI	P
Univariate analysis			
First procedure	2.2	1.18-4.58	0.021
Male gender	1.25	0.86-1.82	0.242
Procedure duration, min	1.01	1.00-1.01	0.016
Multivariate analysis			
First procedure			
Male gender	1.62	1.04-2.55	0.036
Procedure duration, min	1.01	1.00-1.01	0.008

combined with Ic-class drugs for the prevention of complications). Furthermore, despite the lack of data on prior AAT, considering the overall population characteristics, there was insufficient prescription of Ic-class drugs, with a preference for class III AADs. While amiodarone is clearly indicated as a medication for structural heart disease or as a last-line therapy in various clinical guidelines, the approach to sotalol differs significantly between national and international guidelines. In national guidelines, sotalol may be used for preventing AF recurrences in patients without severe organic heart disease, without impaired pumping function, and without CHF (Class IIA, Level 2b), while ESC and AHA/ACC guidelines classify sotalol under Class IIb and Level 2b, respectively. The likely reason for this difference is the study by L. Valembois et al., which showed an increased risk of death from all causes when using sotalol compared to the placebo group (OR=2.23; 95% CI: 1.03-4.81). Additionally, it is known that sotalol significantly affects the QT interval, and there is evidence of individual «hypersensitivity» to sotalol due to reduced repolarization reserve. Given this, experts from AHA/ACC recommend initiation and titration of sotalol therapy only in hospital settings [26-31].

A separate discussion is warranted regarding ACT. Unfortunately, there remains a category of patients who did not receive ACT in the preoperative and postoperative periods, despite formal indications based on the CHA_2DS_2-VASc score. It is known that catheter ablation of AF (including «effective» ablation) is not a reason to discontinue ACT, and in the initial postoperative period (the first 2 months), ACT is actually indicated, even for patients at low thromboembolic risk. Subsequently, the decision to discontinue ACT is made based on CHA_2DS_2-VASc scores and data on arrhythmia recurrence [26, 27].

Additionally, the registry data demonstrate that the issue of perioperative ACT remains unresolved. It is important to note that catheter ablation of AF is a procedure with a high risk of bleeding and increased risk of thromboembolic complications. According to the registry, about one-third of all patients were managed with a bridging therapy regimen, which contradicts current guidelines for the diagnosis and treatment of AF [26]. Currently, the most relevant perioperative ACT regimens are: continuous therapy and temporary interruption. Meta-analyses of large studies have shown a reduction in major bleeding rates with continuous NOAC therapy compared to vitamin K antagonists [33, 34]. Continuous vitamin K antagonist therapy, compared to bridging therapy, also showed no difference in the rate of major bleeding [35]. Limitations to the use of continuous therapy may include the official instructions for NOACs. Current clinical guidelines, approved by the Ministry of Health of Russia's expert council, allow for continued oral anticoagulation during the perioperative period and a short interruption of NOACs before ablation.

Compared to the results of the first survey of specialists on CBA [17], the average procedure time and the number of cryoapplications have significantly decreased, as well as the need for additional radiofrequency catheter applications to complete the isolation of pulmonary veins. This is explained by the use of second-generation balloons and increasing operator experience. There is also an increase in CBA efficiency; however, direct comparison of this indicator is difficult, as the 2015 survey considered arrhythmia recurrences during the first 6 months, while the registry shows a low percentage of patients remaining under observation. Additionally, there is a noted increase in the proportion of procedures performed under the control of electroanatomical mapping.

Study limitations

A significant limitation of the study is the lack of 12-month follow-up data for two-thirds of patients, which could have influenced the results of the assessment of predictors for arrhythmia recurrence. As a result of this limitation, there may also be an underestimation of delayed complications from ablation and adverse clinical events. The registry did not provide for the standardization of ablation procedures and arrhythmia recurrence registration, but this allowed for an analysis of real-world clinical data. Another limitation of the study is its conduct during the COVID-19 pandemic, which impacted the quality of postoperative data collection and potentially affected the ablation outcomes in patients who had contracted the infection.

CONCLUSION

Cryoballoon ablation is an effective and relatively safe procedure for the treatment of paroxysmal and persistent atrial fibrillation. Data from real clinical practice reflect a low proportion of serious complications from the procedure. For the first time, data have been obtained on the dynamics of medication therapy, including anticoagulant and antiarrhythmic treatment. Attention is needed from specialists performing AF catheter ablations and monitoring patients, as deviations in patient management from the approaches outlined in clinical guidelines have been identified.

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SHORT- AND LONG-TERM RESULTS OF CATHETER ABLATION FOR ATRIAL FIBRILLATION UNDER THE GUIDANCE OF THE "ABLATION INDEX" MODULE

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

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

Aim. Comparative evaluation of short-term and long-term outcomes of radiofrequency pulmonary vein isolation using the "Ablation Index" module versus without in patients with paroxysmal and persistent forms of atrial fibrillation.

Methods. The study included 286 patients with paroxysmal and persistent forms of atrial fibrillation, divided into 2 groups: the study group (110 patients) underwent radiofrequency pulmonary vein isolation using the "Ablation Index" module, while the control group (176 patients) underwent isolation without the use of the "Ablation Index" module.

Results. The average follow-up period was 38.1±9.6 months. There was no significant difference in freedom from atrial tachyarrhythmias in the long-term follow-up between the study and control groups (58.1% vs. 62.3%, p=0.667), or in the number of perioperative complications (3.6% vs. 8.5%, p=0.106). A significant reduction in the duration of the procedure was observed when using the "Ablation Index" module (92.7±20.9 min vs. 126.4±29.2 min, p<0.001), as well as in the recurrence rate of atrial fibrillation in the blanking period (1.8% vs. 8.5%, p=0.020).

Conclusion. Interventional treatment of atrial fibrillation under the control of the "Ablation Index" module shows significantly lower recurrence rates of atrial tachyarrhythmias in the blanking period and comparable safety and long-term efficacy results compared to interventional treatment using catheters with contact force sensor over a period of more than three years.

Key words: atrial fibrillation; radiofrequency ablation; pulmonary vein; ablation index; recurrence; long-term outcomes

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Corresponding author: Khuziakhmetov Rustam, E-mail: rustam-huziahmetov@yandex.ru

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

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Radiofrequency ablation (RFA) has become an increasingly popular treatment for atrial fibrillation (AF) over the past decade. The primary electrophysiological endpoint of ablation is achieving electrical isolation of the pulmonary veins (PVs) [1]. AF is associated with atrial dysfunction, leading to structural and electrical remodeling, which may contribute to the development of heart failure [2]. Ensuring durable PV isolation requires standardization of each radiofrequency application around the PV. Ideally, this should result in transmural myocardial damage while avoiding necrosis extending to extracardiac structures.

In recent years, hardware and software modules predicting ablation lesion depth have been integrated into three-dimensional (3D) electrophysiological navigation systems from various manufacturers. These modules help standardize radiofrequency applications in the atrium. One such module is the Ablation Index (AI; Biosense Webster, USA). AI is a dimensionless parameter calculated based on a combined analysis of three key factors: contact force (CF) of the catheter, ablation time, and power [3].

Experimental studies in canine models have demonstrated that AI reliably predicts lesion depth at catheter application sites on the endocardial surface [4, 5]. Thus, with 3D navigation system guidance, the extent of tissue injury at ablation sites can be assessed in real-time, ensuring that each application is adequate but not excessive [6], thereby potentially reducing the risk of procedure-related complications [7, 8].

METHODS

Study Protocol

This study was conducted at the Federal Center of Cardiovascular Surgery named after S.G. Sukhanov, Ministry of Health of the Russian Federation. The study included 286 patients scheduled for catheter ablation of AF who

were divided into two groups: study group (110 patients) uderwent pulmonary vein isolation (PVI) using the SmartTouch catheter (Biosense Webster, USA), which enables real-time assessment of contact force between the catheter and myocardial tissue. The procedure was performed using the VisiTag module (Biosense Webster, USA), which allows the navigation system to automatically identify application points based on pre-set contact force and catheter stability parameters, in combination with the Ablation Index (AI) module. Control group (176 patients) underwent PVI using the SmartTouch catheter with only the VisiTag module, without the Ablation Index module.

Patients were enrolled in the study between 2018 and 2021. Group allocation was determined by the availability of disposable materials required for AI module usage at the time of catheter intervention.

The primary endpoint was freedom from atrial tachyarrhythmias (AF, atrial flutter, or atrial tachycardia) in both the short-term period (first 3 months, also known as the "blanking period") and the long-term follow-up period (up to 38 months) after ablation.

The secondary endpoints included: total procedure duration, incidence of intraoperative and postoperative complications, recurrence rate during the blanking period, rate of repeat catheter interventions due to recurrent atrial tachyarrhythmias.

The primary endpoint was assessed based on the absence of symptomatic or asymptomatic atrial tachyarrhythmias lasting more than 30 seconds. Arrhythmias occurring during the blanking period were not considered when evaluating the long-term effectiveness of ablation. Recurrence detection was conducted using 24-hour ECG monitoring, implantable device data (pacemakers, ICDs), and medical record analysis.

The secondary endpoints were evaluated based on medical records (procedure duration, rate of repeat interventions), patient-reported symptoms and clinical condition, and instrumental and laboratory investigations (assessment of intraoperative and postoperative complications).

All patient data were anonymized and processed in a secure database without personal identifiers. Patients provided informed consent for study participation and for the AF ablation procedure, in accordance with current clinical guidelines.

Patient selection

The study included symptomatic patients aged from 18 to 83 years with paroxysmal or persistent AF and ineffective drug therapy (Class I or III agents). AF episodes were documented in all patients on resting electrocardiogram (ECG) or during Holter ECG monitoring.

The exclusion criteria were as follows: Previous catheter ablation for AF; unstable angina or acute myocardial infarction within the past 3 months; need for valve or coronary pathology correction; contraindications to oral anticoagulant therapy; severe chronic renal or hepatic failure.

The clinical characteristics of the patients are presented in Table 1.

Preoperative investigations

Before the procedure, all patients underwent a clinical examination, including a detailed collection of

Table 1.

Clinical characteristics of patients by groups

Characteristics	Control group (n=176)	Study group (n=110)	P
Average age, years	59.4±8.6	64.4±7.4	<0.001
Gender (male/female), %	56.3/43.8	48.2/51.8	0.183
Body mass index (BMI), kg/m^2	30.6±4.1	30.9±4.9	0.701
PAF/PeAF, %	59.7/40.3	76.4/23.6	0.004
Disease duration, months	49.9±41.9	58.3±46.1	0.105
AIS, %*	10.8	5.5	0.120
Coronary artery disease, %	32.4	35.5	0.593
Myocardial infarction, %*	6.3	7.3	0.735
Diabetes mellitus, %	11.9	8.2	0.314
Hypertensive heart disease, %	85.2	93.6	0.030
Pacemaker implantation, %*	5.7	11.8	0.063
Myocardial revascularization, %*	11.9	11.8	0.977
LVEDV, ml	97.3±23.0	96.8 ± 25.9	0.874
LVEF, %	55.5±6.7	55.2±6.1	0.674
LA volume (TTE), ml	73.2±18.6	73.9±24.5	0.643
LAVI (TTE), ml/m^2	37.2±9.2	38.0±11.2	0.984
Interventricular septum, mm	13.4±2.1	13.2±3.3	0.070
Mitral regurgitation grade 0, %	26.9	33	0.159
Mitral regurgitation grade I, %	62.3	50.5	
Mitral regurgitation grade II, %	10.3	16.5	
Mitral regurgitation grade III, %	0.6	0	
Systolic PA pressure, mmHg	35.6±5.9	37.9±7.3	0.158
Mean PA pressure, mmHg	20.1±6.5	20.8±8.2	0.684
LA volume (MSCT-CTA), ml	121.8±31.4	112.9±28.5	0.024
LAVI (MSCT-CTA), ml/m^2	60.7±14.9	57.8±15.1	0.201

Note: * - in medical history; PAF and PeAF - Paroxysmal Atrial Fibrillation and Persistent Atrial Fibrillation; AIS - Acute Ischemic Stroke; LVEDV - Left Ventricular End-Diastolic Volume; LVEF - Left Ventricular Ejection Fraction; LA - Left Atrium; TTE - Transthoracic Echocardiography; LAVI - Left Atrial Volume Index; MR - Mitral Regurgitation; PAS and MPAP - Systolic and Mean Pulmonary Artery Pressure; MSCT-CTA - Multislice Computed Tomography with Intravenous Contrast.

complaints, medical history, and assessment of objective status, as well as standard laboratory and instrumental diagnostic tests. To further detail the anatomy of the left atrium and pulmonary veins and to exclude any additional formations within the left atrium, all patients underwent multislice computed tomography (MSCT-CTA) of the left atrium and pulmonary veins with intravenous contrast enhancement.

Catheter ablation

The anesthesia method, vascular access, navigation system, and ablation catheter used were identical for both groups. The surgical procedure was performed under local anesthesia. Vascular access was achieved by catheterization of the right and/or left femoral vein. Under fluoroscopic control, the interatrial septum was punctured twice.

A three-dimensional model of the left atrium and pulmonary veins was created using the Carto3 navigation system (Biosense Webster, Johnson & Johnson, USA), through rapid anatomical modeling after respiratory compensation. The ablation catheter used was the ThermoCool SmartTouch catheter (Biosense Webster, Johnson & Johnson, USA), which includes a pressure sensor.

During PVI, the VisiTag and Ablation Index modules (Biosense Webster, Johnson & Johnson, USA) were used, with the following settings: maximum catheter deviation standard deviation: 2.5 mm, minimum stability retention time: 3 seconds, catheter contact force range: 4 to 40 g, ablation point size: 3 mm, distance between two points: 5 mm.

The first step involved right pulmonary vein isolation, followed by left pulmonary vein isolation through point-by-point ablation, strictly in one direction along the designated ablation path. To confirm PVI, the Lasso circular catheter (Biosense Webster, Johnson & Johnson, USA) was used.

In the study group, the following ablation parameters were applied: ablation power was set to 45 W for all walls of the left atrium (LA); physiological saline flow rate: 2 ml/min without ablation, 30 ml/min during ablation; target Ablation Index ranged from 400-420 for the posterior wall of the left atrium and 460-500 for the anterior wall.

In the control group, the following ablation parameters were used: ablation power was set to 45 W for the anterior wall of the left atrium and 35 W for the posterior wall; physiological saline flow rate: 2 ml/min without ablation, 30 ml/min during ablation; ablation duration was determined individually by the operator based on a combination of factors (contact force, catheter stability, and ablation area).

Postoperative management and follow-up

All patients underwent echocardiographic control (Echo) on the 2nd day after surgery to exclude hemopericardium and assess heart contractility parameters, as well as 24-hour ECG monitoring.

Oral anticoagulant and antiarrhythmic therapy was continued for at least 3 months after the procedure (blanking period). If no documented paroxysms of atrial tachyarrhythmias were observed after the blanking period, antiarrhythmic therapy was discontinued. However, the use of antiarrhythmic drugs by the patient before and after the surgery was not recorded in this study.

Patients were assigned clinical follow-up points for the study, including Holter ECG monitoring at 3, 6, and 12

Table 2.

Immediate and long-term results of catheter-based treatment of atrial fibrillation

	Control group (n=176)	Study group (n=110)	P
Procedure duration, minutes	126.4±29.2	92.7±20.9	<0.001
Recurrence of atrial fibrillation during the blanking period			
Total number of patients, n (%)	15 (8.5)	2 (1.8)	0.02
Paroxysmal form, n (%)	6 (3.4)	1 (0.9)	
Persistent form, n (%)	9 (5.1)	1 (0.9)	
Frequency of repeat pulmonary vein isolations			
Total number of patients, n (%)	55 (33.3)	24 (21.8)	0.083
Paroxysmal form, n (%)	31 (17.6)	16 (14.5)	0.098
Persistent form, n (%)	24 (13.7)	8 (7.3)	0.778

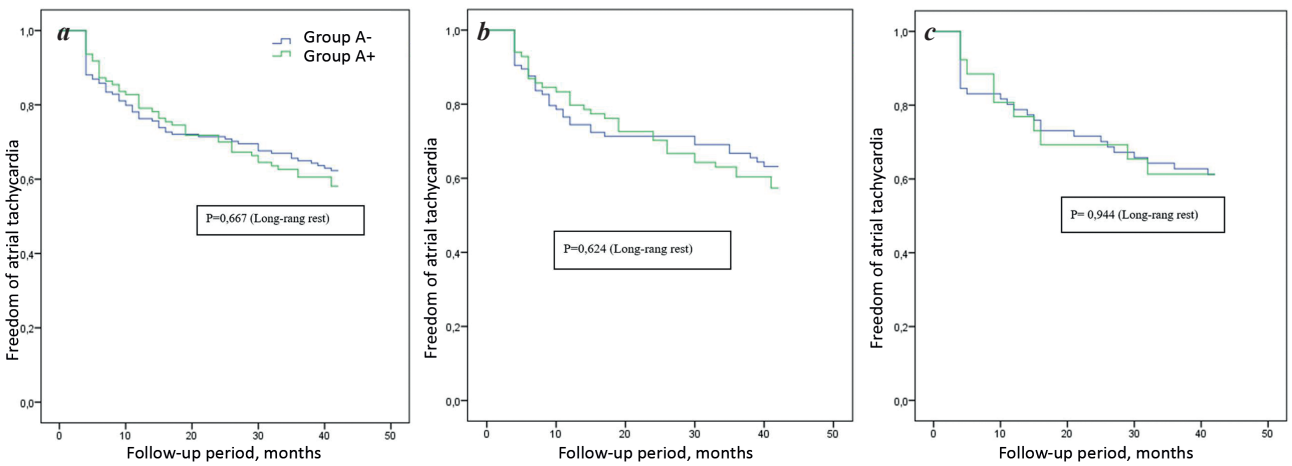

Fig. 1. Comparative graph of freedom from atrial tachyarrhythmia in the study and control groups: a - all patients, b - patients with paroxysmal AF, c - patients with persistent AF.

months, and then every 6 months after the initial treatment.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics v.23. Parametric data were tested for normal distribution, and comparisons were subsequently made using either the Student's t-test or the Mann-Whitney U test. Non-parametric data were compared based on the number of events using either Fisher's exact test or Pearson's chi-square test.

RESULTS

Intraoperative data

Within the scope of the study, the duration of fluoroscopy and the left atrial stage were not assessed, as these data were not recorded in the surgical protocols of the control group. The total procedure duration was significantly shorter in the study group (Table 2).

Intraoperatively, acute PVI was successfully achieved in all patients in both groups.

Postoperative data

The mean follow-up period in the study was 38.1±9.6 months. After 40 months, 95 patients from the control group (out of 176, with 20 patients lost to follow-up and 61 cumulative events) and 35 patients from the study group (out of 110, with 32 patients lost to follow-up and 43 cumulative events) remained under observation.

During the blanking period, AF recurrence was observed in 15 patients in the control group and 2 patients in the study group. The recurrence rates during the blanking period and their distribution by AF type are shown in Table 2. As shown in the table, in the group where RFA was performed using the AI module, the recurrence rate during the blanking period was significantly lower compared to the control group.

During the mean follow-up period of 38.1±9.6 months, freedom from AF (calculated using Kaplan-Meier survival analysis) was 62.3% in the control group and 58.1% in the study group (Figure 1a). A comparative evaluation of freedom from atrial tachyarrhythmias using Kaplan-Meier was also conducted for subgroups with paroxysmal AF(Figure 1b) and persistent AF (Figure 1c). There was no statistically significant difference in freedom from atrial tachyarrhythmias during the follow-up period between the two study groups and their subgroups.

Redo ablation

The number of patients who underwent repeat ablation is shown in Table 2. No statistically significant difference was found in the frequency of repeat interventions between the study group and the control group. However, there was a trend towards a lower frequency of repeat pulmonary vein isolation in the group of patients who used the Ablation Index module (p=0.083).

Complications

No complications leading to fatal outcomes or requiring additional invasive interventions were recorded in either group. In 15 patients (8.5%) in the control group and 4 patients (3.6%) in the study group, complications such as pericardial effusion up to 1 cm or post-puncture hematoma were recorded (p=0.106).

DISCUSSION

As a result of our study, in the comparative evaluation of the two groups, we obtained the following important findings: there was no statistically significant difference in freedom from arrhythmia in the long-term follow-up period; however, the recurrence rate during the blanking period was significantly higher in the control group; the use of the AI module significantly shortened the duration of the procedure; there was a marked trend towards a lower need for repeat ablation in the study group.

Most recent studies focusing on catheter ablation with CF monitoring have shown higher efficacy and safety compared RFA without the use of contact force sensing catheters [13]. There is also evidence suggesting that CF control may positively influence the treatment efficacy in patients with persistent AF [14, 15].

In recent years, an additional marker of lesion quality (the Ablation Index, AI) has been developed, which is calculated based on the analysis of contact force, ablation time, and power. Subsequently, the evaluation of AI's effectivenessbecame relevant, and several studies were published that compared AI with CF-guided ablation. In analyzing these studies, we found that, in most of them, freedom from atrial tachyarrhythmias was significantly higher with AI use, while maintaining a comparable safety profile [9-10, 16-17]. These findings contrast with the results of our study. One of the key limitations of the above-mentioned studies is the postoperative follow-up period, which is typically limited to 12 to 14 months [10, 16-19]. However, it is known that the recurrence rate of AF after the primary procedure continues to steadily rise as the observation period extends, and by the 5th year, freedom from AF may be less than 70% [20, 21]. Our study, with 36 months or more of postoperative follow-up, demonstrates more convincing results regarding the comparative effectiveness of both techniques.

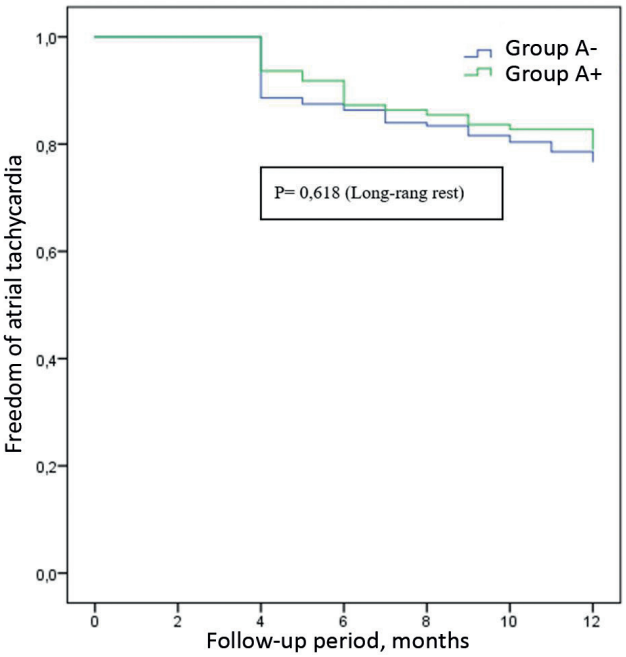

Figure 2. Comparative plot of freedom from atrial tachyarrhythmia in the study and control groups at 12 months.

If we look specifically at the 12-month follow-up results from our study (Figure 2), freedom from atrial arrhythmiaswas also higher in the AI group, although not statistically significant, which partially correlates with the findings of previous studies. Furthermore, in our study, the use of AI significantly reduced the duration of the procedure. This is likely due to the fact that pulmonary vein isolation was more frequently achieved on the first pass, without the need for additional ablations or searching for "breakthroughs". However, we did not record this data during the surgical interventions, and cannot conclusively confirm this hypothesis. Still, the operation duration data we obtained correlate with the results of most authors, whose work was analyzed and published in a large meta-analysis [17].

Our study also demonstrated that the use of the AI module significantly reduces the recurrence rate during the blanking period. This is likely related to the lower need for radiofrequency applications in the study group to achieve intraoperative pulmonary vein isolation, which in turn reduces atrial wall injury and atrial tissue edema.

Thus, according to our data, the use of the Ablation Index module does not result in a significant improvement in long-term efficacy when treating patients with AF, compared to results obtained with a similar catheter and operation protocol (using the VisiTag module and SmartTouch catheter). However, it significantly shortens the duration of the procedure and simplifies the achievement of pulmonary vein isolation, as demonstrated in most studies, including ours, by standardizing and establishing uniform criteria for the effectiveness of each ablation point.

It is likely that multicenter, randomized studies with different AI parameters will demonstrate more significant results in terms of efficacy in the future. Therefore, this topic requires further investigation.

Limitations

1. Recurrence of AF in the postoperative period was assessed using 24-hour ECG monitoring, data from implantable devices (pacemakers), and analysis of medical records. In our study, we did not implant loop recorders for diagnosing atrial tachyarrhythmias.
2. The non-randomized nature of the study means that the effect of confounding factors cannot be excluded.
3. The study was single-center, limiting the generalizability of the findings.
4. Detailed evaluation of antiarrhythmic therapy (e.g., types of medications, duration of therapy) before and after surgery was not performed for patients in either group.

CONCLUSION

Ablation of atrial fibrillation (AF) under the guidance of the Ablation Index module is associated with a lower recurrence rate of atrial tachyarrhythmias during the blanking period (the first three months) after ablation. The rate of complications and the recurrence rate over a 3-year follow-up period were not significantly different between the group using the Ablation Index module and the group without it.

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FACTORS ASSOCIATED WITH RESISTANCE TO RESOLUTION OF LEFT ATRIAL APPENDAGE THROMBUS IN PATIENTS WITH ATRIAL FIBRILLATION: 12-MONTH FOLLOW-UP RESULTS

A.V.Belokurova, A.V.Mamarina, N.Yu.Khorkova, T.P.Gizatulina

Tyumen Cardiology Research Center, Tomsk National Research Medical Center, Russia, Tyumen, 111 Melnikaite str.

Aim. To study the dynamics of left atrial appendage (LAA) thrombosis and to determine the factors associated with resistant LAA thrombus in patients with non-valvular atrial fibrillation (AF) during 12 months of follow-up.

Methods. A prospective study included 83 patients with LAA thrombosis detected by transesophageal echocardiography (TEE). The end point was resolution or stability of the thrombus. All patients underwent clinical examination, complete blood count and biochemical blood test, coagulation testing, transthoracic echocardiography (TTE) and TEE.

Results. According to the results of TEE, the patients were divided into two groups: group 1 (n=45) with resolution LAA thrombus and group 2 (n=38) with resistant LAA thrombus. Group 2 patients were more likely to take beta-adrenoblockers (57.9% and 31.1%, p=0.014), diuretics (60.5% and 35.6%, p=0.023) and rivaroxaban (39,5% и 13,3%, p=0,010). According to TTE data, group 2 had a higher right atrial volume index (30.7 [24.7; 34.7] vs 24.5 [21.0; 32.2] ml/m^2, respectively, p=0.034). Laboratory data analysis showed that group 2 had higher mean platelet volume (MPV) levels (9.1 [8.3; 9.8] vs 8.4 [7.9; 9.4] fl, p=0.035), platelet distribution width (PDW) (15.9 [15.7; 16.2] vs 15.7[15.5; 15.9] %, p=0.007) and platelet large cell ratio (P-LCR) (30.0±9.2 vs 25.3±7.4%, p=0.014).

There were significant direct correlations of MPV and P-LCR with the following parameters: right atrial volume, left atrial volumes, pulmonary artery systolic pressure, red blood cell level, hemoglobin level and hematocrit. The inverse association of MPV and P-LCR was with platelet count.

Conclusions. Resistance of LAA thrombus to resolution in patients with non-valvular AF is associated with morphofunctional parameters of platelets, which correlate with atrial structural remodeling. The results obtained indicate the need to continue research aimed at studying the contribution of the platelet activity to resistance to LAA thrombus, despite taking oral antocoagulants.

Key words: mean platelet volume; platelet distribution width; platelet large cell ratio; left atrial appendage thrombus; atrial fibrillation; transesophageal echocardiography

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Corresponding author: Belokurova Alfira, E-mail: alfira_m@inbox.ru

A.V.Belokurova - ORCID 0000-0002-6049-8985, A.V.Mamarina - ORCID 0000-0002-8160-7060, N.Yu.Khorkova - ORCID 0000-0002-7083-3214, T.P.Gizatulina - ORCID 0000-0003-4472-8821

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Atrial Fibrillation (AF) is a heart rhythm disorder associated with the risk of thrombus formation in the left atrial appendage (LAA). The development of LAA thrombosis occurs with the involvement of the factors of Virchow's triad: reduced blood flow velocity in the LAA, endothelial injury, and hypercoagulability. According to current literature, the prevalence of LAA thrombosis varies from 1.1% to 8% [1-4]. The presence of a thrombus in the LAA is an obstacle to restoring sinus rhythm in patients with persistent AF and performing catheter ablation (CA). To date, clear guidelines for managing such patients have not been developed. However, considering the need for restoring sinus rhythm and performing CA to prevent the progression of chronic heart failure (CHF), attempts are made to perform thrombolysis using various regimens of anticoagulant therapy: the use of oral anticoagulants (OACs) if none were previously taken, switching from one OAC to another, changing from OAC to parenteral anticoagulants, prescribing rivaroxaban 30 mg/day in a twice-daily regimen, or increasing the dose of warfarin to achieve an INR in the range of 2.5-3.5 [5-9]. Despite this, literature reports indicate that, in some cases, LAA thrombosis remains resistant to thrombolysis even with anticoagulant therapy [10-12]. This explains the relevance of identifying factors that impede LAA thrombus resolution in patients with non-valvular AF.

Aim: to study the dynamics of LAA thrombosis and identify factors associated with resistance to LAA thrombus resolution over a 12-month period.

METHODS

A prospective study included 83 patients from a total of consecutively enrolled patients with AF from 2018 to 2024, in whom LAA thrombosis was detected by transesophageal echocardiography (TEE) prior to planned CA or

electrical cardioversion. 76 patients (91.6%) were OAC. During the first 3 months, the OAC regimen was not changed. However, in cases of recurrent LAA thrombus detection on follow-up TEE, a switch between OACs was performed. Patients who had not previously received anticoagulant therapy were prescribed OACs upon admission to the hospital.

Patients with LAA thrombosis were included in a prospective follow-up, the duration of which depended on the thrombus resolution time (ranging from 3 to 12 months) or was limited to 12 months. The end point of the follow-up was either thrombus resolution or stability of the LAA thrombus. In the case of thrombus resolution, the patient was removed from further follow-up.

Table 1.

Clinical and demographic characteristics of the patients included in the study

Indicator	Value
Age, years	62 [55.5; 65.5]
Male sex, n (%)	49 (59)
Female sex, n (%)	34 (41)
AH, n (%)	79 (95.2):
Stage 1 AH, n (%)	8 (10.1)
Stage 2 AH, n (%)	30 (38)
Stage 3 AH, n (%)	41 (51.9)
CAD, n (%)	53 (63.9)
History of MI, n (%)	2 (2.4)
DM, n (%)	14 (16.9)
Obesity, n (%)	55 (66.3):
Stage 1 obesity, n (%)	32 (58.2)
Stage 2 obesity, n (%)	19 (34.5)
Stage 3 obesity, n (%)	4 (7.3)
CKD, n (%)	14 (16.9)
CHF IIA stage and above, n (%)	6 (7.2)
Paroxysmal AF, n (%)	39 (47)
Persistent AF, n (%)	44 (53)
Non-smokers, n (%)	56 (67.5)
Former smokers, n (%)	14 (16.9)
Current smokers, n (%)	13 (15.7)
Average CHA_2DS_2-VASc score	2 [2; 3]
Low risk, n (%)	1 (1.2)
Moderate risk, n (%)	27 (32.5)
High risk, n (%)	55 (66.3)
HAS-BLED	1 [0; 1]
HAS-BLED 0 points, n (%)	41 (49.4)
HAS-BLED 1 point, n (%)	37 (44.6)
HAS-BLED 2 points, n (%)	5 (6)

Note: AH - Arterial Hypertension; CAD - Coronary Artery Disease; MI - Myocardial Infarction; DM - Diabetes Mellitus; CKD - Chronic Kidney Disease (eGFR less than 60 ml/min using the EPI formula); CHF - Chronic Heart Failure. Thromboembolic Risk: Low risk according to the CHA2DS2-VASc scale: 0 points for men and 1 point for women; Moderate risk: 1 point for men and 2 points for women; High risk: 2 or more points for men and 3 or more points for women.

Inclusion Criteria

- Presence of AF (paroxysmal or persistent, non-valvular etiology) lasting more than 30 seconds, confirmed by ECG or 24-hour Holter ECG monitoring, in patients of any gender and age.
- First detected LAA thrombosis by TEE.
- Signed informed consent to participate in the study.

Exclusion Criteria

- Permanent AF.
- Refusal to participate in the study.

All patients underwent general clinical examinations, including complete blood count, biochemical blood tests, coagulation testing, ECG, transthoracic echocardiography (TTE), and TEE. TTE was performed using General Electric "Vivid E9" and General Electric "Vivid S70" machines with a multi-frequency sector probe (2.5-5.0 MHz). TEE was performed using General Electric "Vivid E9" and General Electric "Vivid S70" machines with a transesophageal probe initially and during follow-up at intervals of 3 months until LAA thrombus resolution or up to 12 months. During TEE, the presence of LAA thrombosis, spontaneous echo contrast, and blood flow velocity in the LAA were assessed. The size of the thrombus was not considered at this stage of the study.

Complete blood count was performed using the Mindray BC-5800 automatic analyzer (China), biochemical blood tests using the Mindray BC-480 automatic analyzer (China), and coagulation testing using the Destiny Plus coagulometer (Ireland). ECG was conducted using the Poli-spectr device (Neurosoft).

Statistical analysis

Data were analyzed using the IBM SPSS Statistics software package. The Kolmogorov-Smirnov test was used to assess the normality of data distribution. The results are presented as mean and standard deviation (M±SD) for normally distributed quantitative variables, and as median (Me) and interquartile range (25%; 75%) for non-normally distributed data. The significance of differences between the two groups for normally distributed quantitative data was determined using the Student's t-test, and for non-normally distributed data, the Mann-Whitney U test was used. For comparing categorical variables, the chi-square test or Fisher's exact test was applied. Differences were considered statistically significant when $p < 0.05$.

Correlation analysis between quantitative variables was performed using Pearson's correlation for normally distributed data, and Spearman's rank correlation for non-normally distributed data.

The study was conducted in accordance with the Declaration of Helsinki principles. The study protocol was approved by the local ethics committee (protocol No. 136, 06.04.2018). Informed consent for participation in the study was obtained from all participants.

RESULTS

A total of 83 patients with AF and LAA thrombosis were included in the final analysis. The clinical-de-

mographic characteristics of the overall patient group are shown in Table 1. Among the patients with diagnosed LAA thrombosis, there was a predominance of males, and more than half of the patients had persistent AF. Almost all patients had hypertension, and one in six had chronic kidney disease. Considering that cardiovascular diseases were common in patients with LAA thrombosis, most had a high thromboembolic risk according to the CHA_2DS_2-VASc scale, with no patients having a history of thromboembolic complications or high bleeding risk according to the HAS-BLED scale. It is worth noting that 1 patient had a low thromboembolic risk.

The median thrombus resolution time was 6 [3; 6] months, with the majority of patients (n=24) having thrombus resolution in the first 3 months. During the following 3 months, 14 patients showed resolution, and another 7 patients by the end of the year. Based on TEE results, patients were divided into two groups: Group 1 (n=45), who had thrombus resolution within 12 months, and Group 2 (n=38), who did not have thrombus resolution.

When comparing the clinical-demographic parameters (Table 2), Groups 1 and 2 were comparable in terms of age and sex, with no statistically significant differences in the prevalence of cardiovascular diseases. The analysis showed that patients who did not experience thrombus resolution were more likely to take beta-blockers and diuretics, which is likely related to the need for a rate control strategy and a higher risk of CHF. No significant differences were observed in other drug categories.

A comparative analysis of echocardiographic parameters (Table 3) between groups revealed that patients with persistent thrombus in the LAA had a higher right atrial volume index, while the left atrial volume index did not differ between the groups. Additionally, there was a trend toward a thicker left ventricular posterior wall in Group 2. In Group 1, after thrombus resolution, spontaneous echo contrast persisted in 11 patients (24.4%).

The laboratory data analysis (Table 4) revealed statistically significant differences in the complete blood count parameters related to the platelet component of hemostasis. In patients with persistent LAA thrombus, mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR) were significantly higher. The total leukocyte count, although within the reference range, was higher in Group 2, primarily due to lymphocytes, with a tendency toward higher neutrophil levels. The target INR was achieved in only 4 patients taking warfarin: 1 (14.3%) in Group 1 and 3 (75%) in Group 2.

Statistically significant correlations of MPV and P-LCR with other laboratory parameters and echocardiographic data are shown in Table 5. Significant positive correlations were found between MPV and P-LCR with indexed volumes of both atria and the left atrial diameter, pulmonary artery systolic pressure, and levels of red blood cells, hemoglobin, and hematocrit. An inverse relationship between MPV and P-LCR and platelet count was observed. Our results indicated that, in patients with LAA thrombosis, platelet morphological features are associated with structural remodeling of both atria.

DISCUSSION

The issue of effective LAA thrombus resolution in patients with non-valvular AF raises many questions,

Table 2.

Clinical and demographic data of patients with resolved and persistent LAA thrombus

Indicator	Group 1 (n=45)	Group 2 (n=38)	p
Age, years	61.1±8.4	59.9±7.3	0.490
Male sex, n (%)	26 (57.8)	23 (60.5)	0.800
Female sex, n (%)	19 (42.2)	15 (39.5)	
BMI, kg/m²	31.6±5.7	32.7±4.6	0.332
AH, n (%)	43 (95.6)	36 (94.7)	0.617
Stage 1 AH, n (%)	6 (14)	2 (5.5)	
Stage 2 AH, n (%)	15 (34.9)	15 (41.7)	
Stage 3 AH, n (%)	22 (51.1)	19 (52.8)	
CAD, n (%)	30 (66.7)	23 (60.5)	0.562
History of MI, n (%)	1 (2.2)	1 (2.6)	0.904
CHF IIA stage and above, n (%)	3 (6.7)	3 (7.9)	0.688
DM, n (%)	7 (15.6)	7 (18.4)	0.775
CKD, n (%)	7 (15.6)	7 (18.4)	0.775
History of bleeding, n (%)	2 (4.4)	1 (2.6)	0.564
History of anemia, n (%)	2 (4.4)	4 (10.5)	0.405
Paroxysmal AF, n (%)	24 (53.3)	15 (39.5)	0.208
Persistent AF, n (%)	21 (46.7)	23 (60.5)	
Medication Therapy			
Amiodarone, n (%)	6 (13.3)	1 (2.6)	0.118
Propafenone, n (%)	2 (4.4)	4 (10.5)	0.405
Sotalol, n (%)	14 (31.1)	6 (15.8)	0.127
Allapinin, n (%)	4 (8.9)	4(10.5)	0.801
Beta-blockers, n (%)	14 (31.1)	22 (57.9)	0.014
ACE inhibitors / ARBs, n (%)	34 (75.6)	31 (81.6)	0.398
Statins, n (%)	30 (66.7)	26 (70.3)	0.727
Diuretics, n (%)	16 (35.6)	23 (60.5)	0.023
Calcium antagonists, n (%)	7 (15.6)	13 (35.1)	0.069
Oral Anticoagulants			
Warfarin, n (%)	7 (15.6)	4 (10.5)	0.538
Apixaban, n (%)	15 (33.3)	11 (28.9)	0.668
Rivaroxaban, n (%)	6 (13.3)	15 (39.5)	0.010
Dabigatran, n (%)	13 (28.9)	5 (13.2)	0.111

Note: BMI - body mass index; ACE inhibitors - angiotensin-converting enzyme inhibitors; ARBs - angiotensin receptor blockers

as there are no clear recommendations in the contemporary literature regarding treatment methods and timelines for such patients. According to the results of our study, LAA thrombosis persisted in 45.8% of patients during the 12-month follow-up, which is comparable to the findings of P. Bernhardt et al., where thrombus resolution was also absent in 44% of patients during 1 year of follow-up, despite antithrombotic therapy [11]. In the study by E.S. Kropacheva et al., the results were worse: adequate therapy with vitamin K antagonists led to thrombus resolution in only 43.7% of cases over the course of a year [12]. In contrast, a high efficacy of anticoagulant therapy for LAA thrombus resolution was presented in the study by M.C. Saaed et al.: 67 (12.9%) of 520 patients with non-valvular AF had LAA thrombus; after four weeks of warfarin therapy, 18 (90%) patients showed thrombus resolution [13].

Regarding the timing of LAA thrombus resolution, the median in our study was 6 [3; 6] months, with 53% of patients (n=24) experiencing thrombus resolution within the first 3 months. In the study by A.D. Niku et al., 60% of patients had LAA thrombus resolution based on TEE performed at 96±72 days [14]. In E.S. Mazur et al.'s study, the median thrombus resolution time was found to be 30 [22.0-41.0] days, which is significantly shorter than our result [15].

In our study, we found that patients with persistent thrombus were more likely to use rivaroxaban than those in Group 1: 39.5% vs 13.3% respectively (p=0.010). This aligns with the findings of A. Lenart-Migdalska et al., who showed an increase in circulating microparticles produced by platelets and the endothelium, playing a prothrombotic role at the peak concentration of rivaroxaban in plasma [16]. We attribute these results to the high variation in the drug concentration at its peak and at the end of its action due to single-dose administration. No significant differences were found for other types of OACs, which is consistent with previously published works [14, 17, 18].

The higher NT-proBNP levels observed in patients with persistent LAA thrombus suggest more pronounced subclinical left ventricular systolic dysfunction, although there were no significant differences in left ventricular volumes and LVEF. We also hypothesize that Group 2 patients had more pronounced diastolic dysfunction, which is supported by statistically significant differences in the indexed right atrial volume. In the study by A. Watanabe et al., patients with warfarin-resistant LAA thrombus had a lower LVEF compared to patients with thrombus resolution [19]. Similar results were obtained by M. Hautmann et al.: when comparing 450 patients with LAA thrombus and 481 without LAA thrombus, there was a higher frequency of CHF progression and cardiac chamber dilation in the thrombus group [20].

Key differences in patients with resistant LAA thrombus were identified in the comparison of laboratory data. A higher leukocyte count - due to lymphocytes and to a lesser extent neutrophils - was observed in Group 2, which generally corresponded to reference values and was not associated with an increase in C-reactive protein or neutrophil-lymphocyte ratio. Therefore, we cannot consider these features as manifestations of chronic inflammation in patients with resistant LAA thrombus. However, previous studies by Y. Deng et al. showed that neutrophil-lymphocyte ratio acted as an independent predictor of LAA thrombus presence or spontaneous echo contrast in non-valvular AF patients [21]. Furthermore, research by Y. Feng et al. using Mendelian randomization demonstrated that genetically predicted increases in CD4+ T-lymphocyte count were associated with an increased risk of AF development [22].

Table 3.

Echocardiographic parameters of patients with resolved and persistent LAA thrombus

	Group 1 (n=45)	Group 2 (n=38)	p
RA volume index, ml/m²	24.5 [21.0; 32.2]	30.7 [24.7; 34.7]	0.034
LA volume index, ml/m²	36.6 [30.9; 46.4]	38.5 [31.3; 45.1]	0.942
LV ESD index, mm/m²	17.0±3.0	17.0±2.0	0.997
LV EDD index, mm/m²	24.5±2.8	24.3±3.1	0.869
LV EDV index, ml/m²	49.9±11.0	52.8±16.1	0.334
LV ESV index, ml/m²	18.1 [15.7; 24.6]	19.8 [15.4; 25.7]	0.759
IVS, mm	12 [11; 12]	12 [11; 13]	0.233
PW LV, mm	10 [10; 11]	11 [10; 12]	0.060
MM LV, g	207 [181; 227]	218 [185; 249]	0.271
MM LV index, g/m²	100.0±17.6	107.4±28.2	0.146
SV LV, ml	60.1±13.7	65.4±20.8	0.173
LVEF, %	60 [57; 64]	59.5 [55; 64]	0.787
PASP, mmHg	27 [25; 30]	28 [25; 35]	0.173
Flow velocity in LAA, cm/s	35 [30; 42]	32 [30; 36]	0.113

Note: RA - right atrium; LA - left atrium; EDD, ESD, EDV, and ESV - end-diastolic and end-systolic dimensions and volumes; LV - left ventricle; IVS - interventricular septum; PW - posterior wall; MM - myocardial mass; SV - stroke volume; LVEF - left ventricular ejection fraction; PASP - pulmonary artery systolic pressure; LAA - left atrial appendage.

In our study, patients with persistent LAA thrombus had higher platelet morphological parameters, such as MPV, PDW, and P-LCR. As is known, MPV reflects the degree of platelet maturity circulating in the blood, PDW indicates the degree of anisocytosis and the presence of platelet aggregates or fragments, and P-LCR reflects the number of cells with high thrombus formation activity [23].

High MPV levels were previously found by N. Bayar et al. in patients who had suffered a stroke or transient ischemic attack [24]. Similar results were obtained by S.W. Choi et al.: in their study of 352 AF patients, MPV was identified as a predictor of stroke or the presence of LAA thrombus [25]. Additionally, it has been reported that patients with a low INR level (less than 2.0) had higher MPV, PDW, and P-LCR compared to patients with therapeutic INR levels [26].

Table 4.

Comparison of laboratory parameters in patients with resolved and persistent LAA thrombus

	Group 1 (n=45)	Group 2 (n=38)	p
Complete blood count			
Leukocytes, 10^9/L	5.7±1.7	6.7±1.8	0.014
Erythrocytes, 10^9/L	4.8±0.5	5.0±0.5	0.097
Hemoglobin, g/L	140.6±15.7	146.5±14.0	0.083
Hematocrit, %	43.8±5.3	45.3±4.4	0.160
Platelets, 10^9/L	211.0±45.4	224.3±64.3	0.276
Thrombocrit, %	0.17 [0.15; 0.19]	0.20 [0.15; 0.22]	0.266
MPV, fl	8.4 [7.9; 9.4]	9.1 [8.3; 9.8]	0.035
PDW, %	15.7 [15.5; 15.9]	15.9 [15.7; 16.2]	0.007
P-LCR, %	25.3±7.4	30.0±9.2	0.014
Neutrophils, 10^9/L	3.0 [2.4; 4.0]	3.6 [3.0; 4.3]	0.065
Lymphocytes, 10^9/L	1.7 [1.4; 2.2]	2.1 [1.6; 2.6]	0.033
NLR	1.8 [1.2; 2.2]	1.7 [1.4; 2.0]	0.981
Biochemical blood test			
Glucose, mmol/L	5.7 [5.2; 6.2]	5.6 [5.3; 6.4]	0.955
Creatinine, μmol/L	86 [79; 91]	85.4 [77; 101]	0.531
eGFR, ml/min/$^{1.73}m^2$	75.8±15.2	73.7±12.7	0.507
AST, U/L	23.4 [19.8; 27.5]	22.2 [17.6; 27.4]	0.635
ALT, U/L	24.5 [20.2; 38.5]	26.1 [19.4; 37.1]	0.680
TC, mmol/L	4.3±1.0	4.5±1.0	0.294
HDL-C, mmol/L	1.3 [1.1; 1.5]	1.2 [1.0; 1.4]	0.512
LDL-C, mmol/L	2.4 [1.9; 2.9]	2.6 [2.1; 3.1]	0.162
TG, mmol/L	1.2 [1.0; 1.5]	1.3 [1.1; 1.8]	0.457
CRP, mg/L	1.9 [1.1; 4.4]	1.9 [0.9; 3.7]	0.563
NT-proBNP, pg/ml	280 [78; 639]	599 [128; 1656]	0.058
Coagulation test			
APTT	33.7 [30.8; 38.7]	34.5 [30.8; 40.5]	0.625
Fibrinogen	3.1±0.5	3.0±0.6	0.652
Thrombin Time	18.6 [17.0; 26.6]	18.6 [17.1; 26.0]	0.731
D-dimer	0.29 [0.18; 0.37]	0.29 [0.23; 0.40]	0.374
Antithrombin III, %	93.2±20.8	93.4±21.4	0.974
PT	82.9 [72.6; 91.6]	78.6 [67.5; 87.0]	0.235

Note: MPV - mean platelet volume; PDW - platelet distribution width; NLR - neutrophil-lymphocyte ratio; P-LCR - platelet large cell ratio; eGFR - estimated glomerular filtration rate; AST - aspartate aminotransferase; ALT - alanine aminotransferase; TC - total cholesterol; HDL-C - high-density lipoproteins; LDL-C - low-density lipoproteins; TG - triglycerides; CRP - c-reactive protein; NT-proBNP - n-terminal pro b-type natriuretic peptide; APTT - activated partial thromboplastin time; PT - prothrombin time; INR - international normalized ratio.

Correlation Analysis

Correlation analysis showed that platelet morphological parameters positively correlated with erythrocyte count, hemoglobin levels, and both atrial volumes. In the study by X. Zhou et al., a higher erythrocyte count was observed in patients with LAA thrombus compared to those without it, with RDW (red cell distribution width) being a predictor of LAA thrombus presence in non-valvular AF patients [27].

The direct correlation between MPV and P-LCR with the atrial volume indices confirms the relationship between platelet activation and structural remodeling of the atria. Our research group previously noted an association between LAA thrombosis and polymorphisms in platelet receptor genes for collagen (integrin A2, ITGA2) and fibrinogen (integrin B3, ITGB3). The presence of polymorphisms in both genes was associated with the most pronounced structural remodeling of the left atrium [28].

Table 5.

Results of correlation analysis

	MPV		P-LCR	
	CC r	p	CC r	p
Hemoglobin	0,268	0,017	0,245	0,032
Hematocrit	0,280	0,012	0,300	0,008
Erythrocytes	0,281	0,012	0,248	0,029
Platelets	-0,313	0,005	-0,430	<0,001
RA VI	0,262	0,022	0,282	0,015
LA VI	0,225	0,046	0,270	0,018
PASP	0,235	0,040	0,267	0,021

Note: CC - correlation coefficient; VI - volume index.

Further research is needed to study the development of resistance to LAA thrombus resolution and to develop methods for overcoming this resistance.

Study Limitation

The main limitations of the study are the small sample size and the lack of a unified approach to prescribing antithrombotic therapy.

CONCLUSION

Resistance of LAA Thrombus to Resolution in patients with non-valvular AF is associated with changes in peripheral blood parameters, primarily with morphofunctional platelet characteristics, which correlate with structural remodeling of the atria. The obtained results highlight the need for further research aimed at studying the role of the platelet component of hemostasis in the resistance to LAA thrombus resolution, despite the use of oral anticoagulants.

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ASSESSMENT OF THE RISK OF ATRIAL FIBRILLATION AFTER MITRAL VALVE RECONSTRUCTION USING VARIOUS TYPES OF SUPPORT RINGS UP TO 12 MONTHS AFTER OPERATION

D.I.Lebedev, I.V.Dvadtsatov, A.V.Evtushenko

FSBSI "Research Institute for Complex Problems of Cardiovascular Diseases", Russia, Kemerovo, 6 Sosnovy bould.

Aim. To evaluate the effect of mitral valve (MV) reconstruction using rigid and superelastic support rings for up to one year in patients with mitral regurgitation (MR) II according to A. Carpentier on the development of atrial fibrillation (AF).

Methods. The study included 62 patients with indications for surgical correction of MR and sinus rhythm (SR): group I (n=31) - with implantation of the biological semi-rigid saddle closed ring NeoRing and II (n=31) - with implantation of the rigid open ring RIGID. The average age of patients was 56.6±11.2 years and 58.0±10.2 years in groups I and II. Both groups were comparable in gender (men - 67.7% and 61.3%), age, comorbidity, functional class of chronic heart failure according to NYHA. The rhythm in patients was assessed by Holter monitoring at control points after 9 days and 12 months.

Results. The duration of artificial circulation, aortic occlusion, and the incidence of isolated P2-segment prolapse did not differ in the comparison groups. A positive effect on the reverse remodeling of the left heart was revealed: the end-diastolic dimension of the left ventricle ($p<0.001$), the left atrium ($p<0.001$), a decrease in the overload of the pulmonary circulation and a decrease in pressure in the pulmonary artery ($p<0.001$). According to the Holter monitoring data, all patients had SR. Both groups showed a satisfactory result at the hospital stage in the form of restoration of the locking function of the MV ($p<0.001$) and a low frequency of the revealed maximum MR up to grade 1 in group I - 9.7% and II - 29% ($p=0.292$). However, patients with RIGID had higher values of transvalvular diastolic gradient on MV and transvalvular flow velocity ($p < 0.001$). In group II, the values of transvalvular diastolic gradient on MV were Pcp 3.34±1.01 mm Hg, versus 2.39±0.62 mm Hg in group I ($p < 0.001$), transvalvular flow velocity in group II was Vcp 79±15 cm/sec versus 66±12 cm/sec in group I, respectively ($p < 0.001$). After 12 months, the RIGID group more often showed a change from SR to AF - 11 cases (35.5%), in NeoRing - 4 (12.9%). According to echocardiography data after 12 months, freedom from MR ≥ grade 2 in group I was 93.5%, versus 77.4% in group II ($p=0.076$). In addition, patients in group II maintained higher values of transvalvular diastolic gradient on MV - Pcp 3.70 [3.00; 4.40] mmHg, versus 2.3 [2.05; 2.85] mmHg ($p<0.001$), as well as higher transvalvular flow velocity - Vcp 79 [71; 94] cm/sec versus 70 [64; 79] cm/sec ($p=0.017$). AF developed 12 months after surgery in those patients whose transvalvular diastolic gradient on the MV exceeded 2.7 mm Hg, as well as in patients with developed MR ≥ grade.

Conclusions. The development in the medium term, after reconstruction of the mitral valve with a support ring, of an increased transmitral diastolic gradient and MR ≥ grade 2 is the cause of the development of AF, while the implantation of a rigid ring is accompanied by a high risk of developing AF within 12 months after surgery ($p=0.029$).

Key words: mitral regurgitation; atrial fibrillation; mitral valve reconstruction; support ring

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Corresponding author: Denis Lebedev, E-mail: mdlebedevd@mail.ru

D.I.Lebedev - 0000-0001-9764-3982, I.V.Dvadtsatov - ORCID ID 0000-0003-2243-1621, A.V.Evtushenko - ORCID ID 0000-0001-8475-4667

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Mitral regurgitation (MR) is a common form of acquired heart valve disease, affecting approximately 24.2 million people worldwide. Primary or degenerative MR is most often a consequence of myxomatous degeneration of the mitral valve (MV). Mitral valve prolapse is the most prevalent cardiac pathology globally, occurring in 2-3% of the general population [1-3], and is primarily classified as type II MR according to A.Carpentier's classification [6, 7]. The gold standard for the treatment of dysplastic MR is reconstructive surgery [8]. Mitral annuloplasty is the primary method of MR correction, performed alongside leaflet and subvalvular apparatus repair. This technique helps restore the size and shape of the mitral fibrous annulus and reduces the risk of progressive dilation of both the ventricles and atria [9].

Atrial fibrillation (AF) is the most common cardiac arrhythmia and significantly increases the risk of ischaemic stroke and severe heart failure. This arrhythmia is present

in 30-50% of patients undergoing MV surgery [4, 5]. The development of open surgical ablation techniques for AF has led to their widespread use in mitral valve procedures. Numerous studies have focused on surgical correction of MV pathology in patients with pre-existing AF. However, there is a paucity of research tracking newly emerging arrhythmias after open-heart surgery, particularly following MR correction in patients who had sinus rhythm preoperatively. Most clinicians emphasise that the initial onset of AF after open-heart surgery is of particular clinical significance [10]. A recent study [11] demonstrated that postoperative AF is a frequent complication of cardiac surgery, occurring in 10-63% of cases, including 33-37% of patients after valve repair or replacement. Among this patient cohort, those undergoing mitral annuloplasty require particular attention, given the combination of the most common valve pathology with the most prevalent arrhythmia. However, there is a distinct lack of studies assessing the mid-term incidence of AF following MV repair.

This study aimed to evaluate the effect of mitral valve reconstruction using rigid and superelastic support rings for up to 12 months in patients with type II MR according to A. Carpentier on the development of AF.

METHODS

A prospective, randomised study was conducted at the Department of Cardiovascular Surgery-1 of the Research Institute for Complex Problems of Cardiovascular Diseases (Kemerovo, Russia) to assess the impact of MV repair using two types of support rings. The study included 62 patients with severe MR that developed against the background of MV dysplasia. All patients were randomly assigned to two groups using a two-envelope randomisation method: Group I (n=31) underwent implantation of a biological semi-rigid saddle-shaped closed ring, NeoRing (CJSC NeoKor, Kemerovo, Russia), while Group II (n=31) received a rigid open ring, RIGID (CJSC R&D Enterprise MedInzh, Penza, Russia). All participants signed a standard informed consent form.

Table 1.

General preoperative characterization of patients

Indicator	NeoRing (n=31)	RIGID (n=31)	p
Age, years	56.6±11.2	58.0±10.2	0.564
Men, n (%)	21 (67.7)	19 (61.3)	0.241
BSA, m²	1.97±0.23	1.88±0.20	0.057
Barlow's disease, n (%)	6 (19.4)	7 (22.6)	0.325
FED, n (%)	25 (80.6)	24 (77.4)	
NYHA FC I, n (%)	0 (0.0)	0 (0.0)	0.195
NYHA FC II, n (%)	19 (61.3)	18 (58.1)	
NYHA FC III, n (%)	11 (35.5)	11 (35.5)	
NYHA FC IV, n (%)	1 (3.2)	2 (6.5)	
CAD, n (%)	10 (32.3)	11 (35.5)	0.742
AIS, n (%)	7 (22.6)	9 (29.0)	0.528
MAC, n (%)	1 (3.2)	2 (6.5)	0.647
COPD, n (%)	4 (12.9)	3 (9.7)	0.498
CKD, n (%)	4 (12.9)	4 (12.9)	0.891
DM, n (%)	2 (6.5)	1 (3.2)	0.597

Note: BSA - body surface area; FED - fibroelastine degeneration; NYHA FC - functional class; CAD - coronary artery disease; AIS - acute ischaemic stroke; COPD - chronic obstructive pulmonary disease; CKD - chronic kidney disease; DM - diabetes mellitus.

Table 2.

Echocardiographic parameters at 12 months of follow-up

Indicator	Before surgery		p	In 12 months		p
	NeoRing	RIGID		NeoRing	RIGID	
LV EDD, cm	6,29±0,70	6,24±0,73	0,773	5,31±0,44	5,57±0,55	0,031
LV ESD, cm	4,01±0,56	3,89±0,70	0,429	3,70 [3,40; 3,90]	3,60 [3,45; 4,15]	0,354
LV EDV, ml	209 [167; 220]	194 [160; 220]	0,978	135,71±27,36	155,46±37,28	0,008
LV ESV, ml	66 [51; 90]	62 [44; 83]	0,242	55 [46; 63]	61 [50,50; 75,25]	0,071
LVEF, %	65 [63; 68]	67 [65; 71]	0,072	61 [57; 62]	62 [58,50; 65,00]	0,105
LA, cm	5,2 [4,8; 5,75]	5,0 [4,5; 5,6]	0,334	4,30 [4,10;5,05]	4,50 [4,28; 4,90]	0,594
RA, cm	4,8 [4,1; 5,4]	4,5 [4,0; 5,1]	0,401	4,40 [3,95; 4,95]	4,25 [3,80; 4,60]	0,256
Vena contracta, cm	0,8 [0,65;0,80]	0,85 [0,74; 0,90]	0,015	0,1 [0,00; 0,2]	0,3 [0,00; 0,4]	0,102
MR Gr 1, n (%)	-	-	0,528	3 (9,7)	3 (9,7)	0,281
MR Gr 2, n (%)	-	-		2 (6,5)	7 (22,6)	
MR Gr 3, n (%)	7 (22,6)	6 (17,0)		-	-	
MR Gr 4, n (%)	24 (77,4)	25 (83,0)		-	-	
ERO, cm²	0,42 [0,35; 0,55]	0,50 [0,40 ;0,60]	0,095	0,05 [0,00; 0,1]	0,1 [0,00; 0,2]	0,070
Vmean, cm/s	-	-	-	70 [64; 79]	79 [71; 94]	0,017
Pmean, mmHg	-	-	-	2,3 [2,05; 2,85]	3,70 [3,00; 4,40]	<0,001

Note: LV - left ventricle; EDD - end-diastolic dimension; ESD - end-systolic dimension; EDV - end-diastolic volume; ESV - end-systolic volume; LVEF - left ventricular ejection fraction; LA - left atrium; RA - right atrium; MR - mitral regurgitation; Gr - grade; ERO - effective regurgitation orifice

Patients aged over 18 years were eligible for inclusion. The primary inclusion criterion was the presence of severe dysplastic MR classified as type II according to A.Carpentier, with an indication for surgical correction in accordance with the 2017 guidelines of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) [12], and a history of sinus rhythm. Exclusion criteria included prior open-heart surgery, indications for concomitant aortic valve replacement or coronary artery bypass grafting, significantly reduced left ventricular (LV) contractile function (ejection fraction <40%), and a history of AF. The study was conducted in accordance with the principles of the Declaration of Helsinki. Data were analysed at three time points: preoperatively, postoperatively, and at 12 months after surgery.

The mean age of patients in Group I was 56.6±11.2 years, while in Group II, it was 58.0±10.2 years. Both groups were comparable in terms of sex, age, and comorbidities. Coronary angiography revealed haemodynamically insignificant coronary artery stenoses in all patients. The baseline preoperative characteristics of the study population are presented in Table 1.

The primary endpoints in the mid-term period were newly detected arrhythmias. Secondary endpoints included stroke, systemic embolism, and anticoagulant-related bleeding.

Surgical procedure

As the first step, before the surgical intervention, all patients underwent transesophageal echocardiography to assess the morphology of MR. The surgical procedures were performed under normothermic cardiopulmonary bypass. To prevent embolic complications, CO_2 insufflation was performed into the surgical field, and myocardial protection was provided using Custodiol solution (Köhler Chemie, Germany). All surgical procedures were performed via median sternotomy by a single surgeon. Intraoperative differential diagnosis between Barlow's disease and fibroelastic deficiency was conducted according to the A. Anyanwu algorithm [13].

Access to the MV was achieved through a left atriotomy. Based on intraoperative assessment of the MV and identification of the prolapse zone, the following reconstructive techniques were performed: chordal replacement, resection (triangular, quadrangular), translocation of second-order chords to the free edge, and leaflet plication. MV reconstruction was completed with annuloplasty using either the NeoRing or RIGID ring.

Statistical Analysis

Statistical analysis was performed using the StatTech v. 2.8.8 software (StatTech LLC, Russia). Quantitative variables were assessed for normality using the Shapiro-Wilk test. In cases where the data did not follow a normal distribution, they were described using the median (Me) and interquartile range (Q1-Q3). Comparisons between two groups for non-normally distributed quantitative variables were conducted using the Mann-Whitney U test.

Categorical variables were presented as absolute values and percentages. Comparisons of percentage distributions in 2×2 contingency tables were performed using Pearson's chi-square test, provided that the expected frequency in each cell exceeded 10. Statistical differences were assessed using the Kaplan-Meier method with a log-rank test.

A 5% level of Type I error ($\alpha = 0.05$) was adopted, meaning that differences were considered statistically significant at $p < 0.05$.

RESULTS

Intraoperatively, the duration of cardiopulmonary bypass and aortic occlusion time were assessed and did not differ significantly between the comparison groups. In the vast majority of cases in both groups, isolated prolapse of the P2 segment was observed. In the early postoperative period, the need for prolonged mechanical ventilation was noted in the RIGID group.

At the time of hospital discharge, both groups exhibited a reduction in left ventricular ejection fraction (LVEF) compared to preoperative values: in the NeoRing group, the median LVEF decreased from 65% to 55%, while in the RIGID group, it declined from 67% to 60%. However, after 12 months, LVEF recovered in both groups to levels close to baseline, with no significant intergroup differences at this stage (p=0.105). A statistically significant positive effect on reverse remodeling of the left heart chambers was observed, including reductions in left ventricular end-diastolic dimension (p<0.001), left atrial size (p<0.001), pulmonary circulation overload, and pulmonary artery pressure (p<0.001). No significant intergroup differences were identified at the time of discharge. The echocardiographic results for both groups over the study period are presented in Table 2.

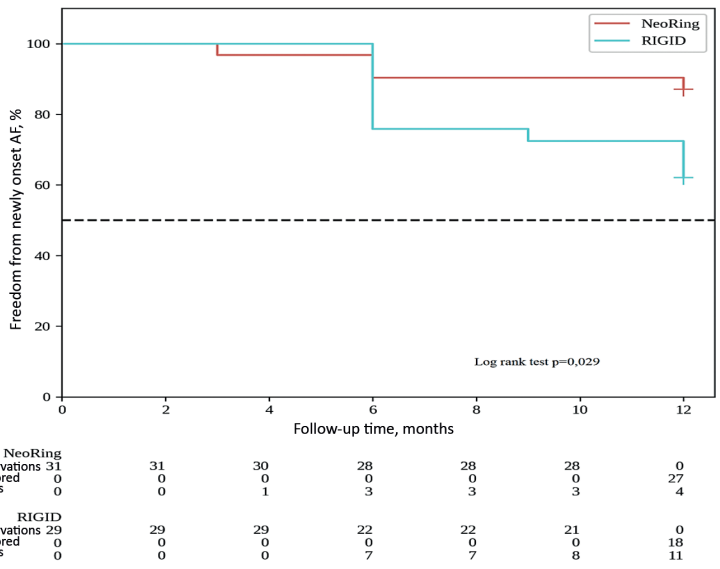

Figure 1. Kaplan-Meier curve for freedom from newly onset atrial fibrillation in the mid-term period.

At 12 months postoperatively, patients in the RIGID group maintained the remodeling parameters achieved during hospitalization, while those in the NeoRing group demonstrated further remodeling improvements, including a reduction in left ventricular end-diastolic diameter (p=0.031) and volume (p=0.008). Both support rings provided satisfactory clinical outcomes at the hospital stage, evidenced

by restoration of MV competency (p<0.001) and a low frequency of residual MR up to grade 1, observed in 9.7% of patients in the NeoRing group and 29% in the RIGID group, though the difference was not statistically significant (p=0.292).

However, patients with the RIGID ring exhibited significantly higher transvalvular diastolic gradient values (p<0.001) and increased transvalvular flow velocity (p<0.001). Echocardiographic assessment at 12 months revealed that freedom from MR ≥ grade 2 was observed in 93.5% of patients in the NeoRing group, compared to 77.4% in the RIGID group (p=0.147). Additionally, patients in the RIGID group continued to exhibit significantly higher transvalvular diastolic gradients (mean: 3.70 [3.00; 4.40] mmHg vs. 2.3 [2.05; 2.85] mmHg, p<0.001) and higher transvalvular flow velocity (mean: 79 [71; 94] cm/s vs. 70 [64; 79] cm/s, p=0.017) compared to those in the NeoRing group.

At the 12-month follow-up, implantation of either support ring did not show a significant impact on the incidence of thromboembolic complications or the need for permanent pacemaker implantation. The most common complaint during follow-up was dyspnoea with moderate physical exertion, reported by approximately one-third of the patients.

Holter ECG monitoring revealed that 11 patients (35.5%) in the RIGID group experienced a transition from sinus rhythm to AF, compared to 4 patients (12.9%) in the NeoRing group, necessitating antiarrhythmic and anticoagulant therapy in the mid-term period. These results were statistically significant (p=0.037). Kaplan-Meier analysis and the log-rank test demonstrated significant statistical differences (p=0.029) (Figure 1).

Further analysis revealed that AF development occurred in patients with transvalvular diastolic gradients exceeding 2.7 mmHg in the mid-term period. Additionally, the onset of paroxysmal AF was associated with the progression of MR to grade ≥2, which had not been previously documented in these patients.

DISCUSSION

Mitral valve reconstruction is recognised as the gold standard for the correction of type II MR according to A. Carpentier's classification [14, 15]. A fundamental requirement for reconstruction is the restoration of the size and shape (resizing, reshaping) of the mitral annulus using support rings. In our study, both support rings effectively reduced MR, with no statistically significant difference in the recurrence of MR within 12 months postoperatively. It is noteworthy that annuloplasty with the superelastic NeoRing was associated with lower transvalvular diastolic gradient (TDG) values compared to the RIGID group.

The durability and effectiveness of MV reconstruction is primarily assessed by the freedom from recurrent MR in the postoperative period. No cases of MR recurrence ≥ grade 3 were recorded in either group within the mid-term follow-up period. Echocardiographic analysis at 12 months showed that freedom from MR ≥ grade 2 was 93.5% in the NeoRing group, compared to 77.4% in the RIGID group (p=0.076). Univariate analysis identified residual MR as a significant factor contributing to MR recurrence ≥ grade 2 (OR 98.0, 95% CI: 9.68-992.5; p<0.001). Our findings are supported by D. Benedetto et al., who concluded that residual MR ≥ grade 1 at discharge was the sole independent predictor of repeat surgery and late MR recurrence [16]. Similarly, A.V. Bogachev-Prokofiev et al. identified residual MR, coronary artery disease, and residual systolic pulmonary artery pressure as major contributors to MR recurrence [17].

In the mid-term follow-up, the incidence of atrial fibrillation (AF) was significantly higher in the RIGID group (11 cases, 35.5%) compared to the NeoRing group (4 cases, 12.9%) (p=0.037). Kaplan-Meier analysis and the log-rank test revealed statistically significant differences (p=0.029). This was likely related to increased intra-atrial pressure due to MV repair failure, which was associated with a higher mean transvalvular diastolic gradient in the rigid ring group.

The primary predictors of AF onset in the mid-term period were: a mean transvalvular diastolic gradient (TDG) > 2.7 mmHg (OR 0.861±0.064, 95% CI: 0.736-0.987; p <0.001); MR recurrence ≥ grade 2.

W.Ma conducted a retrospective analysis of MV reconstruction in 390 patients using closed and C-shaped rings. After a median follow-up of 46 months, AF developed in 31.2% of patients, which was strongly associated with an elevated TDG (OR 3.93; p=0.004). Using minimum p-value analysis, the authors identified a mean gradient ≥4.5 mmHg as the threshold for predicting late-onset AF (χ^2=40.704; p<0.001) [18]. Their study also reported higher TDG values in patients with closed rings compared to open rings.

In our study, AF development in the postoperative period was influenced not only by elevated TDG, but also by MR recurrence ≥ grade 2 and the type of support ring implanted.

CONCLUSION

The development of elevated transvalvular diastolic gradient (TDG) and MR ≥ grade 2 in the mid-term period following MV reconstruction with a support ring is a significant factor contributing to the onset of atrial fibrillation (AF). The implantation of a rigid ring is associated with a higher risk of AF development within 12 months postoperatively (p=0.029). This necessitates modification of patient management strategies, including the initiation of antiarrhythmic and anticoagulant therapy, and increases the risk of adverse events.

The findings of this study highlight the need for further research to identify predictors of AF development in patients following MV reconstruction with a support ring.

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LONG-TERM EVALUATION OF FACTORS POTENTIALLY AFFECTING TRICUSPID VALVE AND RIGHT HEART CHAMBER FUNCTION IN PATIENTS WITH TWO ENDOCARDIAL RIGHT VENTRICULAR PACING LEADS

A.B.Glumskov, S.S.Durmanov, V.V.Bazylev

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

Aim. To assess factors influencing the degree of tricuspid regurgitation (TR) and the function of the right heart chambers in patients with two endocardial right ventricular leads of a permanent pacemaker.

Methods. A retrospective analysis of 5807 electronic medical records of patients who underwent primary implantation or planned replacement of a permanent pacemaker was performed. In 119 cases, a new right ventricular lead was additionally implanted, of which a group of 27 patients was selected according to the selection criteria. A control group of 129 patients was formed. Pseudo-randomization was performed, 27 comparable pairs were formed. To determine the predictors of TR progression, the logistic regression method for a multivariate model was used.

Results. In the late postoperative period, echocardiographic indices of both groups were virtually identical and were within the age norms. In the control group, minor TR was detected in 62.9% (n=17) of patients, moderate indices were diagnosed in 29.7% (n=8) of cases, and no TR was detected in 7,4% (n=2), respectively. In the observation group, minor TR was diagnosed in 74,1% of cases (n=20), moderate indices of insufficiency were diagnosed in 18.5% (n=5), severe TR was recorded in 3,7% (n=1) of patients, and TR was not detected in the same number of patients. Multivariate logistic regression identified the only independent predictor of TR progression in the postoperative period - the presence of non-paroxysmal atrial fibrillation (AF), which increases the probability of progression of the degree of tricuspid valve insufficiency in the remote observation period by 3/8 times. The relationship between the fact of the presence of two electrodes in the right ventricular cavity and the increase in the degree of tricuspid valve insufficiency was not determined.

Conclusion. In patients with two right ventricular leads, TR and right heart function don't change significantly in the long-term observation period. The leading factor influencing TR progression is the history of non-paroxysmal AF.

Key words: tricuspid valve; tricuspid regurgitation; right ventricular electrode; permanent pacemaker; atrial fibrillation.

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Corresponding author: Glumskov Artur, E-mail: artur19401988@yandex.ru

A.B.Glumskov - ORCID ID 0000-0002-7832-0421, S.S.Durmanov - ORCID ID 0000-0002-4973-510X, V.V.Bazylev - ORCID ID 0000-0001-6089-9722

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In 1958, A.Senning and R.Elmqvist in Sweden performed and described the first implantation of a permanent pacemaker (PM) in the anterior abdominal wall with an epicardial ventricular electrode. A few years later, in 1962, Parsonnet et al. (USA) and Ekstrom et al. (Sweden) developed and introduced the technique of transvenous implantation of permanent bipolar electrodes, which allowed for the implantation of pacemaker systems without thoracotomy and general anesthesia [1]. Since then, the use of such devices has increased exponentially. Over the past 60 years, cardiac implantable electronic devices (CIEDs) have become a standard method for treating cardiovascular diseases in patients with heart rhythm disorders: bradycardia, tachycardia, and chronic heart failure. In most cases, cardiac CIEDs are implanted with an electrode passing through the tricuspid valve (TV). The connection between the device electrode and the valve apparatus is a potential cause of tricuspid valve insufficiency, which, in turn, affects morbidity and mortality. Moreover, the severity of tricuspid regurgitation (TR) may progress over time. Early detection of electrode-associated TR is crucial for choosing optimal treatment.

The first reports of device-associated interference with the tricuspid valve apparatus appeared at the end of the 20th century, but only recently targeted efforts have been made to determine the scale of this problem. Since discontinuing the use of these devices is currently impossible and the benefit-to-harm ratio is considered optimal, better understanding of the mechanical complications associated with these interventions may potentially lead to improvements in device designs or, at least, the search for alternatives for certain patients. Implantation of any device requires positioning the endocardial ventricular electrode through the tricuspid valve.

The relationship between surgical intervention and TR has not been widely studied, and published data on its frequency in the postoperative period contradict some authors, who report it as a rare phenomenon. However, interest in this topic has clearly increased due to the understanding that TR is not a benign condition, especially if associated with significant pulmonary hypertension and/or left ventricular dysfunction [2].

It is also important to note that during planned PM replacement, in some cases, the implantation of new electrode(s) is required, and the «old» electrodes are not always safely removable. For these reasons, it is clear that the extraction of a non-functional electrode is generally not required during reimplantation, except for certain infectious and non-infectious causes. The electrode of the device is considered a source of complications, including interference with the function of the tricuspid valve, caused by mechanical impact on the leaflet mobility or coaptation. Theoretically, direct intervention by the electrode in valve closure should increase in proportion to the number of implanted electrodes. The goal of this study was to perform a long-term evaluation of factors influencing the function of the right heart chambers and the degree of TR in patients with two endocardial right ventricular electrodes of a PM.

METHODS

The study was retrospective observational in nature, and the corresponding approval was obtained from the local ethics committee. A total of 5807 electronic medical records were analyzed for patients who underwent primary implantation or planned replacement of a permanent PM between 2008 and 2021. Among these, 119 patients had an additional right ventricular electrode implanted during planned PM replacement.

Inclusion criteria:

- Presence of ≥ 2 endocardial electrodes in the right ventricular cavity (RV).
- Availability of echocardiography (Echo) results before planned PM replacement with implantation of the «new» right ventricular electrode and during long-term follow-up.

Exclusion criteria:

- Severe valvular stenosis.
- Severe valvular insufficiency (excluding TR).
- Persistent severe TR postoperatively.
- History of open heart valve surgery.
- History of endocardial electrode extraction.
- Significant pulmonary hypertension in the preoperative period (pulmonary artery systolic pressure ≤ 50 mmHg).
- Indications for implantation of ICD and cardiac resynchronization therapy (CRT).
- Postoperative follow-up ≤ 12 months.
- Left ventricular ejection fraction ≤ 40%.
- Age ≤ 18 years.

Based on the above conditions, a group of 27 patients was selected. Considering the exclusion criteria, 129 medical records of patients who underwent primary PM implantation during the same period were chosen. The main clinical and demographic characteristics of the groups are presented in Table 1. To ensure maximum comparability of the main and reference groups regarding existing confounders, pseudo-randomization was performed using a pair-matching method 1:1 by the nearest neighbor search. After balancing the groups, 27 pairs were formed, comparable based on the factors used in pseudo-randomization.

All interventions were performed in accordance with the recommendations of the VNOA [3] and the standard procedure [4]. Implantable PMs, both during planned replacements and primary implantations, were from manufacturers including Medtronic (Sensia SR and Vitatron G20

Table 1.

Baseline clinical and demographic characteristics of the patient groups

Indicator	Study group (n=27)	Control group (n=129)	p_1	Control group PP (n=27)	p_2
Male gender, n (%)	15 (55.6)	78 (60.5)	0.073	12 (44.4)	0.414
Age, years	67.6±12.9	74.3±9.8	0.106	73.9±9.8	0.065
Body mass index, kg/m^2	29.7±5.9	30.1±5.9	0.797	30.3±5.9	0.701
Hypertension, n (%)	24 (88.9)	124 (96.1)	0.14	26 (96.3)	0.299
Diabetes mellitus, n (%)	7 (25.9)	31 (24.0)	0.527	8 (29.6)	0.761
Ischemic heart disease, n (%)	9 (33.3)	59 (45.7)	0.263	11 (40.7)	0.573
TIA/ACVA, n (%)	3 (11.1)	25 (19.4)	0.19	4 (14.8)	0.685
Non-paroxysmal AF, n (%)	17 (63.0)	120 (93.0)	0	24 (88.9)	0.064
COPD, n (%)	1 (3.7)	13 (10.1)	0.266	1 (3.7)	1
Follow-up duration, months	64.4±39.9	75.7±39.0	0.085	74.6±37.5	0.339
Ventricular pacing, %	90 [82; 100]	48 [16; 92]	0	56 [28; 92]	0.011
Septal location of RV electrode (n)	22 (81.5)	104 (80.6)	0.485	24 (88.9)	0.444
Single-chamber pacemaker (VVIR) (n)	13 (48.1)	101 (78.3)	0.001	20 (74.1)	0.093
Ventricular pacing ≥40%, n (%)	22 (81.5)	-	-	18 (66.7)	0.089

Notes: PP - post pseudo-randomization; p_1 and p_2 - significance of differences between the study group and control groups; TIA - transient ischemic attack; ACVA - acute cerebrovascular accident; AF - atrial fibrillation; COPD - chronic obstructive pulmonary disease; PVE - right ventricular electrode; PM - permanent pacemaker.

SR); BIOTRONIK SE & Co. KG (Effecta SR, Philos SR, and Talos SR); St. Jude Medical (Verity ADx XL SR and Sustain XL SR); Boston Scientific Corporation (Altrua 20 SR). The new implanted right ventricular endocardial electrodes used were coated with silicone and silicone polyurethane and had active fixation, including Capsurefix® Novus 5076-58cm (Medtronic) and Safio S 60 (BIOTRONIK SE & Co. KG), with diameters of 2.0 mm (6 Fr), Flextend 2 (Guidant Corporation) with a diameter of 2.4 mm (7.2 Fr), and Tendril ST (St. Jude Medical) with a diameter of 2 mm (6 Fr).

Conservative management, both during hospitalization and outpatient follow-up, was aimed at providing patients with optimal multi-component pharmacological therapy for both primary and comorbid diseases. In the postoperative period, routine evaluations of PM function were carried out, including interval echocardiography. The Echo studies were performed following current recommendations [5] using General Electric diagnostic ultrasound systems (Vivid 9, Vivid 7 Pro) with frequency-adjustable transducers ranging from 1.5/3 MHz to 2.3/4.6 MHz for thoracic studies. TR progression was defined as an increase in the degree of insufficiency by 1 or more levels.

Statistical analysis

The statistical analysis of the study results was performed using the IBM® SPSS® Statistics version 26 software (SPSS, Chicago, IL, USA). For the analysis, pseudo-randomization (propensity score matching, PSM) was used to balance the indicators in the groups to minimize the limitations of observational studies. Logistic regression with pair matching of corresponding observations was used based on a 1:1 ratio with the closest propensity score (PS) values. Matching of the observation pairs was carried out based on several factors, including gender, age, body mass index, duration of follow-up, history of hypertension, diabetes, ischemic heart disease, transient ischemic attack and/or acute cerebrovascular accidents, non-paroxysmal (persistent/permanent) atrial fibrillation (AF), chronic obstructive pulmonary disease, as well as the location of the right ventricular electrode and the type of implanted PM.

According to a number of studies, the threshold value for right ventricular stimulation is considered to be 40%, with exceeding this threshold potentially triggering the appearance or progression of signs of congestive heart failure and the progression of TR as a consequence [6]. Both groups differed in the absolute median value of cumulative right ventricular stimulation percentage both before and after matching the observation pairs. However, this parameter in both groups exceeded known threshold values for any type of implanted pacemaker. Thus, both groups were comparable in this regard.

Normality of the distribution of parameters was assessed using the Shapiro-Wilk test. For normally distributed data, the arithmetic mean with standard deviation (M±SD) was used, while for data with non-normal distribution, the median with interquartile range (25th and 75th percentiles) was reported. Frequencies and proportions (%) were used for qualitative data. Data from populations with normal distribution were compared using the Student's t-test for independent samples. Data from populations with non-normal distribution were compared using the Mann-Whitney U test and the chi-square ($\chi 2$) test (Fisher's exact test was applied in some cases). For dependent samples, the Wilcoxon test was used. The critical level of statistical significance for hypothesis testing was set at 0.05.

To analyze the predictors of the appearance/progression of TR, multiple logistic regression was used. The dependent variable was defined as the increase in the degree of TR by 1 or more grades according to Echo during the follow-up period. The independent variables included age, body mass index, history of ischemic heart disease, non-paroxysmal AF, number of right ventricular electrodes, and electrode position (apical/septal).

RESULTS

When evaluating the dynamics of Echo indicators in both groups, a slight increase in left heart overload markers (degree of mitral regurgitation and/or left atrial volume)

Table 2.

Comparison of EchoCG parameters in preoperative and remote follow-up periods

EF, %	Study group (n=27)			Control group (n=27)			p*
	EDV, ml	PostOp	p	PreOp	PostOp	p	
Degree of MR	57 [53; 66]	60 [53; 65]	0,703	59 [55; 64]	60 [53; 62]	0,622	0,917
LA volume, ml	112 [101; 141]	113 [87; 137]	0,153	120 [106; 150]	116 [92; 150]	0,171	0,698
Degree of TR	1 [0; 1]	1 [1; 1]	0,035	1 [0; 1]	1 [1; 1]	1,000	0,978
TV FR, mm	71 [49; 83]	75 [68; 114]	0,005	80 [67; 108]	108 [86; 147]	0,001	0,013
RV size, mm	1 [1; 1]	1 [1; 1]	0,071	1 [0; 1]	1 [1; 2]	0,346	0,144
RA volume, ml	35 [29; 35,5]	34 [32; 37]	0,127	35,5 [33; 39]	36 [34; 38]	0,615	0,690
TR gradient, mm Hg	25 [23; 29]	27 [25; 34]	0,001	28 [25; 29]	28 [26; 30]	0,464	0,060
TAPSE	69 [48; 79]	62 [54; 102]	0,055	75 [52; 83]	81 [55; 115]	0,002	0,421
Градиент ТР, мм рт.ст.	22,1 [20; 29]	28,7 [24; 33]	0,018	22,1 [15; 33]	28 [22; 37]	0,064	0,959
TAPSE, см	20,3 [19; 23]	21 [19; 23]	0,440	20,3 [20,3; 21]	21 [19; 21]	0,474	0,591

Note: PreOP and PostOP - preoperative and postoperative periods; p* - level of statistical significance for comparison of echocardiographic parameters in the distant postoperative period; EF - ejection fraction (by Simpson's method); EDV - end-diastolic volume (by Simpson's method); MR - mitral regurgitation; LA - left atrium; TR - tricuspid regurgitation; FR - fibrous ring (diameter); TV - tricuspid valve; RV - right ventricle; RA - right atrium.

was observed. There was also a minor increase in the RV, right atrial volume, and TR gradient, which indirectly indicated volume overload of the right heart chambers and subthreshold progression of TR. However, no change in the TR indicator was detected. Other ultrasound parameters showed no significant differences and were within the age-related norm (Table 2).

In the long-term postoperative period, Echo parameters for both groups showed no differences and were generally within the age-specific norms. The only exception was the left atrial volume in the control group, which was higher compared to the study group.

In the control group, 62.9% (n=17) of patients showed mild TR, 29.7% (n=8) had moderate TR, and 7.4% (n=2) had no TR. In the observation group, mild TR was diagnosed in 74.1% of cases (n=20), moderate TR in 18.5% (n=5), and severe TR was recorded in 3.7% (n=1) of patients, with the same percentage of patients having no TR (3.7% (n=1)) (Fig. 1).

Using multivariate logistic regression, the only independent predictor of TR progression in the postoperative period was the presence of non-paroxysmal AF, which increased the likelihood of progression by 3.8 times. No correlation was found between the presence of two electrodes in the right ventricular cavity and the degree of tricuspid insufficiency (Table 3). Additionally, no relationship was found between the dependent variable and the position of the stimulating electrode in the right ventricle (septal/apical).

DISCUSSION

TR is classified as primary (organic, degenerative) and secondary (functional). Primary TR is caused by structural damage to the TV apparatus and is observed in 8-10% of patients [7]. Secondary TR is more commonly seen, caused by either RV dilation due to volume or pressure overload (e.g., from pulmonary hypertension associated with left heart failure), «senile» degeneration of the tricuspid valve ring, or isolated dilation of the tricuspid valve ring due to long-standing persistent AF [8]. A special form of TR is associated with implantable electronic devices (CIEDs), occurring in 20-30% of patients with an implanted right ventricular electrode [9]. This type of insufficiency is also divided into primary and secondary. Primary TR is caused by the direct impact of the electrode on the structures of the tricuspid valve, while secondary TR occurs due to right ventricular dilation (as a result of chronic cardiac pacing and heart failure).

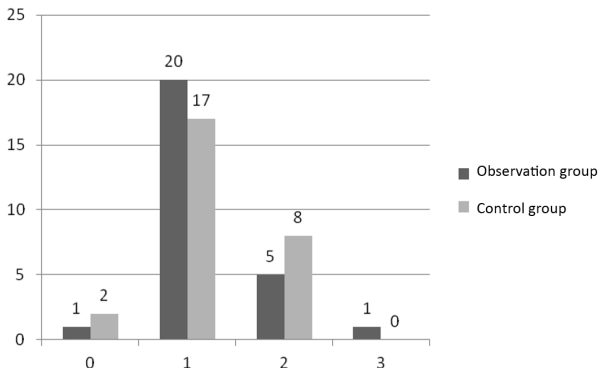

Fig. 1. Prevalence of tricuspid regurgitation in the long-term postoperative period

According to recent meta-analyses addressing the issue of electrode-associated TR, factors influencing the progression of TR were identified, including the interference of the TV leaflets with the electrode and the time of CIED implantation on one hand [10], and the enlargement of the right atrium and female gender on the other [11]. No significant difference was found between the type of implanted device (ICD or permanent pacemaker) and the degree of TR progression in the postoperative period. Additionally, in a meta-analysis by S. Alnaimat et al. (2023), seemingly logical predictors such as RV dysfunction, pulmonary artery pressure, preoperative significant mitral regurgitation, left ventricular ejection fraction, preoperative non-paroxysmal AF, and patient age were not associated with postoperative TR progression [11].

This issue in patients with multiple electrodes in the right ventricular cavity is not well addressed in meta-analyses and is generally underexplored. Part of this may be due to the extraction of «excess» electrodes and the characteristics of this patient group. The need for electrode removal arises in several situations, including when an electrode stops functioning properly, hindering optimal patient treatment, or when infection-related complications arise due to the implanted device [12]. In Russia, just over 40,000 devices are implanted annually, and the total number of patients with such devices is approaching 1 million (reliable statistics are unavailable). Of these, up to 5% of the total number of electrodes require removal [13]. The decision regarding transvenous extraction of electrodes is based on the opinion of several authors, such as M.S. Silvetti et al. (2008) and L.M. Epstein et al. (2017), who, despite the lack of randomized controlled studies comparing extraction with non-extracted electrodes, confirm the argument that «the potential future benefit of electrode removal outweighs the risks of not removing the electrode, and this refusal should be considered as a 'palliative procedure,' simply postponing the inevitable electrode removal in the future» [14, 15]. Transvenous extraction of electrodes may not be justified in patients with a poor prognosis or those whose intervention risks clearly outweigh the risks of not removing the electrodes [16]. In such cases, the electrode is left in the heart cavity, and it is essential to understand how this «additional» electrode will «coexist» with valve structures. Theoretically, the direct intervention of the electrode in the valve closure process should increase proportionally to the number of implanted electrodes in the RV cavity. The relationship between the number of electrodes in the RV and the degree of potential TR progression is reflected in a few studies. N. Postaci et al. (1995) [17] showed that the frequency of TR progression was predominant in patients with two right ventricular electrodes. In the study by C. Celiker et al. (2004), the overall frequency of mild and moderate TR did not show a significant difference between the groups (83% in the group with two right ventricular electrodes vs. 77% in the group with one) [18]. Compared to the results of N. Postaci et al. (1995), TR was less frequent and less pronounced in the two-electrode group. No significant TR or substantial differences in RV function were found in any group.

The frequently discussed idea of a connection between the progression of TR and RV failure with the location of RV

stimulation is reflected in several studies. Apical stimulation leads to «delayed» contraction of the RV papillary muscles, resulting in TR [9, 19]. The assumption that RV remodeling, dilation of the tricuspid ring, and, consequently, the development of functional TR, are outcomes of either systolic dyssynchrony in the case of apical stimulation or progressive reduction of LV systolic and diastolic function is supported by the retrospective study of M. Sadreddini et al. (2014). It was found that the degree of TR increased significantly after the implantation of a dual-chamber pacemaker but did not progress under biventricular stimulation, suggesting the «suppression» of the pathophysiological mechanisms of valve insufficiency development due to ventricular dyssynchrony in the CRT group [20]. In contrast, the analysis of the PROTECT-PACE study (145 patients, of whom 76 had apical and 69 had non-apical stimulation) showed that after 2 years of follow-up, the degree of TR increased, but the location of stimulation in the RV was not associated with changes in the echocardiographic parameters of the right heart chambers [21].

The choice of an alternative stimulation site, such as the outflow tract of the RV according to several authors [22], is a priority. Experts believe that apically implanted electrodes carry a higher risk of damaging the TV apparatus, especially the posterior leaflet, compared to electrodes fixed in the outflow tract of the RV [23, 24]. However, in the study by S. Hemayat et al. (2014), comparing both strategies [25], no clear influence of the implantation site on the progression of TR was found. It is important to note that stimulation of the RV septum is also far from physiological, but it leads to a narrower QRS complex on the ECG and may be associated with less negative long-term effects on both left and right ventricular echocardiographic and hemodynamic parameters. Despite the theoretical justification for positioning the RV electrode in the interventricular septum, clinical study data have contradictory results due to the lack of uniform criteria on this aspect. The middle part of the interventricular septum near the septomarginal trabecula is considered to be the most optimal site for electrode positioning [23].

In the review article by F. Akerström et al. (2013), a cumulative right ventricular pacing percentage of 40% was recognized as the threshold value, above which progression of heart failure and, consequently, an increase in TR could occur [6]. However, some studies show that a high percentage of right ventricular pacing does not correlate with TR progression [26, 27]. In our 2019 study, we evaluated the consequences of short-term active right ventricular pacing (60-90 minutes), and no acute effects on the function of the right heart chambers or degree of TR were observed [28]. Another mechanism of electrode-associated TR is the fibrotic and inflammatory reaction to the foreign body. Chronic repeated contact between the device electrodes and the valve leaflets or chordal structures leads to the formation of neoendocardium and the development of a fibrinous shell that can extend along the entire length of the electrode. This results in encapsulation, possible adhesion to the leaflets and chordal apparatus, and subsequent malcoaptation [29]. It should be noted that such valve dysfunction manifests as significant increases in TR during the postoperative period and typically requires surgical correction of the developed defect.

It is worth mentioning that TR is present in 70-90% of the general population, not necessarily in those with implanted devices. Demographic aging, i.e., the increase in the elderly population within the general population, both globally and in the Russian Federation specifically, remains one of the most pressing issues in modern society [30]. The prevalence of moderate or severe TR increases with age and reaches 4% in patients aged 75 and older [31]. In other words, the onset and progression of TR is a natural process of age-related degeneration of cardiac structures and is not always directly or indirectly related to implanted electronic devices.

Our study results are similar to those of the research groups of N. Postaci et al. (1995) and C. Celiker et al. (2004), where no significant increase in TR was observed in the group with two electrodes. No effect of the RV stimulation site on the measured parameter was found either. However, the increase in TR and a number of linear and volumetric parameters in the postoperative period in both observation groups is most likely due to the «burden» of AF. This finding supports the study of M.F. Dietz et al. (2020) [8] and aligns with the results we obtained. Despite this, the normal range of ultrasonographic parameters suggests that these changes do not cause significant hemodynamic overload at this stage of patient follow-up.

Limitations of the study

The limitations of our study include the typical drawbacks of retrospective research. The selected patient group is limited to a single center, which prevents the avoidance of sample bias. The intervals between Echo studies were variable, making it impossible to fully assess the chronological structural and functional changes in the heart chambers and structures. This certainly requires prospective observation. Additionally, this study lacks 3D Echo data, which hinders the ability to determine the exact mechanism of TR progression, and the true severity of valve insufficiency after pacemaker implantation may have been underestimated. There are also questions regarding the differences in defining the progression of tricuspid valve insufficiency in various studies, which could lead to discrepancies in the final results.

Table 3.

Predictors of TR progression: results of multiple logistic regression.

	B	Significance	Exp (B)	95% CI
Age	0,005	0,797	1,005	0,970-1,041
Body mass index, kg/m²	-0,024	0,446	0,977	0,919-1,038
Ischemic Heart Disease	0,123	0,730	1,131	0,562-2,279
Group*	0,489	0,349	1,631	0,586-4,544
Electrode Position	-0,066	0,882	0,936	0,390-2,246
Non-paroxysmal AF	1,341	0,025	3,824	1,179-12,401
Constant	-0,902	0,627	0,406	-

Note: * - observations or controls.

CONCLUSION

In patients with two right ventricular electrodes, tricuspid regurgitation and the function of the right heart chambers do not change significantly in the long-term follow-up period. The main factor influencing the progression of tricuspid regurgitation in the long-term follow-up period is a history of non-paroxysmal atrial fibrillation.

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NATURAL HISTORY AND PROBABILITY OF SPONTANEOUS CLOSURE OF ARTERIOVENOUS FISTULAS AFTER RADIOFREQUENCY CATHETER ABLATION OF ATRIAL FIBRILLATION

N.V.Makarova, S.S.Durmanov, S.V.Sivushchyna, V.V.Bazylev

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

Aim. To evaluate the clinical outcomes of persistent arteriovenous fistulas (AVF) after catheter ablation (CA) of atrial fibrillation (AF), to determine potential predictors and the likelihood of self-resolution while taking anticoagulants.

Methods. Thirty-six patients with AVF after CA AF (14 men, age 59.9±8.4 years) were included. Pulmonary veins were isolated for everyone. Femoral vein catheterization was performed according to anatomical guidelines. Hemostasis was performed with a "figure of eight" type suture, a pouch suture or a compression bandage. With symptoms suggesting the presence of vascular access complications (VAC), ultrasound duplex scanning (UDS) was performed the next day after the CT. When AVF was detected, compression bandages were treated. While maintaining AVF, outpatient follow-up continued, including UDS, echocardiography, and questionnaires. Surgical treatment was performed with a combination of AVF with other VAC, with paired AVF, and with refusal of observation.

Results. The incidence of AVF was 1.19%. Compression therapy was effective in 8 (22.2%) patients, surgical treatment was performed in 7 (19.4%). In no case was AVF symptomatic, and there were no indications for immediate surgical treatment. Outpatient follow-up was continued 14. The duration of follow-up was 24 [12; 28] months. In 8 patients, AVF resolved on its own, in 1 previously closed AVF relapsed. Minor local symptoms were noted in 4 out of 7 patients with persistent AVF. In 15 (41.7%) of 36 patients, AVF resolved independently or with the help of compression therapy. The only independent predictor of self-closure of AVF in a single-factor logistic regression analysis was the age of patients (odds ratio (OR) 0.807; confidence interval (CI) 95% 0.651-1,000; p=0.050). Using ROC analysis, it was shown that the age over 65.5 years reduced the chance of self-closure of AVF by 93.7% (OR 0.067; CI 95% 0.007-0.614; p=0.017).

Conclusion. The frequency of spontaneous closure of AVF after AF was 57.1%. The only independent predictor of AVF persistence was the patient's age over 65.5 years. None of the patients with persistent AVF developed symptoms of heart failure and vascular symptoms that required immediate surgical closure.

Keywords: atrial fibrillation; catheter ablation; complications of vascular access; arteriovenous fistula; spontaneous resolution; ultrasound duplex scanning; compression therapy

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Corresponding author: Makarova Natalia, E-mail: maknatven@mail.ru

N.V.Makarova - ORCID ID 0000-0001-7141-2262, S.S.Durmanov - ORCID ID 0000-0002-4973-510X, S.V.Sivushchyna - ORCID ID 0009-0003-6007-7843, V.V.Bazylev - ORCID ID 0000-0001-6089-9722

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Vascular access complications (VAC) are the most common complications of catheter ablation (CA) for atrial fibrillation (AF). The incidence of VAC requiring observation is 1-7%, and those requiring surgical treatment range from 0.1% to 0.3% [1]. In all AF CA procedures, femoral venous access is used to insert diagnostic and ablation electrodes, and sometimes femoral arterial access is also used for invasive monitoring of blood pressure, blood gas analysis, and aortic visualization during transseptal puncture [2]. One of the complications of femoral vascular access is arteriovenous fistula (AVF). The incidence of AVF varies depending on the study design and diagnostic method, ranging from 0.006% to 6.9% [3, 4]. The clinical presentation of iatrogenic AVF ranges from asymptomatic to the development of congestive heart failure, lower limb ischemia, and bleeding [5-7]. There is no unified approach to the management of AVF, with each healthcare institution often following its own treatment protocol. Options include simple observation, compression therapy, endovascular closure methods, and surgical treatment [8, 9]. Surgical treatment is traditionally considered the standard approach but is associated with complications such as bleeding, infection, femoral artery stenosis, cosmetic defects, and economic burden for the healthcare institution [3, 10]. However, several studies have demonstrated that AVF following heart catheterization may resolve spontaneously in the absence of anticoagulant and antithrombotic therapy [11, 12]. Various studies have analyzed predictors of AVF occurrence after cardiac interventions. However, the likelihood of spontaneous AVF closure during prolonged an-

ticoagulant therapy and the complications associated with the long-term persistence of AVF after CA for AF have not been previously studied. Aim of the study: to evaluate the clinical outcomes of persistent AVF after CA for AF, identify potential predictors, and assess the likelihood of spontaneous resolution while taking anticoagulants.

METHODS

From 2018 to 2023, the Federal Center for Cardiovascular Surgery of the Ministry of Health of Russia (Penza) performed 3037 radiofrequency CA procedures for paroxysmal and persistent AF. The procedure was conducted under intravenous sedation with dexmedetomidine and fentanyl. During the procedure, heparin was administered intravenously at doses that maintained the activated clotting time (ACT) above 300 seconds. All patients received therapy with warfarin or new oral anticoagulants without interruption for the surgical treatment. No femoral arterial access was used in any case. Access to the femoral veins was performed either from one side, predominantly the right, or from both sides. Femoral vein catheterization was performed 2-3 cm below the inguinal ligament using anatomical landmarks and palpating the pulse on the femoral artery (FA), with no ultrasound visualization used. Non-guided introducers with diameters of 7 and 8 Fr were used to introduce diagnostic and ablation electrodes. The number of venous introducers used on one side ranged from 1 to 3. To neutralize the anticoagulant effect of heparin before the removal of the introducers, protamine sulfate was administered intravenously. Hemostasis was achieved on the operating table with a "figure-eight" suture or a purse-string suture. If excessive bleeding occurred after the introducer removal or if a hematoma appeared or increased in size, or if there were doubts about the quality of hemostasis, manual compression followed by the application of a compression bandage at the site of puncture was performed.

Table 1.

Clinical-demographic and instrumental parameters of patients with AVF included in the study (n=36)

Indicator	Value
Age, years, M±SD	59.9±8.4
Male gender, n (%)	14 (38.9)
BMI, kg/m^2	32.1±3.8
Arterial hypertension, n (%)	31 (86.1)
Diabetes mellitus, n (%)	2 (5.6)
Smoking, n (%)	8 (22.2)
HAS-BLED, score	2 [1; 2]
History of femoral catheterizations, n (%)	15 (41.7)
Warfarin, n (%)	18 (50)
INR before surgery, units	1.5 [1.1; 2.4]
Platelet count, x10^9/L	236.3±51.9
Creatinine level, µmol/L	91.8±23.6
Right atrial volume index, mL/m^2	29.2±8.7
Right ventricular size, mm	26.8+3.4
Left ventricular ejection fraction (n, %)*	59.3±8.9
TR grade 2-4, n (%)	2 (5.6%)

Notes: HAS-BLED - a scale for assessing the risk of bleeding; INR - international normalized ratio; * - by Simpson's method; TR - tricuspid regurgitation.

The duration of bed rest after hemostasis with a suture was 6 hours, and after applying a compression bandage, it was until 7 a.m. the following day. All patients, even those with minimal complaints and/or clinical symptoms suggesting the presence of VAC (pain, hematoma, swelling in the groin, bruit on auscultation at the puncture site, tremor over the vessel projection area), as well as patients who had a compression bandage applied for hemostasis, underwent screening with UDS the day after the procedure. In cases of difficulties with ultrasound diagnostics (e.g., diffuse hematomas, soft tissue edema in the leg, obesity, or individual anatomical features), computed tomography angiography (CTA) was performed.

When AVF was detected, the artery and vein involved in its formation were identified, and the diameter and linear blood flow velocity in the AVF were determined if possible. According to the treatment protocol adopted in our center, treatment started with compression therapy. Manual compression was performed in the area of the AVF marked on the skin by the ultrasound specialist for 20-30 minutes. Afterward, regardless of the presence of bruit on auscultation, tight bandaging with an ordinary bandage was applied, and an elastic bandage was placed on top. The elastic bandage was left in place for 4-6 hours. Due to leg swelling, which impaired venous outflow, local skin ischemia, and associated hematoma, painful sensations were noted, requiring the administration of analgesics. After the prescribed time, the elastic bandage was removed to avoid venous thrombosis and skin trophic disorders, and a tight pressure bandage was kept in place until 7 a.m. the following day. During this period, the patient was on strict bed rest. After the bandage was removed, a physical examination, auscultation for bruit at the puncture site, and follow-up UDS were performed. If no AVF was detected, compression therapy was discontinued. In case of persistent AVF, a repeated tight pressure bandage was applied. A total of 1-4 attempts at compression therapy were made, with the number of attempts often limited by the presence of painful inguinal hematomas and macerated skin, which made proper compression difficult, and in some cases, the patient refused due to pain and required bed rest.

In order to improve the success of treatment, anticoagulants were discontinued for 1-2 days during the compression therapy period, if there were no absolute indications for their use. If conservative treatment was unsuccessful, the patient was discharged with recommendations for consultation and follow-up UDS in 3 months or an unscheduled examination if clinical symptoms associated with VAC worsened. Further follow-ups were scheduled according to an individual timetable, with mandatory UDS performed at each visit. Surgical treatment was performed in patients with AVF associated with a pulsatile hematoma (PH) of the FA, unresponsive to compression therapy, in cases of expanding or paired AVFs, and if the patient refused passive observation.

This study is retrospective in nature, despite the prospective observational registry, and was approved

by the local ethics committee (protocol No. 103, dated 25.01.2024). The study included all cases of diagnosed AVF, either isolated or combined with other VAC, in 36 patients who underwent radiofrequency CA for AF between 2018 and 2023. Clinical and instrumental data were extracted from electronic medical records, and procedural data were obtained from the operative treatment protocols. Patient characteristics are presented in Table 1.

Paroxysmal AF was present in 25 (69.4%) patients, and in 23 (63.9%) patients, AF was recorded on the electrocardiogram (ECG) prior to CA. Fifteen patients (41.7%) had a history of diagnostic and interventional procedures. All previous access sites were femoral venous, ranging from 1 to 5 times. None of the patients received antiplatelet agents, and none had significant concomitant atherosclerosis of the lower extremity arteries or congestive heart failure. All patients underwent pulmonary vein isolation (PVI) using the standard technique, and in 8 (22.2%) cases, the procedure design included additional interventions in the left and/or right atria. Perioperative indicators for patients with AVF are presented in Table 2.

At the time of study completion, all patients with a history of AVF were invited for a follow-up consultation. In addition to physical examination and UDS, ECG was recorded, echocardiography (Echo) was performed, and patient questionnaires were completed to assess the clinical significance of AVF. The questionnaire included questions reflecting clinical symptoms of right heart overload (shortness of breath, weakness, reduced performance, etc.) and symptoms related to the lower extremities typical for AVF persistence, including those associated with arterial steal and venous hypertension (pain and "tremor" in the groin, vein expansion and lower extremity edema, weakness, and rapid fatigue in the lower extremity, etc.). The ECG registration evaluated rhythm characteristics, right heart overload symptoms, while Echo assessed the size and volumetric characteristics of the right atrium and right ventricle, the degree of tricuspid regurgitation, and left ventricular ejection fraction (LVEF). The standard UDS protocol included an assessment of the relative positioning of the FA and femoral vein and the degree of venous artery overlap in the transverse projection at the AVF level or 2 cm below the inguinal ligament in the absence of AVF.

Statistical analysis

The statistical analysis of the results was performed using IBM® SPSS® Statistics Version 23 (23.0). All quantitative variables were tested for distribution type using the Kolmogorov-Smirnov test. For symmetrical distributions, the results are expressed as the mean and standard deviation (M±SD). If the distribution was asymmetrical, values are presented as the median (Me) and interquartile range, which is the difference between the third and first quartiles. The Mann-Whitney test was used for analysis. For comparison of nominal scale variables, the Pearson $\chi 2$ test was used. The impact of potential predictors on the dependent variable (the probability of spontaneous closure of the AVF) was assessed using multivariate logistic regression analysis. To assess the sensitivity and specificity of predicting spontaneous closure of AVF based on the obtained indicators, ROC analysis was performed. The data are presented with the achieved significance level (p) and 95% confidence interval (CI 95%). A critical significance level was set at ≤0.05.

RESULTS

The incidence of AVF in our study was 1.19%. In 8 (22.2%) of 36 cases, AVF was associated with PH, and in 21 (58.3%) cases with soft tissue hematomas. Soft tissue hematomas were defined as visible changes in tissue in the projection of the femoral vein puncture site over a distance >5 cm. In 15 (41.7%) patients, there were no complaints or visible symptoms of VAC; the reason for the examination was the presence of bruit at the puncture site or intraoperative hemostasis with a tight compression bandage. In half of the cases, UDS was used as a diagnostic method, while in the other half, it was supplemented by computed tomography angiography.

Compression therapy was effective in 8 (22.2%) patients. Surgical treatment was performed in 7 (19.4%) patients. In no case was there an indication for immediate surgery. No case of symptomatic AVF was observed. Indications for surgery included paired AVF in 3 cases, the combination of PH with AVF in 1 case, and AVF in young patients whose work was physically demanding and who preferred surgical treatment over observation, in 3 cases. The postoperative period in one patient was complicated by the development of a seroma and stenosis of the superficial femoral artery up to 50%.

Of the 21 patients discharged with AVF, 14 continued outpatient follow-up. Seven patients, who did not attend in-person visits, explained their refusal by feeling well and the absence of typical VAC symptoms when contacted by phone. The follow-up duration was 24 [12; 28] months. In 8 of 14 patients, AVF resolved spontaneously. In 1 patient, a previously closed AVF recurred. Four of 7 patients with persistent AVF complained of local discomfort and pulsation in the groin (n=2), swelling of veins, edema, and weakness in the lower limb (n=2). Two patients underwent surgical treatment due to local complaints, and five patients continued follow-up (Fig. 1). None of the patients reported hemodynamic symptoms associated with the progression of heart failure. According to the ECG data, all patients maintained sinus rhythm, and no signs of right heart overload were detected. Echocardiography revealed no statistically significant differences in the right atrial volume

Table 2.

Perioperative characteristics of patients with AVF (n=36)

Indicator	Value
Duration of surgery, min	97.6±28.1
Heparin dose, thousand units	20.7±7.8
Activated clotting time, s	342 [316; 413]
Number of introducers*, n (%)	28 (77.8)
Left femoral access, n (%)	4 (11.1)
Hemostasis with tight compression bandage, n (%)	16 (44.4)
INR after surgery, units	1.9 [1.4; 3.2]

Note: * - 2 or more on one side; INR - international normalized ratio.

index, right ventricular size, degree of tricuspid regurgitation, or LVEF before the procedure and at the end of the observation period.

In 30 (83.3%) cases, the common femoral vein was involved in the formation of AVF, and in 32 (88.9%) cases, the superficial femoral artery was involved. In all cases, duplex ultrasound showed some degree of overlap between the artery and vein: complete overlap in 66.7% and partial overlap in 33.3%, either at the level of AVF or 2 cm below the inguinal ligament if the AVF had resolved.

In 15 (41.7%) of 36 patients, AVF resolved spontaneously or with the help of compression therapy. Possible independent predictors of spontaneous closure of AVF were considered, including clinical-demographic, instrumental, and perioperative factors: sex, age, body mass index (BMI), hypertension, diabetes, smoking, platelet count, creatinine level, HAS-BLED score (for bleeding risk assessment), warfarin anticoagulation, combined with other VAC (PH and soft tissue hematomas), previous femoral catheterizations, duration of the procedure, heparin dosage, ACT, 2 or more introducers on one side, hemostasis with tight compression bandage, and the international normalized ratio before and after surgery. The only independent predictor of spontaneous AVF closure in univariate logistic regression analysis was the patient's age (odds ratio (OR) 0.807; 95% confidence interval (CI) 0.651-1.000; p=0.050).

The diagnostic significance of age for predicting spontaneous AVF closure was assessed using ROC curve analysis (Fig. 2). The area under the curve was 0.832, and the optimal cut-off age was found to be 65.5 years (sensitivity 71.4%, specificity 85.7%). Age over 65.5 years reduced the chance of spontaneous AVF closure by 93.7% (OR 0.067; 95% CI 0.007-0.614; p=0.017). Thus, patients over 65.5 years have a minimal chance of spontaneous AVF obliteration.

DISCUSSION

The absence of recommendations regarding the management strategy and indications for surgery in patients with iatrogenic AVF prompted us to conduct this study. According to published data, surgical treatment is considered the "gold standard" for managing patients with acquired AVFs. Based on this opinion, we previously referred all patients with diagnosed AVFs and unsuccessful compression therapy directly to surgery. However, significant edema, soft tissue imbibition, skin maceration, and active anticoagulation posed certain difficulties for surgical intervention and created conditions for the development of complications. Endovascular methods, while offering advantages such as early mobilization, a shorter hospital stay, and a lower risk of infectious complications, also have potential drawbacks. These include the possibility of thrombosis, stent kinking in active patients, and the closure of collateral arterial branches [6, 13, 14].

We adhered to an active surgical approach until the case of spontaneous obliteration of AVF in a young patient with a recommendation for surgical closure, where the operation was postponed for 3 months until the resolution of a large inguinal hematoma. The natural course of AVF has been studied in a small number of patients following coronary angiography and coronary angioplasty. The potential for spontaneous obliteration of AVF in the context of prolonged anticoagulation therapy after CA of AF had not been previously investigated. On the contrary, in some studies, prolonged anticoagulation was considered an indication for surgical treatment of AVF [11, 12]. Furthermore, the prognosis of long-term AVF persistence is unknown, as published reports describe only isolated high-symptom cases of AVF that required surgical closure.

The frequency of arteriovenous fistulas after catheter ablation of atrial fibrillation

In this study, the incidence of iatrogenic AVF was 1.19%. The true frequency of AVF development after CA of AF remains unknown. The detection rate is influenced by the study design and the method used for validating VAC. As demonstrated in a systematic review of complications in CA for AF (192 studies, n=83,236), the frequency of VACs is higher in prospective studies than in retrospective ones [15]. When the frequency of AVF was assessed based on surgical intervention data, it ranged from 0.006% to 0.14% [3, 16]. In a study similar to ours, where UDS was used as the primary diagnostic tool for minimal complaints such as pain and local hematomas, the frequency of AVF was higher, at 4.8% [4]. This study included patients (n=479) who received continuous anticoagulant therapy and underwent CA for supraventricular (AF ablation, n=293, 68%) and ventricular tachycardia. In the study by K. Bode et al. (2019), the incidence of AVF after CA for AF (n=1152) was 1.22%, with 14 cases of AVF [10], which is comparable to our findings. According to B. Aldhoon et al. (2013), small AVFs were diagnosed in 7 patients (0.59%) after CA for AF (n=1192) [17]. In a small study by T.F. Kresowik et al. (1991), where UDS was routinely performed for all patients to assess VACs, 114 patients underwent coronary angioplasty, and all had femoral artery (FA) and femoral vein punctures on

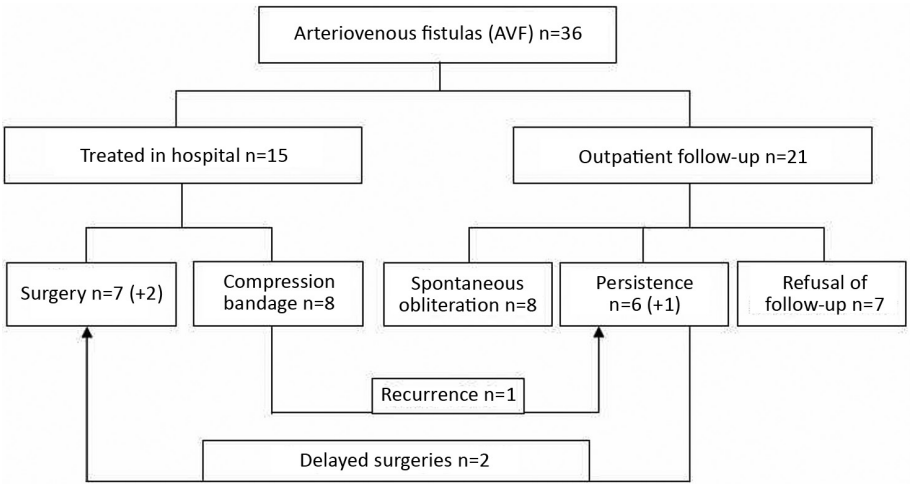

Fig. 1. Course and outcomes of arteriovenous fistula after radiofrequency ablation of atrial fibrillation.

one side. The incidence of AVF was 2.8% (n=4) [18]. In no study of VACs after CA for AF was UDS performed routinely, which likely means that some asymptomatic small AVFs were not diagnosed. Additionally, most studies did not analyze the frequency of AVF separately from other VACs, or only analyzed symptomatic AVFs that required blood transfusions, interventions, or prolonged hospitalization [19, 20].

The characteristics of the progression and outcomes of arteriovenous fistulas after catheter ablation of atrial fibrillation

The key event in AVF closure is the formation of a thrombus. The fact that all patients after AF CA are on anticoagulant therapy reduces the likelihood of spontaneous obliteration and the effectiveness of compression therapy. In the study by B. Toursarkissian et al. (1997), the natural history of 81 isolated and 9 combined AVFs with PH after cardiac catheterization for diagnostic (56%) and therapeutic purposes was analyzed. Spontaneous obliteration occurred in 81% of AVFs, and 90% resolved within 4 months, with an average time of 28 days. None of the patients with spontaneous closure received anticoagulants. The need for prolonged anticoagulant therapy was the most common indication for surgical treatment [12]. In the study by M. Kelm (2002), 10,271 patients who underwent cardiac catheterization were followed prospectively for 3 years. Femoral artery puncture was performed in all cases, unlike femoral vein puncture. Of 88 patients with AVF, 79 received long-term therapy with 100 mg/day of aspirin. Within 12 months, 38% of AVFs closed spontaneously. In the first 4 months, 69% of AVFs closed spontaneously, and the rest closed within a year [5]. Clinical outcomes of 6 AVFs after femoral artery catheterization were evaluated in the prospective study by K.C. Kent (1993). Spontaneous resolution occurred in 4 of 6 AVFs [11]. In contrast, in the study by T.F. Kresowik et al. (1991), no spontaneous closure occurred in any of the 3 AVFs during an 8-week follow-up [18]. According to the results of this study, 8 (57.1%) of the 14 patients with AVF who continued follow-up had spontaneous obliteration of the AVF.

To date, no predictors have been found to predict the likelihood of spontaneous closure and the timeline for AVF resolution. According to the study by M. Kelm (2002), none of the factors (sex, age, body mass index, hypertension, intraoperative high doses of heparin, warfarin therapy, puncture site, number and diameter of introducers) affected the frequency and speed of spontaneous AVF thrombosis. A trend towards prolonged AVF persistence was observed with high procedural doses of heparin (p=0.065) and warfarin therapy (p=0.091) [5]. It would be logical to assume that the linear blood flow velocity in the AVF and the shunt volume would influence obliteration. Asymptomatic AVFs with low flow have a higher chance of spontaneous resolution [12]. This correlates with studies on AVF closure for hemodialysis, where a reduction in flow volume below 500 ml/min and a decrease in the fistula vein diameter to less than 2 mm increases the likelihood of thrombosis [5, 21]. However, in the study by M. Kelm et al. (2002), the shunt volume measured by UDS was 310 ml/min (250-350) in closed AVFs and 350 ml/min (160-510) in persistent AVFs (p=NS) [5]. The blood flow velocity (30-150 cm/s) in the AVF and the size of the initial arterial puncture did not correlate with spontaneous thrombosis [11].

In the present study, age over 65.5 years was the only predictor of AVF persistence. Age-associated changes in the arteries include increased stiffness and thickening of the walls, which is linked to an increase in collagen, a decrease in elastin, and the deposition of calcium and other substances. Similarly, in veins, the number of muscle fibers in the middle layer decreases, while the number of elastic fibers increases [22]. Clinically and histologically, it has been confirmed that the main cause of thrombosis in AVFs formed for hemodialysis is neointimal hyperplasia of the anastomosis or the fistula vein [23]. It can be assumed that younger patients have a greater chance of spontaneous AVF closure after AF CA due to a more active lifestyle, more movement in the hip joint, which causes transient extravascular compression of the AVF, and more active neointimal hyperplasia. According to numerous publications, advanced age is a predictor of complications after AF CA [1, 17, 19]. Naturally, it can be assumed that older age will also be associated with AVF persistence.

The effectiveness of compression therapy in this study was 22.2%. Compression therapy with or without ultrasound guidance is considered effective in two-thirds of cases of all complications after AF CA [10], but it is less successful in patients with AVF (33-50%) [24]. In several studies, compression therapy was ignored after AVF diagnosis, and a passive wait-and-see approach was chosen [10, 17, 25]. In the study by M.T. Massie et al. (1998), it was shown that there was no effect of compression therapy under ultrasound control for 60 minutes in patients with linear AVFs with high flow velocity (128 to 500 cm/s, with an average of 331 cm/s), whereas for non-linear AVFs with low flow velocity, compression was likely to be successful [26]. In our study, not all patients could have their linear blood flow velocity in the shunt assessed by ultrasound, so its impact on AVF persistence could not be determined. In the study by F. Schaub et al. (1994), 3 out of 9 AVFs were obliterated with compression in 80 minutes under ultrasound control [27]. The only limiting factor for the effectiveness of compression therapy is insufficient compression time to induce thrombosis in the AVF. This is related to fatigue in both the doctor and the patient, the overall

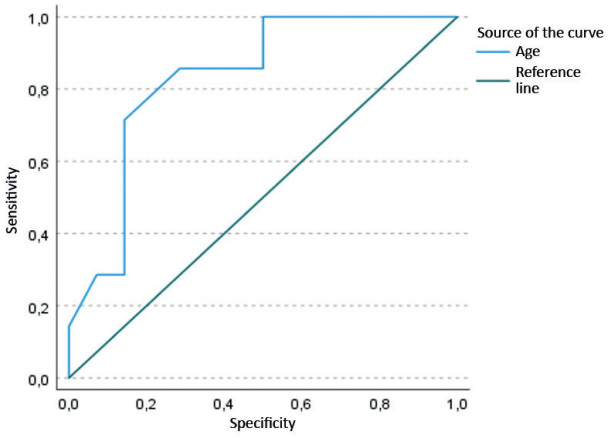

Fig. 2. ROC curve showing sensitivity and specificity for predicting spontaneous closure of AVF based on patient age.

busyness of the medical staff, severe pain, and vasovagal reactions [24]. In the original study by T. Zhou et al. (2007), 16 patients with AVF were treated with prolonged compression bandages using either a standard (n=12) or elastic bandage (n=4). The patients continued to receive clopidogrel 75 mg/day if clinically needed. The bandage was removed daily for 45 minutes to evaluate the compression result, and the patients performed minor everyday activities. All AVFs resolved as a result of compression within 4 to 46 days (on average 15±10 days). Despite the 100% effectiveness, the method is not without potential complications such as pneumonia, thromboembolic events, and skin ulceration [3]. Given the above, we believe that attempting compression therapy for AVF is justified.

Clinical manifestations of arteriovenous fistulas after catheter ablation

The clinical manifestations of AVF typically include symptoms related to both central and peripheral hemodynamics. These manifestations depend on factors such as the size of the shunt, the duration of persistence, and the diameter of the vessels involved. An arteriovenous fistula represents a connection between a high-pressure, high-resistance vessel (artery) and a low-pressure, low-resistance vessel (vein). According to hemodynamic principles, blood will flow from the artery into the vein. Significant shunting of blood from the arterial to the venous system increases the load on the right heart chambers, leading to heart failure. Distal to the AVF, arterial "steal" occurs due to decreased blood perfusion, potentially leading to arterial thrombosis and limb ischemia, especially in the presence of atherosclerotic damage. On the venous side, increased pressure further impairs capillary blood flow, leading to ectasia and even aneurysmal transformation of the venous wall, which increases the risk of rupture and bleeding [6, 28].

Clinical manifestations typically characterize AVFs resulting from trauma, vascular surgeries, or those created for hemodialysis [28, 29]. These AVFs are usually highly symptomatic and require interventional or surgical treatment. The natural course and management of post-traumatic AVFs cannot be extrapolated to AVFs that occur due to catheterization. Most iatrogenic AVFs are asymptomatic and are often detected incidentally [6, 30, 31]. However, recent years have seen an increase in publications reporting severe outcomes of AVFs following catheter-based diagnostic and interventional procedures [32-35].

In our study, 4 out of 7 patients with persistent AVFs exhibited minor peripheral symptoms. None of the patients with persistent AVFs showed signs of heart failure. In the study by M. Kelm et al. (2002), none of the patients with persistent AVFs (n=88) showed signs of heart volume overload or limb damage. In cases of interatrial or interventricular septal defects with left-to-right shunting, right ventricular function deteriorates only if the shunt volume exceeds 30% of cardiac output (normal resting cardiac output is 4-6.5 L/min). In mature AVFs for hemodialysis, the shunt volume ranges from 600-1200 ml/min [36]. In M. Kelm's study (2002), the shunt volume was much lower, ranging from 160-510 ml/min, which likely accounts for the asymptomatic course of AVFs in that cohort [5]. However, in some patients, clinical manifestations develop, and surgical treatment becomes necessary. In the study by M.A. Ohlow et al. (2009), 11% of all AVFs (n=107) required surgery due to the development of symptoms during an average follow-up of 48±10 months [37]. In another study, 2 out of 6 iatrogenic AVFs ultimately required surgical intervention due to the onset of peripheral symptoms [11]. Among 23,291 patients following heart catheterization, 6 AVFs required surgical treatment due to progression of heart failure, swelling, varicose veins in the lower limbs, claudication, or a combination of these symptoms [38].

It is worth noting that no prognostic indicators have yet been identified to predict which patients with persistent AVFs will develop clinical symptoms. It has been decided that AVFs with a diameter of 3 mm or more, formed after coronary angiography, should be surgically treated even in the absence of symptoms due to the potential risk of complications later on, if the AVF does not close within a year [13]. Complicated AVF course (heart failure, limb ischemia, nerve compression, bleeding, groin infection, etc.), the inability to continue observation or patient refusal, and the need for surgical treatment on the limb for other reasons are the most common indications for surgical treatment of AVF [6]. In our view, it is justified to observe patients for up to one year after unsuccessful compression therapy, with regular check-ups and ultrasound monitoring, in the unlikely event of developing heart failure or vascular complications.

Study limitations

Only patients with symptoms or clinical signs suggesting the presence of VAC and those who had hemostasis with a tight compression bandage underwent ultrasound examination. It is likely that some AVFs in asymptomatic patients were not diagnosed, meaning the true incidence of this complication may be higher than reported. The data on AVFs were obtained from only a subset of patients, which reduces the initial sample size. In 7 cases, surgical treatment was performed, which also limits the ability to evaluate the natural course of this complication. The results analyzed were from a single center, which restricts the generalizability of the findings.

CONCLUSION

The incidence of spontaneous closure of AVF after radiofrequency CA for AF was 57.1%. The only independent predictor of AVF persistence was the patient's age above 65.5 years. None of the patients with persistent AVF developed symptoms of heart failure or vascular symptoms that required immediate surgical closure. For AVFs with a diameter of less than 3 mm, it is reasonable to start treatment with compression therapy. In the absence of success with asymptomatic AVF, observation for one year is justified with the expectation of spontaneous obliteration. After this period, and for AVFs with a diameter greater than 3 mm, the decision regarding surgical treatment should be made.

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COMPARISON OF THE EFFICACY AND SAFETY OF PULMONARY VEIN CRYOBALLOON ABLATION ALONE AND WITH ADDITIONAL ISOLATION OF THE SUPERIOR VENA CAVA IN PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION

E.S.Livadny, S.E.Mamchur, N.S.Bokhan

FSBI "Research Institute for Complex Issues of Cardiovascular Diseases", Russia, Kemerovo, 6 Sosnovy blvd

Aim. To study the impact and safety of cryoballoon ablation of the pulmonary vein (PV), supplemented by isolation of the superior vena cava in patients with persistent atrial fibrillation (AF).

Methods. The study is single-center, randomized, prospective. The total number of patients was 40. All of them underwent cryoballoon isolation of the PV for persistent AF. The patients were then divided into two groups: the first group included patients who underwent the standard procedure, and the second group included patients with the standard procedure supplemented by isolation of the superior vena cava. Patients in both groups had similar anatomical and clinical-anamnestic parameters. The duration of the surgical intervention was not statistically different.

Results. The average follow-up period was 354±19 days. In the group of classical cryoballoon PV isolation, after 12 months of observation without antiarrhythmic therapy, sinus rhythm was maintained in 40% of patients (8 people), in the group of extended cryoballoon PV isolation - in the same number of patients (40%, P=1). In the PV isolation group, persistent phrenic nerve palsy was observed in no patients, and in the extended ablation group, in eight patients (40%, P= 0.0016). At the end of the observation, no remote complications were registered.

Conclusions. In patients with persistent AF, cryoballoon PV isolation supplemented by superior vena cava isolation is a less safe technique than standard cryoballoon pulmonary vein isolation, with comparable efficacy.

Key words: persistent atrial fibrillation; superior vena cava; cryoballoon ablation; safety; pulmonary vein

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Corresponding author: Liovadny Egor, E-mail: egorlivadnyi@mail.ru

E.S. Livadny - ORCID ID 0000-0003-1716-782X, S.E. Mamchur - ORCID ID 0000-0002-8277-5584, N.S. Bokhan - ORCID ID 0000-0002-1135-5144

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Atrial fibrillation (AF) is of particular interest in real clinical practice. The high prevalence of this arrhythmia, the severity of its symptoms, and the low effectiveness of drug treatment currently make interventional treatment of AF the top priority [1, 2]. The standard treatment for this arrhythmia is pulmonary vein isolation (PVI) [3]. Modern research results show similar effectiveness of two main technologies used for this purpose: radiofrequency ablation using contact force-sensing catheters and cryoballoon ablation with second- and third-generation balloon catheters [4, 5]. The effectiveness of interventional treatment for paroxysmal AF is reported to be 70-80% according to various authors and methods, while in the case of persistent AF, the effectiveness of interventions sharply decreases, with a wide range of results depending on the tools used, the criteria, and the methods of post-operative monitoring [6, 7].

One of the reasons for the failure of treatment in patients with persistent AF is the presence of non-pulmonary foci of arrhythmia, which can be localized in the posterior wall of the left atrium (PWLA), autonomic ganglionic plexuses, the border ridge, the Marshall ligament, the coronary sinus, and the superior vena cava (SVC), and participate in the arrhythmogenesis process, despite the previously achieved isolation of the pulmonary veins [8, 9].

Studies have shown that the SVC can act both as a trigger for AF and as a substrate supporting the fibrillation process [10]. Given the common origins of sinoatrial node cells and cardiomyocytes in the upper and lower parts of the vena cava, these areas may exhibit automaticity and participate in arrhythmogenic activity [11].

During embryogenesis, on the 7th-8th week, the right common cardiac vein, along with the right horn of the venous sinus, begins the formation of the superior vena cava. As development progresses, the openings of the SVC, inferior vena cava, and coronary sinus are formed. The venous sinus and part of the right horn also participate in the formation of the sinoatrial node. According to subsequent histological studies, on the 8th week, thickening is found in the intrapericardial sections of the SVC and inferior vena cava, represented by muscle-like cells that may serve as myocardial sphincters for the vena cava [12].

In the adult population, muscle-like cells are also found at the junction of the SVC and the right atrium

(RA), represented by the expansion of the atrial myocardium (myocardial sleeves) at the SVC opening, with sizes up to 14 mm, the maximum size of the "sleeves" reaching 47 mm. However, based on the conducted study, the relationship between the anatomical features of myocardial sleeves and the presence of AF in patients has not been proven [13]. Based on the above data, it can be assumed that isolating the SVC could increase the effectiveness of the intervention by eliminating non-pulmonary foci involved in the initiation and maintenance of AF.

There are three main approaches to isolating the SVC: 1) when an ectopic focus is proven in this localization using isoproterenol; 2) using electrophysiological studies to prove the earliest activation in this area or the shortest tachycardia cycle; 3) empirically, when there is confirmed complete isolation of the pulmonary veins [14].

The aim of our study was to assess the results of the effectiveness and safety of cryoballoon ablation of the pulmonary veins supplemented by isolation of the superior vena cava, compared with the standard pulmonary vein isolation procedure in patients with persistent atrial fibrillation.

METHODS

A randomized, prospective, single-center study included 40 patients with persistent AF aged 64.3±6.5 years, treated at the Department of Surgical Treatment of Complex Heart Rhythm Disorders and Cardiac Pacing at the Research Institute for Complex Issues of Cardiovascular Diseases from July 2022 to July 2023. The study was approved by the local ethics committee and conducted in accordance with the Helsinki Declaration. The 2020 ACC/AHA/ESC classification for AF was used during the study [3].

Inclusion criteria:

- At least two 12-lead electrocardiogram (ECG) recordings documenting AF.
- Results of 24-hour rhythm monitoring showing AF during the entire observation period.
- Objective medical documentation confirming the presence of persistent AF (initial examinations, discharge summaries).
- The patient showed clinical manifestations of arrhythmia and ineffectiveness of one or more antiarrhythmic drugs of class I or III in the history.
- All patients of both sexes over the age of 18 who provided written informed consent to participate in the study.

Exclusion criteria:

- Previous PVI.
- Ischemic heart disease with untreated hemodynamically significant coronary artery stenosis.
- Valvular disease requiring surgical treatment.
- Chronic heart failure of NYHA functional class IV.
- Previous cardiac surgery.
- Refusal to participate in the study or continuation of participation.
- Presence of a thrombus in the left atrial appendage.
- Left atrial anterior-posterior size >55 mm.
- Left ventricular ejection fraction <35% according to Simpson's method.
- Any other condition that would prevent surgery (e.g., thyroid diseases, musculoskeletal trauma, decompensated pulmonary diseases, etc.).
- Maximum diameter of one of the pulmonary veins >26 mm based on multidetector computed tomography (MDCT) of the heart or venous system developmental anomalies.

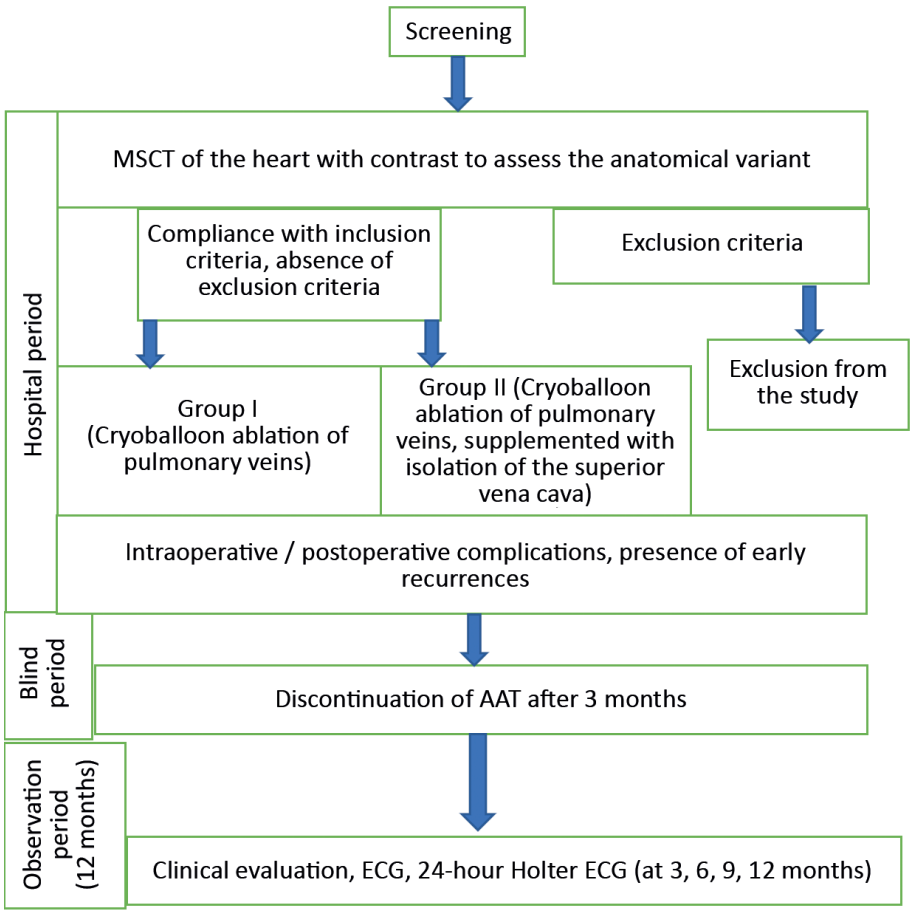

Fig. 1. Study Design.

The study included 40 patients, who were randomly divided into two groups: Group I (n=20) underwent cryoballoon PVI, and Group II (n=20) underwent cryoballoon pulmonary vein isolation supplemented with superior vena cava isolation. Randomization was performed using a random number generator in Excel (Microsoft, USA) with a 1:1 allocation. After cryoablation, all patients continued antiarrhythmic therapy for 3 months according to the current clinical guidelines. Class IC drugs were used for patients without structural heart disease, heart failure, or ischemic heart disease. For preventing AF recurrence in patients with ischemic heart disease but without structural damage, sotalol was prescribed. Amiodarone was

recommended for patients with structural heart damage, significant hypertrophy, heart failure, or ischemic heart disease. The observation period was 12 months, with follow-up visits at 3, 6, and 12 months after the catheter procedure. The procedure's efficacy was evaluated based on 12-lead ECG results and 24-hour ECG monitoring during in-person visits. Additional ECG recordings provided by patients, documenting the onset of arrhythmia symptoms, were also assessed. After the "blind period," at the first in-person visit, all patients discontinued antiarrhythmic therapy. A recurrence was defined as any documented episode of AF lasting more than 30 seconds. The study design is presented in Figure 1.

The average duration of AF history was 3.4±1.4 years. All patients were prescribed optimal antiarrhythmic and anticoagulant therapy with new oral anticoagulants during the outpatient stage. In the presented cohort of patients, 45% (18 patients) had ischemic heart disease, 100% (40 patients) had hypertension, and 40% (16 patients) had a history of acute cerebrovascular accidents or transient ischemic attacks.

All patients underwent a full preoperative protocol in accordance with the institution's internal orders, which included coronary angiography, transthoracic and transesophageal echocardiography on GE Vivid 7 Dimension and Philips iE33 equipment. If transesophageal echocardiography was not possible, cardiac and thoracic multislice CT with contrast enhancement was performed. Clinical-demographic characteristics of the patients are presented in Table 1.

Cryoballoon ablation was performed under local infiltrative anesthesia with a 5% levobupivacaine solution at the surgical access stage. Additional anesthesia during the ablation was achieved with intravenous infusion of fentanyl (5 μg/kg). Prior to starting the surgical procedure, all patients had an invasive arterial pressure monitoring system installed using radial access. Then, using the Seldinger method, both femoral veins were catheterized, and intracardiac catheters were placed: the right ventricle was accessed with the Polaris X catheter (Boston Scientific, USA), the right atrium with the Preface Multipurpose introducer (Biosense Webster, USA-Israel) with a Brockenbrough needle (Medtronic, USA), and the intracardiac ultrasound sensor AcuNav (Siemens, Germany) was also used. Heparinization was performed to achieve an activated clotting time of 300 seconds or more before performing the transseptal puncture.

The transseptal access was performed under intracardiac echocardiographic guidance. After the transseptal puncture, a guided FlexCath Advance (Medtronic, USA) was inserted into the left atrium via a guidewire, through which the cryoablation catheter ArcticFront Advance 28 mm (Medtronic, USA) was inserted. A diagnostic catheter Achieve (Medtronic, USA) was introduced through its lumen. To monitor electrophysiological parameters, the Biotoc Unity electrophysiological system (Biotoc, Russia) was used. Left vein occlusion by the balloon was confirmed by injecting the contrast agent Omnipaque (GE Healthcare, Ireland) into the lumen of the left vein distal to the balloon and with intracardiac ultrasound. Then, cryoablation was performed.

One application was performed for each left PV for 240 seconds, with temperatures ranging from -35°C to -60°C inclusive [15-18]. The isolation of the pulmonary veins was confirmed by the disappearance of electrical activity in the PV with the diagnostic Achieve catheter and the presence of bidirectional conduction block. If residual electrical activity was observed, additional ablation was performed with the same parameters. After isolating the left upper and left lower pulmonary veins, the Polaris X catheter was repositioned on the lateral wall of the superior vena cava to achieve stimulation of the phrenic nerve. With continuous stimulation, the right pulmonary veins were isolated using the previously described parameters. The ablation procedure was stopped when effective phrenic nerve stimulation episodes ceased or when the muscle response amplitude to stimulation decreased.

In the group of patients with additional intervention in the superior vena cava after achieving the criteria for isolation of the pulmonary veins, the FlexCath Advance delivery system was positioned in the right atrium. Electrically active areas at the mouth of the superior vena cava were diagnosed using the Achieve catheter. To achieve contact of the catheter with the walls of the superior vena cava, the FlexCath Advance was used, adjusting the angle of the distal tip to achieve the maximum expressed amplitude of the endogram of the superior vena cava on the diagnostic electrode. Under angiographic control, using the Achieve catheter as a guide, the cryoballoon was positioned at the mouth of the superior vena cava (Fig. 2).

After balloon inflation, complete occlusion was confirmed by injecting contrast medium, after which continuous stimulation of the phrenic nerve was performed with distal pairs of the diagnostic electrode, with an amplitude of

Table 1.

Clinical and demographic characteristics of patients

Indicators	All patients (n=40)	CBI PV (n=20)	CBI PV + SVC (n=20)	P
Age, years	67.8±6.5	67.7±3.9	68.1±3.7	0.364
Gender, male, n (%)	18 (45%)	8 (40%)	10 (50%)	0.525
Duration of AF, months	8.7±1.2	8.5±2.1	8.8±1.7	0.271
History of AIS, n (%)	16 (40%)	10 (50%)	6 (30%)	0.197
LVEF (Simpson Biplane), %	50.8±5.1	50.4±5.4	51.1±4.7	0.403
Anteroposterior size of LA, mm	45±4	44±5	45±4	0.737
CHA_2DS_2-VASc, points	2.7±1.5	3±1.2	2.5±2	0.607
HASBLED, points	2.6±1.6	2.8±1.7	2.5±1.8	0.445

Note: here and below, CBI - cryoballoon isolation; PV - pulmonary veins; SVC - superior vena cava; AIS - acute ischemic stroke; LVEF - left ventricular ejection fraction; LA - left atrium.

16 V and a stimulation frequency of 50 pulses per minute. The next stage involved cryoablation for 180 seconds with temperature parameters ranging from -25°C to -40°C [15-18]. If there were changes in the phrenic nerve response to stimulation, the cryoablation procedure was stopped. The criterion for SVC isolation was the disappearance of electrical activity on the diagnostic Achieve electrode (Fig. 3, 4), followed by confirmation of exit block. The entry block in real-time was achieved in 65% (14) of patients. The exit block was confirmed in 80% (16) of patients after cessation of the procedure, with stimulation from the Achieve and Polaris X catheters. All patients underwent transthoracic echocardiography before catheter removal to monitor the pericardial leaflets. In cases of persistent AF, ECG-synchronized cardioversion was performed.

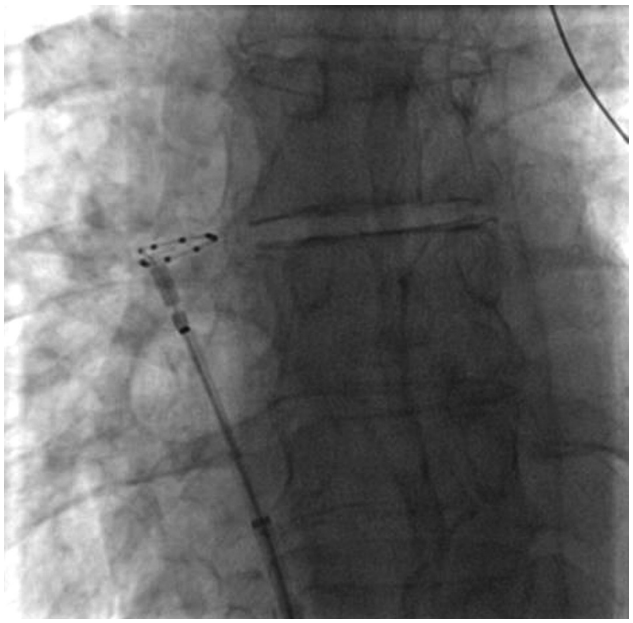

Fig. 2. Moment of cryoballoon inflation at the superior vena cava ostium.

Statistical analysis

Statistical data processing was performed using Statistica 12.0 (StatSoft, USA) and included descriptive statistics in the form of mean values of quantitative indicators, standard deviations, and absolute and percentage values of qualitative indicators. The normality of distribution was assessed through visual analysis of histograms and the Shapiro-Wilk test. To assess differences between groups, Student's t-test and χ^2 tests were used. Differences were considered statistically significant at a level of $p < 0.05$.

RESULTS

In the group of patients with classical PVI, one patient experienced a decrease in the amplitude of the diaphragmatic nerve response during cryoablation of the right inferior PV at the 90-second mark. After the procedure was stopped and a two-minute waiting period, the amplitude restored, the balloon was repositioned more anteriorly while maintaining the occlusion criteria, and a second 240-second ablation was performed. At the end of the procedure, isolation of all PVs was achieved, diaphragmatic nerve stimulation remained, and no radiological changes in the diaphragm dome position were noted.

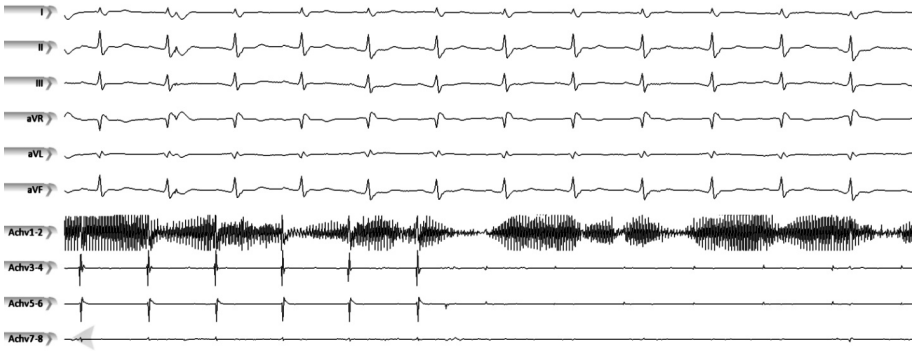

Fig. 3. Ablation during sinus rhythm. Onset of superior vena cava isolation - elimination of the muscle sleeve potentials at the superior vena cava, after which only low-amplitude atrial farfield potentials are recorded on the Achieve catheter.

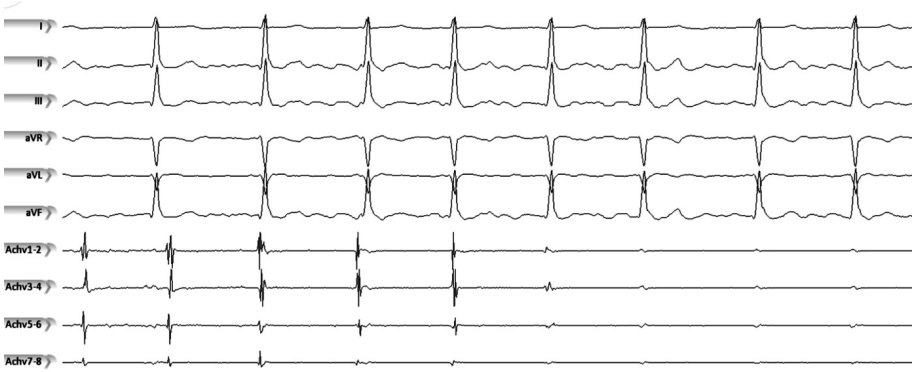

Fig. 4. Ablation during atrial fibrillation with already achieved superior vena cava isolation. Elimination of ectopic activity at the superior vena cava on the Achieve diagnostic catheter.

In the group of patients with extended PVI, during cryoablation in SVC, diaphragmatic nerve paresis symptoms were observed in 12 patients (60%), with the average time from the start of ablation being 65 ± 8 seconds. Further diaphragmatic nerve stimulation was ineffective in 10 (50%) patients. Radiography performed 25 hours after the ablation procedure showed no movement of the right diaphragm dome in 8 (40%) patients. During the hospital phase, 4 (20%) of them showed recovery of the diaphragmatic nerve function according to chest radiography, accompanied by complete regression of symptoms. Two patients were discharged without recovery of diaphragmatic nerve paresis in stable condition for dynamic monitoring. At the follow-up examination three months later, diaphragmatic nerve paresis regression was observed in one patient. In one patient, symptomatic diaphragmatic nerve paresis persisted for 6 months, after which it also regressed.

Thus, in the PVI group, no patient had sustained diaphragmatic nerve paresis, whereas in the extended ablation group, 8 (40%, P = 0.0016) patients had symptomatic paresis, leading to the early termination of the study. No cases of sinus node injury were recorded in either group. PV isolation was achieved in 100% of patients in both groups by the end of the procedure. Isolation of the SVC was achieved in 80% of cases (16 patients). The mean cryoablation time until the disappearance of electrical activity in the SVC was 44 ± 8 seconds. Intra-procedural efficacy and safety parameters are presented in Table 2.

The mean follow-up period was 354 ± 19 days. In the classical cryoballoon PV isolation group, after 12 months of observation without antiarrhythmic therapy, sinus rhythm was maintained in 40% of patients (8 people), and in the extended cryoballoon PV isolation group, sinus rhythm was maintained in the same proportion of patients (40%, P = 1). No long-term complications were registered at the end of the observation period.

DISCUSSION

The method of performing superior vena cava (SVC) isolation remains an open question. The use of second-generation cryoballoons allows for more uniform damage to the myocardial sleeves of the SVC with a lower probability of perforating the walls of the right atrium at the junction area, thanks to the larger area of simultaneous impact. In a study conducted by W. Hui-Qiang et al. (2020) involving 26 patients with paroxysmal AF associated with the SVC, isolation was achieved in 80% of cases using a second-generation cryoballoon. Transient diaphragmatic nerve damage was observed in 19.2% of cases, and sinus node injury occurred in 7.7% of cases [19]. Possible reasons for the differences in complication rates during the procedure compared to the global literature may be the anatomical features of the spatial arrangement of diaphragmatic nerve fibers and sinus node cells.

It should be noted that there are significant limitations to the aforementioned technology. To achieve SVC isolation, its occlusion is required, accompanied by pronounced symptoms of obstruction. To achieve circulatory transmural impact, the area of the diaphragmatic nerve is subjected to permanent contact, which is why its damage rate remains extremely high even in highly specialized centers. Moreover, continuous monitoring of the sinus node is required, as it is also localized near the impact zone. Radiofrequency energy allows for more precise interventions and helps avoid diaphragmatic nerve damage using stimulation mapping and its subsequent visualization on a three-dimensional model. Meanwhile, contact force-sensing catheters allow for stable, controlled contact with the tissue. The use of navigation systems offers the possibility of mapping the sinus node, as well as the morphological and electrophysiological assessment of myocardial sleeves' distribution in the SVC.

The C-shaped method of SVC isolation stands out, with the advantage of a smaller area of impact required to achieve isolation, as well as a reduced risk of complications such as stenosis of the SVC and damage to nearby structures [20]. A limitation of these methods is the documented cases of sinus branch damage to the right coronary artery during the use of radiofrequency energy [21].

Table 2.

Intraprocedural measures of efficacy and safety

Indicators	All patients (n=40)	CBI PV (n=20)	CBI PV + SVC (n=20)	P
Procedure duration, min	85±12	80±10	90±15	0.081
Fluoroscopy time, min	19±4	17±3	21±4	0.078
Absorbed dose, mGy	163±25	160±28	166±23	0.090
Confirmed isolation of SVC, n (%)	-	-	16 (80%)	-
All complications, n (%)	16 (40%)	2 (10%)	14 (70%)	0.0001
Phrenic nerve palsy, n (%)	12 (30%)	0 (0%)	12 (60%)	<0.0001
Sustained phrenic nerve palsy, n (%)	8 (20%)	0 (0%)	8 (40%)	0.0016
Hematomas at puncture site, n (%)	4 (10%)	2 (10%)	2 (10%)	1
Achieved activated clotting time, s	315±21	317±19	314±22	0.674
No. of cryoapplications in LSPV	1.25±0.1	1.2±0.1	1.3±0.1	0.608
No. of cryoapplications in LIPV	1.1±0.1	1.1±0.1	1.1±0.1	1
No. of cryoapplications in RSPV	1.1±0.1	1.1±0.1	1.1±0.1	1
No. of cryoapplications in RIPV	1.2±0.1	1.3±0.1	1.2±0.1	0.608
No. of cryoapplications in SVC	1.1±0.1	-	1.1±0.1	-
AD of cryoapplications in LSPV, s	260±15	250±10	270±15	0.334
AD of cryoapplications in LIPV, s	265±13	266±14	257±15	0.457
AD of cryoapplications in RSPV, s	251±10	252±11	250±10	0.898
AD of cryoapplications in RIPV, s	270±20	273±20	265±15	0.566
AD of cryoapplications in SVC, s	65±6	-	65±6	-

Note: AD - average duration.

According to the literature, the incidence of diaphragmatic nerve injury during SVC isolation using cryotechnology or radiofrequency energy is 2.1-9.2%. These rates are lower than those obtained in our study. However, it is worth noting that in a significant number of studies conducted by our colleagues, only permanent diaphragmatic nerve damage is considered. Transient diaphragmatic nerve damage, most often without pronounced symptoms of respiratory insufficiency, is not included in complications and is not considered in statistical data. Also, in comparison to literature data, the symptoms of transient diaphragmatic nerve damage are notable [19, 22].

An alternative method of SVC isolation may be the use of the rapidly developing pulse field technology, which is currently actively applied in PVI procedures. The main advantage of this method is selective tissue impact, which reduces the risks of damage to surrounding structures. High efficacy in using this method was noted in the study by P. Ollitrault et al. (2024) [23]. In their study, the procedure of PV isolation, supplemented by SVC isolation using pulse field energy, was performed in 105 patients. It was noted that in 80% of cases, the myocardial sleeves of the SVC exhibited electrical activity. SVC isolation was achieved in 100% of cases, and no permanent damage to the diaphragmatic nerve or sinus node was observed during the study.

The question of the impact of SVC isolation on the effectiveness of AF procedures remains open. A limiting factor of our study is the small number of observations. However, first, we were unable to recruit more patients because the safety indicators in the extended cryoablation group were so low that it forced us to terminate the study early. Secondly, despite this, a statistically significant difference was obtained even with such a small sample. Thus, currently, the routine performance of SVC isolation using cryoballoons carries extremely high risks of complications without a positive impact on procedure efficacy and should only be performed in patients with proven ectopic foci in this location. Using alternative methods of impact and careful monitoring of safety parameters would be more advisable.

CONCLUSION

In patients with persistent atrial fibrillation, cryoballoon pulmonary vein isolation supplemented by superior vena cava isolation is a less safe technique compared to standard cryoballoon pulmonary vein isolation, with the frequency of intraoperative complications in the extended ablation group reaching 40% (p=0.0016). No statistically significant differences in the procedural efficacy indicators were observed.

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HEMODYNAMIC SIGNIFICANCE OF VENTRICULAR ECTOPIC BEATS: THE IMPACT OF COUPLING INTERVALS

Yu.V.Shubik[1], A.B.Korneev[1], A.N.Morozov[2]

[1]Saint Petersburg State University, Russia, Saint Petersburg, 7-9 Universitetskaya emb.; [2]First Saint Petersburg State Medical University named after Academician I.P. Pavlov, Russia, Saint Petersburg, 6-8 L. Tolstoy str.

The aim of the study was to evaluate the effect the impact of the coupling interval (CI) of ventricular ectopic beats (VEB) on their hemodynamic properties.

Methods. The hemodynamic properties of VEBs were studied using the example of ventricular parasystoles with typical manifestations. The hemodynamic properties of VEB were studied using the example of ventricular parasystoles with typical manifestations (significant differences in CI, "multiplicity," presence of "fusion" QRS complexes) in two female patients without structural heart abnormalities, each having more than 10000 monomorphic VEB per day. The research method involved measuring blood pressure (BP) with each heartbeat. The duration of the study, over the course of which systolic BP (SBP), diastolic BP (DBP), and pulse BP (PBP) were recorded, was 15 minutes.

Results. The hemodynamic properties of VEB were determined by assessing the correlation between the duration of the CI and the SBP, DBP, and PBP of the VEB. The SBP, DBP, and PBP values showed a highly significant correlation with the CI of the VEB: the shorter the CI, the lower the SBP and PBP, and the higher the DBP. The DBP was more strongly dependent on the CI than the SBP, and the PBP was even more dependent. The relationship between the DBP and CI of the VEB was linear, whereas the relationship between the SBP and PBP with the CI of the VEB was nonlinear: it was more pronounced with short (decreased BP) and long CIs (increased BP). There was also a highly significant correlation between the PBP and SBP of the VEB, as well as between the PBP and DBP of the VEB: the PBP of the VEB was influenced by both the decrease in SBP and the increase in DBP, but more so by the decrease in SBP.

Conclusions. As the CI of VEB shortens, its SBP decreases and DBP increases. The relationship between DBP and CI is linear, whereas the relationships between SBP and PBP with CI are nonlinear: they are more pronounced with short (decreased BP) and long (increased BP) CIs. The PBP of VEB depends on both the decrease in SBP and the increase in DBP, but it is more strongly associated with SBP.

Key words: ventricular extrasystole; parasystole; coupling interval; arrhythmia-associated cardiomyopathy; "beat-to-beat" method; measurement of blood pressure at each heartbeat; hemodynamic effectiveness.

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Corresponding author: Yuri Shubik, E-mail: yshubik@mail.ru

Yu.V. Shubik - ORCID ID 0000-0002-8736-1575, A.B.Korneev - ORCID ID 0000-0002-0116-9591, A.N. Morozov - ORCID ID 0000-0003-2598-7000

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Ventricular premature beats (VPB) are one of the most commonly encountered arrhythmias, which can be detected in patients with cardiovascular and other diseases, as well as in healthy individuals. Their primary clinical significance is their ability to provoke life-threatening ventricular arrhythmias and, as a consequence, sudden cardiac death. This is especially relevant for patients with various organic heart diseases and genetically determined heart conditions, including channelopathies and cardiomyopathies. However, even in the absence of the aforementioned pathology, idiopathic VPBs, including frequent ones, are not rare. These VPBs are not associated with sudden cardiac death. However, like other arrhythmias, such as various supraventricular tachyarrhythmias, they have different clinical significance.

Firstly, these are the symptoms and decreased quality of life. Secondly, they have the potential to form cardiomyopathies associated with arrhythmia (CAA). In contrast to tachyarrhythmias, where CAA is due to the high heart rate and the duration of the rhythm disturbance, in the case of VPBs, CAA is primarily linked to the number of ventricular ectopies. According to literature, when the number of VPBs exceeds 20% of the total number of heartbeats in a 24-hour ECG monitoring period, it is strongly correlated with an increased chamber size and decreased heart pump function. However, while the number of VPBs is an extremely important factor in determining their hemodynamic significance, it is likely not the only one. A clinical case was previously presented

where a burden of ventricular ectopics exceeding 50% of heartbeats per day (including non-sustained and paroxysmal ventricular tachycardia) over 30 years of observation did not lead to the formation of CAA.

In the draft recommendations of the Ministry of Health of the Russian Federation for 2025 «Ventricular Arrhythmias. Sudden Cardiac Death,» it is indicated that the risk of developing CAA, in addition to the proportion of ectopic heartbeats, may be associated with the width of the ectopic QRS complexes. In several publications, alongside this characteristic, the possible significance of the morphology of QRS complexes, the index of premature beats, polymorphism, and several others are also discussed. However, the possible contribution of each of these characteristics to the hemodynamic incompetence of VPBs, which, in turn, leads to the formation of CAA, remains not fully understood.

It is not difficult to assume that the hemodynamic incompetence of premature heartbeats should be related to a decrease in systolic blood pressure (SBP) and an increase in diastolic blood pressure (DBP). The integral parameter – pulse blood pressure (PBP) – should decrease even further. It seems quite a complex task to evaluate the independent influence of each of the aforementioned characteristics on the hemodynamic properties of VPBs. The subject of this study was selected as a typical frequent monomorphic ventricular parasystole, where the only variable parameter was the coupling interval (CI). All VPBs were from a single source, with the same morphology (except for «fusion» beats) and QRS complex width. Thus, we had the opportunity to study the impact of the coupling interval on the hemodynamic characteristics of ectopic beats. To do this, the «beat-to-beat» blood pressure measurement method was used, which has been repeatedly described in previous studies. This method involves continuous registration of the volume of the finger arteries via a photoplethysmographic signal and a monitoring electro-pneumatic system that creates pressure, preventing changes in the diameter of the arteries under the cuff. At the same time, blood pressure is measured routinely on the other arm. The continuous blood pressure signal corresponds to Korotkoff sounds through the application of a special calculation formula. This method allows for the measurement of SBP and DBP during each individual heartbeat: both sinus and ectopic.

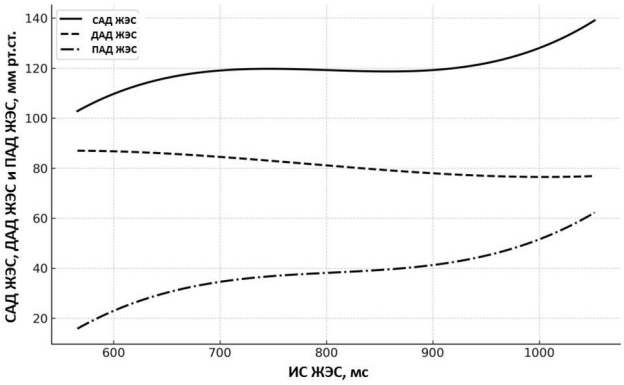

Fig. 1. Patient O. The relationship between SBP, DBP, and PBP of VPBs with the CI of VPBs.

The aim of the study was to assess the impact of the coupling interval of premature ventricular ectopic beats on their hemodynamic propertie.

METHODS

The clinical study adhered to Good Clinical Practice standards and the principles of the Helsinki Declaration and was approved by the local ethics committee of the cardiology clinic «North-West Center for the Diagnosis and Treatment of Arrhythmias» (Saint Petersburg, Russia). Written informed consent was obtained from the patients to participate in the study.

The hemodynamic properties of VPBs were studied using the example of clear (typical) ventricular parasystole (significant differences in CI, «multiplicity,» presence of «fusion» QRS complexes) in two female patients, each having more than 10,000 monomorphic VPBs according to Holter electrocardiogram monitoring. They did not have ventricular ectopic beats of other morphologies. Both patients showed no structural heart abnormalities according to echocardiographic data.

The primary method of the study involved measuring blood pressure («beat to beat») using the «Cardiotekhnika-SAKR» device (NAO «Inkart,» Saint Petersburg, Russia, patents for inventions N RU 2694737 C1, V.V. Pivovarov et al. and RU 2698447 C1, V.V. Pivovarov et al.). The duration of the study, during which SBP, DBP, and PBP were determined for sinus beats and VPBs at each heartbeat, was 15 minutes.

Statistical analysis

For statistical analysis, the SPSS software package was used. The means and standard errors of the mean (M±m) were calculated for each of the four variables (CI of VPB, SBP of VPB, DBP of VPB, and PBP of VPB). Pearson's correlation coefficient (r) was used to assess the linear relationship between two quantitative variables. To evaluate the influence of the independent variable (CI of VPB) on multiple dependent variables (SBP of VPB, DBP of VPB, and PBP of VPB), third-order polynomial regression (cubic regression) was employed. Multiple linear regression was used to assess the influence of multiple independent variables (SBP of VPB and DBP of VPB) on the dependent variable (PBP of VPB). A p-value of <0.05 was considered the threshold for statistical significance.

RESULTS

Patient O., 35 years old. The total number of VPBs during the 15-minute study was 256. The CI of VPBs ranged from 568 to 1052 ms (797.61±27.03 ms). The SBP of VPBs ranged from 93 to 144 mmHg (114.66±0.53 mmHg), DBP ranged from 67 to 96 mmHg (86.10±0.34 mmHg), and PBP ranged from 3 to 44 mmHg (34.63±2.10 mmHg). The SBP of sinus beats ranged from 111 to 129 mmHg (120.23±0.40 mmHg), DBP from 70 to 84 mmHg (78.18±0.31 mmHg), and PBP from 36 to 49 mmHg (42.04±0.26 mmHg). It is evident that VPBs are hemodynamically significant and significantly inferior in efficiency to sinus beats, manifested by a decrease in SBP and an increase in DBP. As an integral parameter, PBP naturally decreases.

The correlation between the hemodynamic properties of VPBs and their CI was determined by assessing the correlation between the CI duration of VPBs and SBP, DBP, and PBP of VPBs. It turned out that the values of SBP, DBP, and PBP of VPBs were closely and highly significantly correlated with the CI of VPBs: the shorter the CI, the lower the SBP and PBP, and the higher the DBP. The coefficients of correlation (r) were 0.78 for SBP, -0.85 for DBP, and 0.87 for PBP. Thus, according to the correlation coefficients, DBP depends on the CI more than SBP, and PBP, as a calculated integral parameter (the difference between SBP and DBP), depends on the CI to an even greater extent. All three correlations were highly significant ($p < 0.001$). The graphical representation of the correlation between SBP, DBP, and PBP of VPBs with CI of VPBs is shown in Figure 1.

From the graph, constructed using third-order polynomial regression (cubic regression), it is evident that the relationship between DBP of VPBs and CI is almost linear, whereas the relationships between SBP and PBP with CI of VPBs are nonlinear: they are more pronounced with short (decreased BP) and long (increased BP) CIs.

The analysis of the correlation between PBP and SBP of VPBs, as well as between PBP and DBP of VPBs, showed that there is a close and highly significant correlation in both cases: between PBP and SBP ($r = 0.98$, $p < 0.001$), and between PBP and DBP ($r = -0.70$, $p < 0.001$). Thus, PBP of VPBs depends both on the decrease in SBP of VPBs and the increase in DBP of VPBs, but more strongly on the decrease in SBP. This correlation is clearly demonstrated in Figure 2.

Patient E., 67 years old. The total number of VPBs during the 15-minute study was 72. The CI of VPBs ranged from 606 to 1156 ms (820.40±26.98 ms). The results obtained for Patient E. were similar to those for Patient O. The SBP of VPBs ranged from 85 to 133 mmHg (117.75±1.33 mmHg), DBP ranged from 79 to 99 mmHg (86.50±0.54 mmHg), and PBP ranged from 0 to 50 mmHg (31.06±1.60 mmHg). The SBP of sinus beats ranged from 123 to 140 mmHg (130.21±0.40 mmHg), DBP from 71 to 87 mmHg (78.07±0.35 mmHg), and PBP from 45 to 61 mmHg (52.14±0.37 mmHg). Thus, in this case, VPBs are also hemodynamically significant, manifested by a decrease in SBP and an increase in DBP. As with Patient O., PBP, as the difference between SBP and DBP, decreases significantly. Notably, these changes are more pronounced in this case.

The correlation between the hemodynamic properties of VPBs and their CI was determined by assessing the correlation between the CI duration of VPBs and SBP, DBP, and PBP of VPBs. It turned out that the values of SBP, DBP, and PBP of VPBs were closely and highly significantly correlated with the CI of VPBs: the shorter the CI, the lower the SBP and PBP, and the higher the DBP. The results for Patient E. followed the same patterns as for Patient O. However, the correlation between the CI duration of VPBs and SBP, DBP, and PBP was somewhat less tight. The coefficients of correlation (r) were 0.45 for SBP, -0.65 for DBP, and 0.76 for PBP. For Patient E., according to the correlation coefficients, DBP depends more on the CI than SBP, and PBP as an integral parameter depends even more. All three correlations were highly significant ($p < 0.001$). The graphical representation (graph constructed using third-order polynomial regression) showed that the relationship between SBP, DBP, and PBP of VPBs with CI of VPBs was identical to that of Patient O. Therefore, it is unnecessary to reproduce the figure. In this case, the relationship between DBP of VPBs and CI of VPBs is linear, and the relationship between SBP and PBP of VPBs with CI of VPBs is nonlinear, being more pronounced with CIs of 600-700 ms and 1100-1150 ms.

The analysis of the correlation between PBP and SBP of VPBs, as well as between PBP and DBP of VPBs, for Patient E. again showed a close and highly significant correlation: between PBP and SBP ($r = 0.85$, $p < 0.001$) and between PBP and DBP ($r = -0.40$, $p < 0.001$). Thus, as in Patient O., PBP of VPBs depends on both the decrease in SBP and the increase in DBP, but more so on the decrease in SBP.

DISCUSSION

The primary cause of CAA in patients with VPBs is commonly considered to be a high frequency of hemodynamically ineffective ectopic ventricular contractions. Much of the scientific literature focuses on the number of VPBs per day that can lead to heart chamber dilation and reduced pump function. However, considerably less attention is given to the characteristics of the VPBs themselves. According to a recent survey conducted by the EHRA among arrhythmologists, 72% of respondents consider the number of VPBs as an important factor in the development of CAA, while 44% mention the source of VPBs and 29% refer to the width of the QRS complex. Other characteristics are not mentioned [37].

As noted earlier, literature suggests that the hemodynamic significance of VPBs, in addition to the factors mentioned above, can also be related to features such as QRS complex fragmentation, morphology, CI, and polymorphism. However, the direct relationship of these features to the localization of the arrhythmogenic substrate is still unclear. Evaluating the contribution of each of these characteristics to the hemodynamic incompetence of VPBs is a complex task, as they are closely interconnected. For this study, we chose ventricular parasystole with its obvious features, such as varying CIs, «multiplicity,» and «fusion» ventricular contractions. The characteristics of this type of VPB imply the presence of only one variable: the CI. All other characteristics are constant. This allowed us

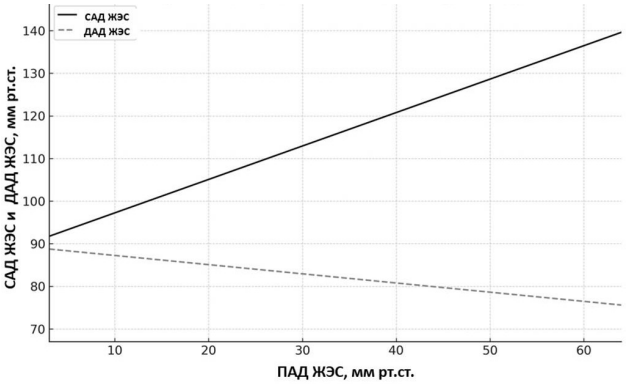

Fig. 2. Patient O. The relationship between PBP and SBP of VPBs, PBP and DBP of VPBs.

to assess the impact of the CI on the hemodynamic properties of VPBs.

For this purpose, we used the «beat to beat» method of blood pressure measurement. The study demonstrated that, as expected, there is a close, highly significant relationship between the CI of VPBs and their hemodynamic incompetence. Shortening of the CI leads to a decrease in SBP and an increase in DBP for VPBs. Comparison of the correlation coefficients showed that DBP depends more on the CI than SBP. At the same time, it was found that the relationship between DBP and CI of VPBs is almost linear, whereas the relationship between SBP and CI is nonlinear: it is more pronounced with short CIs (decreased SBP) and long CIs (increased SBP). The integral parameter, pulse blood pressure (PBP), was strongly associated with both decreased SBP and increased DBP, but, according to the correlation coefficients, it is more strongly correlated with SBP. The relationship between PBP and CI is similarly nonlinear.

It is important to note that this study is a pilot study, based on the analysis of VPBs from just two patients. One limitation of the study is the wide range of CIs for VPBs, which ranged from approximately 570 to 1160 ms. However, as is well known, the CI of VPBs typically falls within the range of approximately 500-600 ms.

CONCLUSION

The findings of the study can be summarized in the following conclusions: as the CI of ventricular premature beats shortens, its systolic blood pressure decreases, and its diastolic blood pressure increases. Moreover, DBP is more strongly correlated with the CI than SBP. The relationship between DBP and CI of VPBs is linear, whereas the relationship between SBP and CI is nonlinear. This relationship is more pronounced at shorter CIs (resulting in decreased blood pressure) and at longer CIs (leading to increased blood pressure). Pulse blood pressure of VPBs depends on both the decrease in SBP and the increase in DBP. However, it is more strongly correlated with SBP. The relationship between PBP and CI is nonlinear, similar to the relationship between SBP and CI.

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SUPPRESSION BY FLECAINIDE OF PREMATURE VENTRICULAR CONTRACTIONS REFRACTORY TO CATHETER ABLATION AND OTHER ANTIARRHYTHMIC DRUGS: A CASE REPORT

Yu.G.Shchukina, E.I.Condori Leandro, D.S.Lebedev, E.N.Mikhaylov

FSBI "V.A.Almazov National Medical Research Center" of the MH RF, Russia, Saint Petersburg, 2 Akkuratova str.

We describe suppression of frequent premature ventricular contractions from the papillary muscle by flecainide in a patient with a history of reversible cardiomyopathy associated with arrhythmia and ineffective antiarrhythmic therapy with other IC and III class drugs, as well as refractory to repeated catheter ablation.

Key words: premature ventricular beats; flecainide; IC class of antiarrhythmics; left ventricle; papillary muscles

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Corresponding author: Yulia Shchukina, E-mail: shchjulia@gmail.com

Yu.G.Shchukina - ORCID ID 0000-0001-7891-4708, E.I.Condori Leandro - ORCID ID 0000-0003-3246-5948, D.S.Lebedev - ORCID ID 0000-0002-2334-1663, E.N.Mikhaylov - ORCID ID 0000-0002-6553-9141

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Premature Ventricular Contractions (PVCs) are a common form of arrhythmia, which can also occur in the absence of structural heart disease. Besides symptoms such as irregular heartbeats, weakness, and dizziness, frequent PVCs can lead to a reduction in the systolic function of the left ventricle, resulting in reversible cardiomyopathy associated with arrhythmia (CAA).

The most common location for ectopic foci in PVCs is the outflow tract of the right and left ventricles [1]. Other possible sites include the sinus of Valsalva, the mitral or tricuspid valve rings, papillary muscles, the basal section of the antero-septal zone of the left ventricle (summit of the left ventricle), epicardial foci near the heart vessels (both venous and arterial), and some other regions [2].

Treatment of PVCs can be pharmacological, catheter ablation, or a combination of both. Catheter ablation is recommended as the first-line treatment for arrhythmia originating from the right ventricular outflow tract. In other cases, an attempt at pharmacological therapy is recommended initially. Pharmacological therapy for idiopathic PVCs is limited and consists of beta-blockers, calcium channel blockers, some IC and III class antiarrhythmic drugs, requiring individualized selection based on multiple factors [7, 8]. The efficacy of catheter ablation is up to 84% and depends on the location of the ectopic focus. For example, the basal section of the antero-septal zone of the left ventricle (summit) and papillary muscles are more challenging areas for endovascular intervention and have the lowest ablation success rates [3-6, 9]. Papillary muscles are movable structures with thick myocardium at their base, which prevents both stabilization of the ablation catheter when the arrhythmia focus is near the apex of the muscle and effective radiofrequency ablation when the focus is located at the base of the muscle.

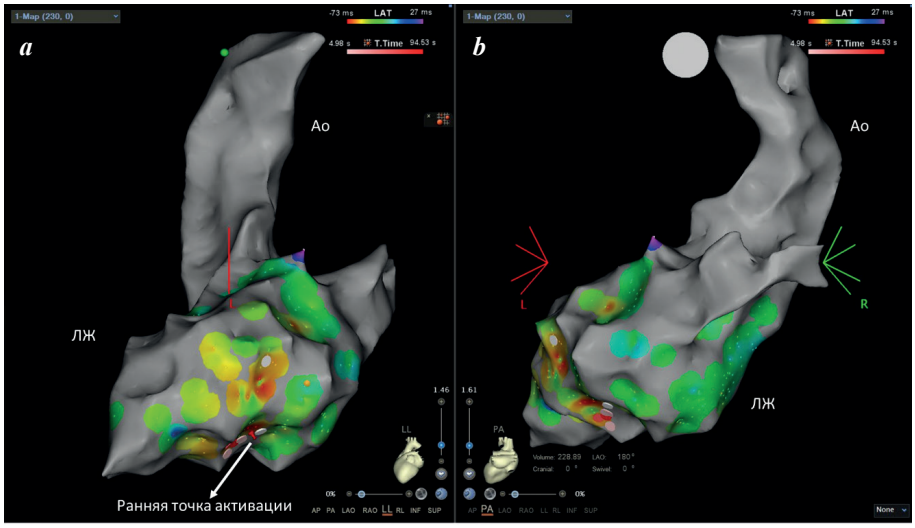

Fig. 1. Three-dimensional reconstruction and activation mapping of the left ventricle (CARTO 3 system, Biosense Webster, USA): a - left ventricle (LV) in the left lateral projection (LL), with the earliest activation point (base of the posterior-medial papillary muscle) marked by a white arrow; b - LV in the posterior-anterior projection (PA).

The aim of this case presentation is to demonstrate the effective suppression of frequent PVCs originating from the papillary muscle of the mitral valve apparatus in a patient who had previously failed antiarrhythmic therapy and multiple catheter ablations.

A 64-year-old patient with no comorbidities presented to a cardiologist in September 2022 with complaints of shortness of breath, irregular heartbeats, and decreased tolerance to routine physical activities. The examination revealed frequent monomorphic PVCs (over 20,000 per day). There was no effect from therapy with beta-blockers and sotalol. Echocardiography showed preserved left ventricular ejection fraction, no local contractility disturbances, and no valve or structural pathology. Coronary angiography showed no atherosclerotic changes in the arteries. Cardiac magnetic resonance imaging indicated an ejection fraction of 65%, normal heart chamber sizes, no local contractility disturbances, and no fibrotic changes.

The patient underwent catheter ablation of the left ventricular ectopic substrate three times using non-fluoroscopic navigation (CARTO 3 (Biosense Webster, USA) and RHYTHMIA HDx (Boston Scientific, USA)) in 2022 and 2023 (Fig. 1). The arrhythmia focus was mapped at the base of the posteromedial papillary muscle of the mitral valve apparatus. Multiple radiofrequency applications (35-40 W, irrigation at 30 ml/min) resulted in transient reduction of PVCs. Due to the inefficacy of ablation, attempts at pharmacological therapy continued with propafenone (150 mg twice daily). However, over the next four months, there was worsening exercise tolerance and increased shortness of breath. On follow-up examination, the patient experienced 35,000 PVCs per day with paroxysms of non-sustained ventricular tachycardia (Fig. 2), a reduced left ventricular ejection fraction of 44%, and left ventricular dilation. Following combined therapy with amiodarone and metoprolol succinate, the number of PVCs decreased to 1,079 per day, with clinical improvement and restored myocardial contractility. Thus, the patient experienced development of CAA with restored myocardial contractility following a reduction in PVCs.

However, after six months, the patient reported gradual progression of shortness of breath, even with minimal exertion. A subsequent ECG monitoring after 11 months showed 46,000 PVCs per day. At this time, the left ventricular systolic function remained normal.

After a medical board assessment of potential risks and benefits, therapy with flecainide (50 mg twice daily) combined with metoprolol succinate (25 mg twice daily) was initiated. The therapy was monitored via an ECG device (Fig. 3a). Upon increasing the flecainide dose to 100

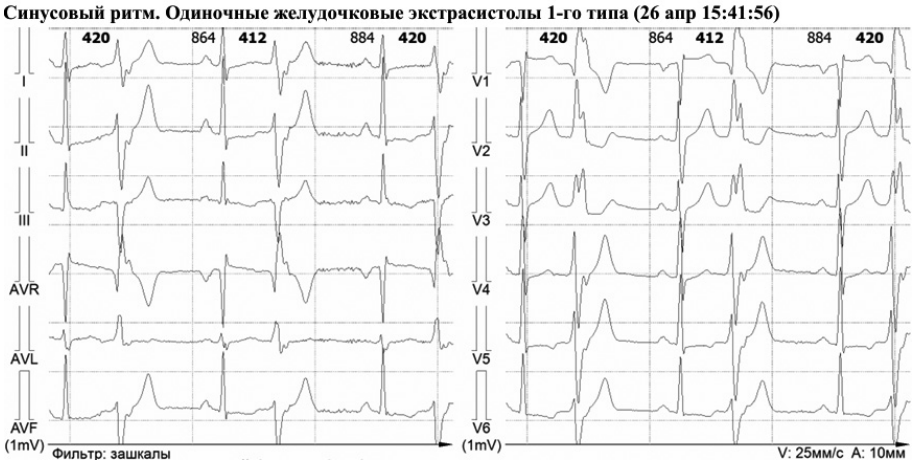

Fig. 2. Fragment of the 24-hour ECG monitoring from 26.04.2023 (analyzator "Cardiotekhnika-07-3/12", INKART, Saint Petersburg, Russia) 25 mm/s, 1 mV/cm - monomorphic ventricular premature beat (PVC) of the bigeminy type.

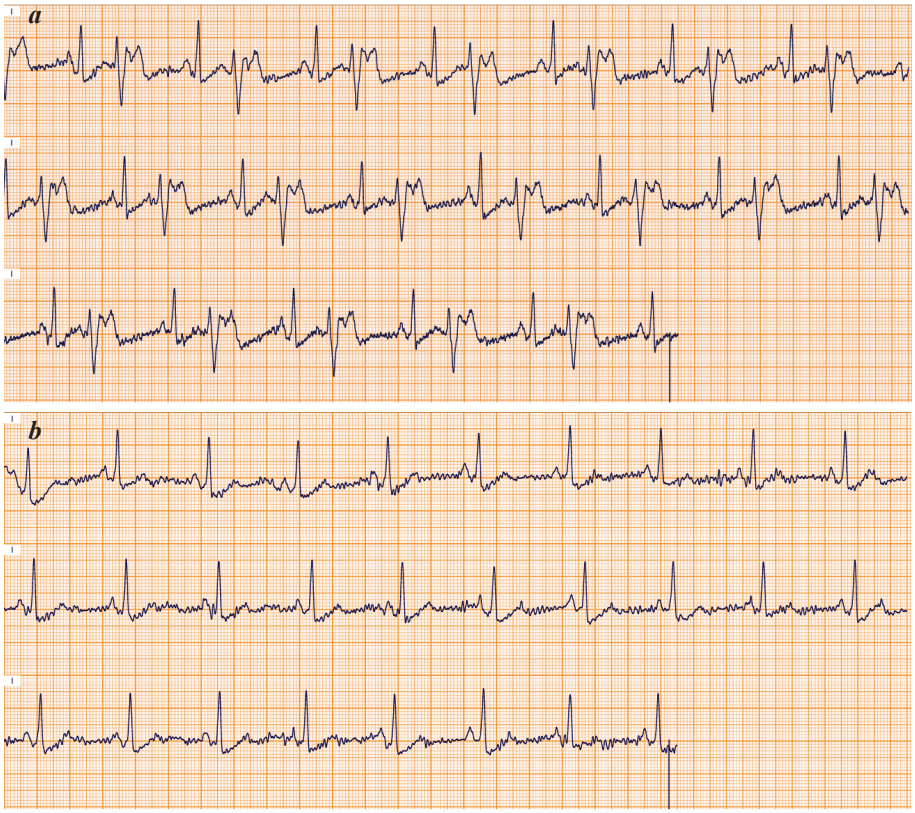

Fig. 3. Self-registration of ECG by the patient using a portable recorder (cardiorhythm indicator single-channel sound "IKRZ-1" Serdyechko, Bioss, Moscow, Russia) 25 mm/s, 20 mm/mV, lead I: a - 28.08.2024, sinus rhythm with HR 76 bpm, single ventricular premature beat of the bigeminy type; b - 29.08.2024, sinus rhythm with HR 54 bpm.

mg twice daily, there was complete suppression of PVCs, confirmed by multiple recordings from the ECG monitor (Fig. 3b) and 24-hour Holter monitoring.

Three months later, the patient independently reduced the flecainide dose to 50 mg twice daily, without adjusting the beta-blocker dose. A 24-hour Holter monitoring on November 21, 2024, showed sustained antiarrhythmic effect (Table 1). The total duration of therapy with flecainide was 5 months.

DISCUSSION

The main results of the presented clinical case are as follows: (1) effective suppression of PVCs with flecainide in a patient with arrhythmia originating from the papillary muscle, refractory to multiple catheter ablations and treatment with other antiarrhythmic drugs of classes III and IC; (2) the effectiveness of a low dose of flecainide in the long-term period, despite its initial inadequacy (the starting dose of flecainide, 50 mg twice a day, had no significant effect, while increasing the dose to 100 mg twice a day completely eliminated PVCs). Further reduction of the dose to the original level did not lead to arrhythmia recurrence.

Flecainide received registration certification in April 2024 and is not included in the Russian clinical guidelines for the treatment of ventricular arrhythmias (2020). According to the official instructions for the drug, flecainide is indicated for patients with documented life-threatening ventricular arrhythmias, such as ventricular tachycardia. At the same time, it is contraindicated for patients with asymptomatic and non-life-threatening ventricular arrhythmias. It is important to note that there is no scientific data limiting the use of flecainide for the treatment of clinically significant PVCs in patients with no structural heart pathology and preserved left ventricular function [10-14].

According to the 2022 clinical guidelines of the European Society of Cardiology for the management of patients with ventricular arrhythmias and prevention of sudden cardiac death, flecainide may be used to treat idiopathic PVCs and tachycardia. It is also recommended to consider flecainide therapy when catheter ablation of the arrhythmia substrate is impossible or carries high risks, including in cases of left ventricular fascicular arrhythmias [15].

This drug may also serve as an alternative treatment in cases where catheter ablation of complex ectopic focus locations, such as papillary muscles, is difficult.

Given the risks of side effects from flecainide, such as widening the QRS complex, prolongation of the PR interval on ECG, and bradycardia, it is advisable to use portable ECG monitors for safety and to assess the effectiveness of therapy. This allows for daily monitoring of the ECG recorded by the patient and timely adjustment of medication doses.

According to the manufacturer's guidelines, for ventricular arrhythmias, the starting dose is 200 mg per day, with a maximum allowable dose of 400 mg per day. It is also possible to reduce the dose to an acceptable low level, at which rhythm disturbances are controlled. The question remains regarding the possibility of taking a 100 mg per day dose, which proved effective in the patient in this clinical case.

Table 1.

The dynamics of the change in the number of PVCs according to the daily ECG monitoring data

Date	Therapy (mg per day)	PVC	LVEF, %
11.2022	Bisoprolol (5) / sotalol (180)	>20000	65
Ablation 1			
11.2022	Propafenone (300)	35501	44
Ablation 2			
Ablation 3			
09.2023	No AAT	25078	44
09.2023	Amiodarone (200), metoprolol (50)	1079	61
08.2024		46946	63
09.2024	Flecainide (200), Metoprolol (50)	1	65
11.2024	Flecainide (100), Metoprolol (50)	72	64

Notes: PVC - premature ventricular contraction, AAT - antiarrhythmic therapy, LVEF - left ventricular ejection fraction.

CONCLUSION

The presented clinical case demonstrates the successful use of flecainide for the suppression of PVCs originating from the papillary muscle in a patient without structural heart pathology and with no effect from multiple catheter ablations of the ectopic focus and the use of other antiarrhythmic drugs.

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https://doi.org/10.35336/VA-1436

CLINICAL SIGNIFICANCE OF PREMATURE ATRIAL CONTRACTIONS AND APPROACHES TO ITS TREATMENT

A.M.Baimukanov[1], E.I.Kotlyarevskaya[2], A.V.Melekhov[2], G.E.Gendlin[2]

[1]State Budgetary Healthcare Institution "V.M.Buyanov City Clinical Hospital of the Moscow City Health Department, Russia, Moscow, 26 Bakinskaya str.; [2]FSAEI HE "N.I.Pirogov Russian National Research Medical University" of the MH RF, Russia, Moscow, 1 Ostrovityanova str.

Supraventricular premature beats (PACs) are common in the general population. Previously considered a benign ECG finding with little clinical significance. However, increasing evidence now suggests a positive correlation between the frequency of PACs and the risk of developing atrial fibrillation, ischemic stroke, transient ischemic attack, and all-cause mortality. This has highlighted the importance of determining the clinical significance of PACs and the management strategies for affected patients.

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Corresponding author: Kotlyarevskaya Elizaveta, E-mail: doctor.liza999@gmail.com

A.M.Baimukanov - ORCID 0000-0003-0438-8981, E.I.Kotlyarevskaya - ORCID ID 0009-0003-2918-9804, A.V.Melekhov - ORCID ID 0000-0002-1637-2402, G.E.Gendlin - ORCID ID 0000-0002-7846-1611.

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Premature atrial contractions (PACs) are premature electrical activations of the heart (relative to the sinus rhythm), caused by impulses originating in the atria, pulmonary veins, or the atrioventricular junction. PACs can be single or paired, as well as exhibit an allorhythmia pattern (bi-, tri-, quadrigeminy).

PACs are one of the most common arrhythmias in clinical practice and can be found in individuals of all ages. According to D. Conen et al. (2012), among patients over 50 years of age, the detection rate of PACs during 24-hour Holter monitoring reached 99% [1]. According to domestic researchers, the prevalence of PACs in men and women over the age of 20 was 92.1% and 90.8%, respectively, reaching 100% in men and 94% in women in the group over 60 years of age [2]. In a study by V.M. Tikhonenko et al. (2018), heart rhythm and conduction disorders were recorded in most healthy individuals (97%), with ventricular arrhythmias in 59% and supraventricular arrhythmias in the majority (92.5%) [3].

The development of PACs is associated with various risk factors, such as age [1], ischemic heart disease [4], obstructive sleep apnea syndrome [5], heart failure, structural heart diseases, physical activity, dyslipidemia, and chronic obstructive pulmonary disease [6].

Previously, PACs were considered a benign ECG finding with little clinical significance. However, increasing data point to a positive relationship between the frequency of PACs and the risk of atrial fibrillation (AF), ischemic stroke, transient ischemic attacks, and overall mortality [7-9].

Several explanations have been proposed for the relationship between PACs, AF, and adverse outcomes, primarily with stroke. The presence of frequent PACs identifies patients at high risk of developing AF in the future, which leads to an increased risk of stroke and death. Another explanation suggests that frequent PACs are a marker of subclinical atrial cardiomyopathy, which may contribute to both the development of AF and the increased risk of stroke [7, 9-12]. Convincing evidence for this hypothesis has been provided by genetic studies demonstrating a connection between mutations in specific genes and the development of AF [13, 14].

According to the EHRA/HRS/APHRS/SOLAECE consensus, atrial cardiomyopathy is defined as any combination of structural, contractile, or electrophysiological changes affecting the atria and potentially causing clinically significant manifestations [10].

Among the structural changes, authors note hypertrophy of cardiomyocytes, atrial fibrosis (interstitial, perivascular), and infiltration by adipose tissue or amyloid deposits. These changes can be caused by long-term pressure or volume overload, such as in hypertension, heart failure, or valvular disease. It is important to note that the atria are more sensitive to pathological changes than the ventricles, and these processes often begin earlier and manifest more strongly.

Architectural changes involve alterations in the cellular structure of the atria. These include disruptions in the arrangement of muscle fibers and the formation of ab-

normal intercellular connections, leading to asynchronous contractions and impaired electrical conductivity. For example, the redistribution of myofibrils and damage to intercellular connections create conditions for the development of micro re-entry, contributing to AF.

Contractile changes include a reduction in the ability of the atria to contract effectively. This occurs due to the loss of normal architectural structure and the accumulation of fibrous tissue, which reduces myocardial contractility.

Electrophysiological changes include slowed conduction, decreased refractoriness, and heterogeneity in the electrical activity of the atria. These occur due to alterations in ion balance, dysfunction of sodium, potassium, and calcium channels, as well as increased oxidative stress and inflammation.

The key primary factors for changes in the atria are chronic increases in filling pressures, aging, obesity, and comorbidities such as hypertension, ischemic heart disease, and diabetes. These factors trigger a chain of pathological processes, starting from increased stress on the atria and culminating in remodeling and the development of arrhythmias.

Currently, there are no clinical guidelines on the management of patients with PACs, either domestic or international. Unresolved questions include: what is considered "frequent" or clinically significant PACs, how to assess the risk of developing AF, stroke, and mortality in patients with PACs, what are the indications for prescribing anticoagulants, antiarrhythmic drugs, and/or interventional treatments, how benign is the asymptomatic course of PACs, and does the treatment of patients with high PAC burden with antiarrhythmic drugs or catheter ablation reduce the risk of developing AF, stroke, and mortality?

METHODS

In the PubMed database, 51 publications were selected using a search strategy based on the following keywords: supraventricular premature beats, atrial fibrillation, stroke, transient ischemic attack. An additional manual search was also conducted using references from articles identified as relevant. No date restrictions were applied. Articles not available in English and Russian were excluded. Furthermore, reference lists were manually checked for other suitable studies.

RESULTS

What Defines Frequent PACs? Risks Associated with PACs

Currently, there is no established threshold for the frequency of premature atrial beats (PACs) that determines an increased risk of AF and other cardiovascular outcomes. Additionally, a precise definition of excessive supraventricular ectopic activity (ESVEA) is lacking. In most studies on PACs/ESVEA and their cardiovascular outcomes, the most common screening method is 24- or 48-hour Holter monitoring (Holter monitoring). Although routine 12-lead ECGs, 15-second ECGs, 2-minute ECGs, and loop recorders are also used, Holter monitoring is considered the most reliable method for determining the burden of PACs and predicting cardiovascular outcomes.

The definition of frequent PACs varies among different authors and is not solely based on the frequency of PACs but also on their clinical significance, i.e., the association with patient prognosis. K. Sasaki et al. (2021) defined frequent PACs as >0.4% of heartbeats per day, which was independently associated with the development of AF (odds ratio (OR) = 5.28; 95% confidence interval (CI): 1.28-26.11; p = 0.023).

N. Prasitlumkum et al. (2018) proposed a cut-off of 100 PACs per day for patients with symptoms (palpitations, syncope, dizziness). This criterion was based on the results of a study by T. Acharya et al. (2015), where a value of >100 beats/day had a sensitivity of 77.8% and specificity of 75.8% for predicting the development of AF in this patient group.

B. Chong et al. (2012), in a study of 428 patients with complaints of palpitations, dizziness, and syncope, showed that a threshold of >100 PACs per day was an independent predictor of the development of AF, ischemic stroke, congestive heart failure, and death during 6.1 years of follow-up.

According to S. Suzuki et al. (2013), in patients with frequent PACs, the development of AF was associated with the presence of additional negative factors: the risk of its occurrence was approximately 10 times higher in patients with >102 PACs per day and at least 2 points on the $CHADS_2$ score compared to those with <102 PACs per day and less than 2 points on the $CHADS_2$ score. Additionally, patients with high-frequency PACs (>102 per day) had a significantly higher prevalence of hypertension (39.9% vs. 25.4%, $p < 0.001$) and chronic kidney disease (17.3% vs. 8.5%, $p < 0.001$) compared to the low-frequency group. Furthermore, patients with frequent PACs had more pronounced structural heart changes, such as increased left atrial size (mean diameter 35.4±6.7 mm vs. 33.4±5.7 mm in the low-frequency group, $p < 0.001$). However, the left ventricular ejection fraction (LVEF) was similar in both groups: 66.5±9.7% vs. 65.8±9.1%, respectively. 15.6% of patients with frequent PACs had ≥2 points on the $CHADS_2$ score, whereas only 6.6% of patients in the low-frequency PAC group had this ($p < 0.001$).

Other authors have defined frequent ectopic beats as >30 PACs per hour, which is equivalent to >720 PACs per day. The presence of more than 30 PACs per hour in apparently healthy individuals was associated with the development of AF. Given this, it becomes relevant to determine the threshold value for the number of PACs to assess the risk of AF development and prognosis in different patient groups.

In the study by V.M. Tikhonenko et al., it was concluded that for healthy individuals, single, paired, and group PACs up to 50 per day (up to 2 per hour) can be considered «normal.» However, five or more consecutive PACs or a frequency of 500 or more PACs per day (20 or more per hour) are considered «abnormal» and not «normal» for healthy individuals [3].

In the consensus document by D. Arnar et al. (2019) [11], a high burden of PACs was defined as more than 500 PACs per day. This choice was based on the EMBRACE study, which included 287 patients aged over 55 years with a history of cryptogenic stroke or TIA and without AF. The

average age of the patients was 72.2±8.6 years, 46% of whom were women, and 71% had hypertension, with 16% having experienced a prior stroke. The mean $CHADS_2$ score was 3 (range 3-4). According to this study, the predicted probability of AF was 7-9% in patients with <100 PACs per 24 hours, 9-24% in those with 100-499 PACs, 25-37% in those with 500-999 PACs, 37-40% in those with 1000-1499 PACs, and plateaued at approximately 40% in those with ≥1500 PACs per day [22].

Based on the results of the EMBRACE study and possible mechanisms linking PACs with AF, stroke, and mortality, D. Arnar et al. (2019) proposed the following:
1. Patients with a high burden of PACs (>500 PACs per 24 hours as determined by Holter monitoring) should be considered at increased risk for developing AF. These patients should be informed about the symptoms of AF and referred for further investigation, including more detailed or extended rhythm monitoring. In some cases, structural heart disease should be evaluated, such as with transthoracic echocardiography or magnetic resonance imaging.
2. Patients with a high burden of PACs should undergo comprehensive modification of cardiovascular risk factors.
3. Short episodes of AF and a higher burden of PACs (>500 PACs per 24 hours or any episode of >20 PACs) can influence the decision to start anticoagulation therapy.
4. Low and moderate PAC burdens without documented AF do not indicate the need for oral anticoagulants.

It is important to note that the EMBRACE study investigated the role of frequent PACs in predicting AF in patients with cryptogenic stroke, which could have been caused by subclinical episodes of AF. Therefore, the prognostic role of the threshold of >500 PACs per day has been proven only for patients who have had cryptogenic stroke. It is unclear whether this threshold is applicable to patients with PACs who do not have a history of stroke, AF, or other known risk factors for cerebrovascular events, where the increased risk of stroke may be directly related to atrial cardiomyopathy.

In the study by Z. Binici et al. (2010), the association between PACs and various outcomes, such as the development of AF, stroke, and death, was investigated using data from the Copenhagen Holter Study. The study included 678 participants aged 55-75 years without a history of cardiovascular disease, stroke, or AF. According to the results of 48-hour Holter monitoring monitoring, patients were divided into two groups: 99 patients (14.6%) with excessive supraventricular ectopic activity (ESVEA ≥30 PACs per hour or episodes with ≥20 PACs) and 579 patients (85.4%) without ESVEA. It should be noted that, at baseline, the groups were comparable in terms of gender, body mass index, alcohol consumption, smoking frequency, low physical activity, and the prevalence of diabetes. However, patients with ESVEA had significantly higher age (67.6 vs. 63.9 years, p<0.0001), systolic (162 vs. 155 mmHg, p=0.009) and diastolic (92 vs. 91 mmHg, p=0.016) blood pressure, and NT-proBNP levels (12.4 (5.5-25.7) vs. 6.3 (3.3-12.3) pmol/L).

Over 6.3 years of follow-up, 27 strokes were recorded, with 10 cases (18.8%) occurring in the ESVEA group and 17 cases (4.9%) in the non-ESVEA group (OR 3.88, 95% CI 1.78-8.48, p=0.0007; after adjusting for sex and age, OR 2.79, 95% CI 1.23-6.30, p=0.014; after adjusting for other risk factors—smoking, diabetes, systolic blood pressure, and body mass index, OR 2.37, 95% CI 1.02-5.50, p=0.044).

AF was statistically significantly more common in the ESVEA group (OR 3.19, 95% CI 1.30-7.86, p=0.011; after adjusting for sex and age, OR 2.73, 95% CI 1.07-6.96, p=0.035; adjusting for other risk factors did not change the result). Moreover, frequent PACs were associated with higher overall mortality (OR 2.12, 95% CI 1.30-3.47, p=0.003); however, after adjusting for other risk factors, this relationship lost statistical significance. Thus, in patients without diagnosed cardiovascular pathology, a connection was observed between frequent PACs and an increased risk of stroke and the development of AF [23].

A longer follow-up (15 years) of patients from the Copenhagen Holter Study confirmed the clinical significance of PACs. Frequent ectopic activity was associated with a twofold increase in stroke risk. However, less than 15% of patients with frequent PACs and a subsequent stroke had previously been diagnosed with AF. Moreover, the annual stroke risk in patients with excessive atrial ectopic activity combined with a CHA_2DS_2-VASc score >2 was 2.4% per year, which is within the same range as patients with AF and a CHA_2DS_2-VASc >2. This supports the view that PACs may be a potential surrogate marker for AF [24].

Currently, there are four meta-analyses dedicated to frequent PACs and their association with adverse outcomes such as AF, stroke, and all-cause mortality. In the meta-analysis conducted by L. Meng et al. (2020), frequent PACs were defined as >30 PACs per hour and/or any tachycardia with ≥20 PACs per day. The combined analysis showed that frequent PACs doubled the risk of AF (OR 2.19, 95% CI 1.70-2.82) and stroke (OR 2.23, 95% CI 1.24-4.02). Frequent PACs were also associated with higher all-cause mortality (OR 1.61, 95% CI 1.25-2.07) [9].

Another systematic review conducted by J. Himmelreich et al. (2019) did not identify a threshold value for defining frequent PACs due to the high heterogeneity of the included studies. However, it showed that frequent PACs doubled the risk of AF (OR 2.96, 95% CI 2.33-3.76), stroke (OR 2.54, 95% CI 1.68-3.83), and all-cause mortality (OR 2.14, 95% CI 1.94-2.37) [8].

In the meta-analysis by B. Huang et al. (2017), frequent PACs were shown to be associated with an increased risk of stroke (unadjusted OR 2.20, 95% CI: 1.79-2.70; adjusted OR 1.41, 95% CI: 1.25-1.60) and all-cause mortality (unadjusted OR 2.17, 95% CI: 1.80-2.63; adjusted OR 1.26, 95% CI: 1.13-1.41) [7].

M. Yang et al. (2022) demonstrated that frequent PACs are associated with an increased risk of developing AF (OR 2.57, 95% CI 2.16-3.05), a higher risk of developing AF in patients with ischemic stroke (OR 2.91, 95% CI 1.80-4.69), and all-cause mortality (OR 1.41, 95% CI 1.24-1.59) [25].

Thus, the presence of frequent PACs identifies patients prone to developing AF, which increases the risk of stroke and mortality. Another important result of these observations is that frequent PACs may be an independent marker of subclinical atrial cardiomyopathy, which contributes to both the development of AF and the increased

risk of stroke [23, 24]. This «atrial cardiomyopathy» hypothesis suggests that the development of AF and PACs is an epiphenomenon, unrelated causally to the cardiomyopathy and stroke [11].

In patients with cryptogenic stroke without AF, PACs are considered a possible cause of cardioembolism. K. Todo et al. (2009) retrospectively studied patients with ischemic stroke, including 163 with non-cardioembolic stroke (group A), 24 patients with stroke of unknown etiology (group B), and 37 patients with cardioembolic stroke and previously diagnosed paroxysmal AF but in sinus rhythm (group C). The frequency of PACs was significantly higher in groups B and C compared to group A. Moreover, more than half of the patients with cryptogenic stroke had frequent PACs (≥200 per day). The authors suggest that frequent PACs should be considered as a masked form of paroxysmal AF and should be included among the causes of cardioembolic stroke [26].

In the study by Y. Shimada et al. (2024), the relationship between PAC frequency and the detection of AF in patients with cryptogenic stroke was examined. Among 381 patients with cryptogenic stroke who had a loop recorder implanted, 227 patients (59.6%) had hypertension, and 82 patients (21.5%) had diabetes. The patients were divided into three groups based on the number of PACs on 24-hour Holter monitoring: ≤200 (group L), 200-500 (group M), and >500 (group H). The frequency of hypertension and diabetes in the groups was 56.7% and 22.0% in group L, 61.9% and 26.2% in group M, and 70.1% and 16.1% in group H. The frequency of new AF cases was higher in the groups with more frequent PACs (15.5% per year in group L (n=277) vs. 44.0% per year in group M (n=42) vs. 71.4% per year in group H (n=62)). Compared with group L, the adjusted ORs for detecting AF in groups M and H were 2.11 (95% CI, 1.24-3.58) and 3.23 (95% CI, 2.07-5.04), respectively, and the adjusted odds ratios for high AF burden in groups M and H were 2.57 (95% CI, 1.14-5.74) and 4.25 (95% CI, 2.14-8.47), respectively. This study demonstrated a dose-dependent relationship between PAC frequency and AF detection in patients with cryptogenic stroke [16].

here are publications reporting the development of heart chamber dilation and heart failure in patients with PACs. It is well known that tachyinduced cardiomyopathy occurs in cases of persistent atrial arrhythmias (such as AF) and frequent ventricular premature contractions (VPCs). However, impaired systolic function of the left ventricle (LV) secondary to frequent PACs is rarely described.

A case was reported of a 44-year-old man who had a reduction in LV ejection fraction (EF) to 40% due to frequent PACs (19% per day on 24-hour Holter monitoring). After catheter ablation of the ectopic focus located in the area of the tricuspid valve ring, the LV EF increased from 40% to 56% over 8 weeks, as assessed by echocardiography [27].

C. Hasdemir et al. (2013) described a patient with frequent PACs (20.9% per day) and an LV EF of 48%. Ten months after successful ablation of PACs from the junction of the superior vena cava and the right atrium, his LV EF normalized [28].

A similar case was described by P. Vervueren et al. (2012). They reported a 40-year-old man who was hospitalized with severe heart failure, the cause of which remained undetermined after magnetic resonance imaging and coronary angiography. A 24-hour Holter monitoring showed 40,000 PACs, which were resistant to treatment with beta-blockers and amiodarone. Radiofrequency ablation of the arrhythmic substrate on the posterior wall of the left atrium was performed. Seven months later, the patient had no complaints, the size of the left atrium decreased from 32 to 12 cm², the left ventricular end-diastolic dimension decreased from 71 to 58 mm, and the LV EF increased from 28% to 50% [29].

All these cases demonstrate the reversible nature of PAC-induced cardiomyopathy after successful interventional treatment.

Medical treatment

In domestic clinical guidelines, drug therapy for asymptomatic and mildly symptomatic PACs is not recommended (III C). In cases where PACs are accompanied by significant subjective discomfort, beta-blockers (bisoprolol, nebivolol, metoprolol) or verapamil are recommended as symptomatic therapy (IIa C). If PACs are a factor in the development of symptomatic supraventricular tachycardia, atrial flutter, or AF, the guidelines suggest following the recommendations for treating these arrhythmias (IIa C). For patients with a high burden of PACs, comprehensive modification of cardiovascular risk factors (treatment of hypertension, weight reduction, identification and correction of obstructive sleep apnea) is recommended to reduce the risk of supraventricular tachycardia [30].

The EHRA and ESC consensus document on the use of antiarrhythmic drugs (2018) [31] recommends the following:

1. For symptomatic patients with frequent PACs and unstable paroxysms of atrial tachycardia without structural heart disease, beta-blockers, sotalol, flecainide, or propafenone are recommended.
2. For patients with structural heart disease, experiencing symptoms and/or a high burden of PACs and/or short paroxysms of atrial tachycardia, beta-blockers or amiodarone are recommended. Additionally, optimization of drug therapy for the underlying disease may reduce arrhythmia burden and prevent the development of arrhythmic cardiomyopathy.

Magnesium sulfate (MS) has been considered for treating PACs in several studies, based on the hypothesis that low intracellular magnesium may contribute to arrhythmia [32-34]. For example, in the study by C. Falco et al. (2012), patients with symptomatic PACs and VPCs (>240 PACs or VPCs per day) were randomized into two groups: one received placebo, and the other received MS orally at a dose of 3.0 g/day for 30 days. The outcome was measured using questionnaires. Clinical success was considered as a reduction of premature beats by more than 70% from baseline. In the MS group, 76.6% had a reduction of >70%, 10% had a reduction of >50%, and 13.4% had a reduction of <50%. In the placebo group, 40% had a slight improvement, with a reduction of <30%. A decrease in symptom severity was achieved in 93.3% of the MS group compared to 16.7% in the placebo group ($p<0.001$) [35]. However, after 15 months of observation, it was found that 37.8% of patients in the MS group ex-

perienced a recurrence of ectopy. In these patients, MS treatment was repeated, and a statistically significant reduction in the burden of premature beats was observed, with 78.5% showing clinical improvement. Patients who had initially received placebo and continued to experience symptoms were switched to MS, and their PAC and VPC burden significantly decreased, with 71.4% showing improvement in symptoms. The results of the study indicate that while MS has an antiarrhythmic effect, it does not persist after discontinuation. A limitation of this study is that it evaluated PACs combined with VPCs, considering the total number of premature beats per day. Notably, the treatment mostly reduced the number of VPCs rather than PACs [36].

In another small pilot double-blind randomized study by P. Lutsey et al. (2018), magnesium 400 mg daily for 12 weeks did not reduce the frequency of PACs. The authors attributed this to the small sample size (n=59), which did not allow detection of clinically significant differences [37].

D. Reĭngardene et al. (2004) evaluated the antiarrhythmic effectiveness of amiodarone for treating refractory PACs. The antiarrhythmic effect of amiodarone was studied in 70 patients with an average age of 49.6 ± 1.7 years and an arrhythmia burden of 4.9 ± 1.5 years. The dose was 600-1200 mg over 10 days, followed by a maintenance dose of 1656.25 mg per week. The treatment duration was 27.5 ± 3.2 months. According to the study, amiodarone had a therapeutic effect in 78.5% of patients during the loading phase and 65.7% during the maintenance phase. A partial antiarrhythmic effect was observed in 8.57% and 16.41% of patients, respectively [38].

In the study by T. Huang et al. (2022), the role of beta-blockers in reducing mortality in patients with frequent PACs was examined. Patients were divided into subgroups with high PAC frequency (>100 PACs per 24 hours) and low PAC frequency (<100 PACs per 24 hours). In each subgroup, patients who regularly received beta-blockers for ≥80% of the entire observation period were designated as the treatment group, while patients who never or rarely (<20% of the observation period) used beta-blockers were designated as the non-treatment group. The results showed that beta-blockers reduced all-cause mortality both in the high PAC frequency group (OR = 0.521, 95% CI = 0.294-0.923, p = 0.025) and in the low PAC frequency group (OR = 0.601, 95% CI = 0.396-0.913, p = 0.017). However, no differences were found in the incidence of new stroke or AF between the groups receiving and not receiving treatment [39].

An open question remains regarding the need for anticoagulant therapy in patients with frequent PACs to prevent ischemic stroke. Despite studies showing an increased risk of AF and stroke, current clinical guidelines indicate that anticoagulants and antiplatelets are not necessary for patients with frequent PACs. Two studies failed to prove the effectiveness of direct oral anticoagulants in patients with cryptogenic strokes in the absence of AF compared to antiplatelet therapy [40, 41]. The ARCADIA study showed that in patients with cryptogenic stroke and atrial cardiomyopathy, apixaban did not reduce the risk of recurrent stroke compared to low-dose aspirin [42].

Eleclazine (Eleclazine GS-6615) is an experimental selective sodium channel inhibitor that predominantly suppresses late sodium currents. In the study by H. Fuller et al. (2016), a good treatment effect was demonstrated in pigs: the number of ectopic beats caused by adrenaline decreased more than threefold after the infusion of eleclazine (0.9 mg/kg). The combined administration of adrenaline and acetylcholine stimulated the development of PACs, leading to AF in all tested animals. When eleclazine was administered beforehand, the development of AF was suppressed in all animals (p = 0.04). Moreover, the drug did not produce a negative inotropic effect or proarrhythmic action, which distinguishes it from current antiarrhythmic drugs [43].

Interventional treatment

It is known that PACs originating from the pulmonary vein ostia (PVs) act as triggers for AF, and such sources can be eliminated through pulmonary vein isolation via catheter ablation [44]. There is a limited number of reports in the available literature on ablation of arrhythmic substrates from other locations [28, 45-49].

Currently, there are no specific guidelines or expert consensus regarding radiofrequency catheter ablation for treating PACs, however, increasing data suggests the feasibility and effectiveness of catheter ablation for eliminating PACs.

The efficacy of interventional treatment for PACs was evaluated in the study by X. Huang et al. (2018), which included 81 patients with symptomatic, frequent (13,199 ± 5744 PACs per day), and drug-resistant PACs. All patients underwent electrophysiological study of the heart, and based on the source of ectopic activity, three groups were formed: Group A - PACs originating from PVs, Group B - PACs from other sources, Group C - PACs from both PVs and other sources. The most common ectopic localizations were: PVs, coronary sinus, upper and lower caval vein ostia, mitral and tricuspid valve annuli, non-coronary aortic valve cusp, ridge crest, and left and right atrial appendages. Paroxysmal AF was present in the medical history of 44.4% of patients in Group A and 50.0% in Group C, while it was observed in only 12.5% in Group B (p < 0.05). The authors confirmed the hypothesis that frequent PACs originating from PVs are linked to an increased incidence of AF compared to ectopy from other locations. Depending on the source of the ectopy, all patients underwent PV isolation, focal ablation, or superior vena cava isolation. After a postoperative follow-up of 21.3 ± 14.3 months, atrial arrhythmias did not recur in 40 (88.9%) patients from Group A, 21 (87.5%) from Group B, and 10 (83.3%) from Group C. On average, the frequency of PACs decreased from 13,199 ± 5744 to 439.3 ± 146.1 beats per day [50].

In a similar study by X. Wang et al. (2017), 70 patients with PACs (mean frequency 25,567 ± 12,508 PACs per day) were divided into two equal groups: Group A - PACs without AF, and Group B - AF induced by PACs. The study compared coupling intervals from ECG data. It was found that PACs that triggered AF had shorter coupling intervals compared to Group A, regardless of their source (PVs or other foci) (362.8 ± 23.0 ms vs. 470.6 ± 60.1 ms and 515.6 ± 77.2 ms, p < 0.001). Electrophysiological study identified 35 different ectopic focus loca-

tions in Group A. Most of them were located in the PVs, the ridge crest, and the proximal part of the His bundle. In Group B, ectopic foci were located in the left PVs in 21 patients, right PVs in 13 patients, and in the upper caval vein in 1 patient. Focal ablation of the superior vena cava or PV isolation was performed based on the clinical situation. Immediately after the procedure, PACs were not recorded in 32 (91.4%) patients in Group A and in all patients in Group B. After 12 months, PACs did not recur in 29 (82.8%) patients in Group A and 28 (80%) patients in Group B after discontinuation of antiarrhythmic therapy. Six patients with recurrent PACs were referred for repeat ablation, which was successful in 1 patient in Group A and 3 patients in Group B [44].

PACs are the most common type of cardiac arrhythmia. Frequent PACs may serve as a marker for atrial cardiomyopathy and an increased risk of AF, which in turn raises the risk of stroke and mortality. This makes PACs an important indicator for patient prognosis.

Currently, there are no clear clinical guidelines for managing patients with frequent PACs. Issues regarding threshold values for PAC frequency and indications for treatment remain unresolved. However, by consensus among experts, a high burden of PACs is considered to be more than 500 PACs per 24 hours according to Holter monitoring data. Despite limited evidence, radiofrequency catheter ablation may be an effective treatment option for patients with frequent and symptomatic PACs resistant to pharmacological therapy. The results of pharmacological treatment are conflicting, and more research is required to optimize it. Furthermore, there is currently no data indicating whether treatment of patients with a high burden of PACs using antiarrhythmic therapy or catheter ablation reduces the risk of developing AF, stroke, or mortality [51].

In 2023, the American College of Cardiology introduced a new 4-stage classification for AF, which for the first time introduces the concept of «pre-AF» – structural and electrical changes in the heart that predispose the patient to develop AF, such as atrial enlargement and frequent supraventricular ectopic activity [52]. The inclusion of the «pre-AF» stage emphasizes the importance of early detection and monitoring of PACs as a potential precursor to more serious arrhythmias.

Additional research aimed at developing modern guidelines for the treatment of PACs and choosing the optimal management strategy for patients is needed to improve outcomes and reduce the risk of cardiovascular complications.

CONCLUSION

Thus, PACs, which were once not considered a serious condition, now require more careful attention and close monitoring, as they are a predictor of the risk of developing atrial fibrillation and stroke.

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ON THE QUESTION OF ASSESSING THE QUALITY OF ELECTROCARDIAC SIGNAL REGISTRATION

M.M.Medvedev[1,2], A.B.Parizhskiy[2]

[1]Saint-Petersburg State University, Russia, Saint-Petersburg, 7/9 Universitetskaya emb.;

[2]NJSC Institute of Cardiology Engineering «INCART», Russia, Saint-Petersburg, 22A Viborgskoye h.

The results of recording the same electrocardiogram by different devices are compared, the role of filtration in displaying fragmented QRS complexes is discussed.

Keywords: electrocardiogram; electrocardiographs; digital-to-analog converter; signal recording quality; filtration; fragmented QRS complex

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Corresponding author: Medvedev Mikhail, E-mail: mikhmed@mail.ru.

M.M.Medvedev - ORCID ID 0000-0003-4903-5127, A.B Parizhskiy - ORCID ID 0009-0004-7018-9360

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In recent years, with the shift of patient discussions, examination results, and treatments from ward rounds led by department heads or professors, as well as consultations, to chats, groups, and channels, there has been a growing trend of discussing electrocardiograms (ECGs) presented as photos on smartphones. Typically, these are photographs of ECGs either recorded on paper or displayed on computer screens. It is evident that the process of photographing, despite the high resolution offered by modern smartphones, does not improve the quality of the ECG displayed. Furthermore, it appears that even the original ECGs, whether recorded on paper or electronically, do not always adequately convey the full details of the electrocardiographic signal.

On the other hand, all ECG devices are required to conform to national standards and undergo regular calibration. Thus, it remains unclear why ECGs recorded by different devices, all of which comply with the relevant standards, still exhibit discrepancies, sometimes quite significant. In the era of analog ECG machines, the quality of the recording could be assessed based on the form of the millivolt, which was primarily determined by the method of registration. The highest quality was achieved using photo and recording, which was attributable to the minimal inertia of string and other galvanometers and the absence of direct contact with the moving paper. In contrast, «pen» ECG machines were influenced by the mass of the pen, which determined its inertia, as well as the friction between the pen and the paper. The friction varied depending on whether the ink or thermal printing technique was used. To improve the quality of recordings made with pen-based ECG machines, various methods were applied, such as introducing low-amplitude high-frequency oscillations (50 Hz) to the pen or applying a wax coating on the paper that would melt under the heat of the pen.

At the end of the last century, analog ECG machines were replaced by digital systems, fundamentally changing the process of ECG recording. The enhanced, digitized, and processed ECG signal is now printed by printers devoid of inertia or friction between the «pen» and the paper. In digital ECG machines, pressing the millivolt button commands the printer to produce a signal of known form and amplitude, which typically provides little information about the underlying characteristics of the ECG signal. This digital transformation was accompanied by the widespread use of filters designed to «improve» ECG quality. However, these filters, which are intended to reduce or eliminate power line interference, muscle noise, and baseline fluctuations, primarily create the illusion of improved quality while significantly simplifying the process of ECG registration. These filters inevitably alter the ECG signal to varying degrees across different devices. This issue can be avoided by recording the unfiltered (native) signal in the device's memory, with filters applied during viewing and printing. Unfortunately, even if this option exists, it is seldom utilized.

The issue of ECG signal filtering has been extensively addressed in both the AHA/ACC/HRS guidelines and in Russian guidelines [1, 2]. The AHA/ACC/HRS recommendations stipulate that the ECG signal bandwidth should range from 0.05 to 150 Hz, with the upper frequency limit extended to 250 Hz in pediatric practice. It is clearly stated that the use of other filters, such as increasing the lower frequency limit to 0.5 Hz or reducing the upper limit (for example, to 40 Hz), is unacceptable. Regrettably, compliance with these recommendations is not always strictly enforced for medical device manufacturers. Therefore, the AHA/ACC/HRS guidelines recommend that when «non-optimal» filters are used, they should be «reset» after each ECG recording, ensuring that medical personnel manually reconfigure them,

thereby acknowledging the distortion of the ECG signal caused by the filters [1].

How can we compare ECG signal registration results from different devices? It seems that the standard calibration using test signals, which is likely performed with filters turned off, does not provide the desired outcome. An optimal approach might involve a study in which ECG is recorded from the same electrodes on patients using different ECG machines and different signal filtering methods. It is understood that as the number of devices being compared increases, the labor intensity of such a study will also rise, and it will require approval from an ethics committee, informed consent forms, etc. The results obtained would be limited by the specific characteristics of the patients' ECG data.

An alternative possibility is offered by the device created by the NPO «Inkart,» which allows recording the digital ECG signal and then outputting it through a digital-to-analog converter in a «patient format.» This format enables the connection of devices with a standard lead cable to register the ECG in the twelve commonly accepted leads. We present the first experience of using this device to compare the characteristics of ECG recording from different machines.

For the test signal, we selected a fragment of a Holter ECG monitoring recording (Holter ECG) in twelve standard leads from patient A., whose examination and treatment were discussed in the Journal of Arrhythmology [3, 4]. This selection was made due to the presence of various P waves and QRS complexes. To reduce the influence of muscle noise, a signal recorded during nighttime sleep starting from 4 a.m. was used. As a «starting point,» we compared low-amplitude fragmented QRS complexes recorded in lead II when registered by different devices (Fig. 1). It is important to note that the term «low-amplitude» here is used simply to describe fragmented complexes whose amplitude is significantly smaller than that of non-fragmented ones.

Figure 1a shows a fragment of the original Holter ECG, uploaded into the device for subsequent output in the «patient format.» Two QRS complexes in lead II were «cut» from the ECG example, included in the report after being converted to PDF format. This and all subsequent recordings are presented with a «tape speed» of 50 mm/s at a scale of 1 mV = 2 cm. All filters, except for the overrange filter (which, with this quality of recording, obviously does not function), are turned off. The first of the two QRS complexes, with an amplitude of about one millivolt, exhibits pronounced fragmentation. The dynamics of this fragmentation when outputting this signal to other devices will be the focus of our evaluation.

Figure 1b shows the same fragment as Figure 1a, output to a «Cardiotech» system monitor, the same one used to record the original signal. The result is not identical to the original. A decrease in the amplitude of the discussed QRS complex and a moderate reduction in its fragmentation are observed. This could be due to both the conversion of the signal from digital to analog and vice versa, as well as the relatively low sampling frequency (256 samples per second). It is evident that for future studies, we will need to select an ECG signal recorded with a higher sampling frequency of 1024 samples per second. By analyzing this signal, the impact of sampling frequency on the final result can be assessed when outputting it to modern ECG machines (see below). It should be emphasized that in future comparisons, we will primarily compare the results of outputting the signal to various devices, not with the original signal, but with its representation in Figure 1b.

The result of exporting the discussed fragment of Holter ECG to a single-channel thermographic analog ECG machine «Salyut» from 1974 is shown in Figure 1c. It is noteworthy that despite maximum amplification (which is smoothly adjustable on this machine), it does not reach the scale of 1 mV = 2 cm. Additionally, the distance between the complexes has noticeably decreased, indicating a reduction in the tape speed. This ECG machine does not have any filters. It should be emphasized that the fragmented QRS complex decreased in amplitude (not only due to scale changes), but almost unchanged in configuration compared to Figure 1b. In our view, this indicates that the old analog ECG machine demonstrates quite respectable recording quality. The change in its amplitude characteristics certainly requires further study.

Figures 1d and 1e show the same ECG fragment recorded on a three-channel digital electrocardiograph Siemens-31S, produced in the early 1990s. The recording with filters turned off (Fig. 1d) shows moderate network interference, likely due to room conditions (the recordings on different machines were made in different rooms) and the grounding of the device itself. The fragmented QRS complex is similar to those previously discussed. When the 35 / 50 Hz filter is applied, the network interference is significantly reduced, but at the same time, the amplitude of the fragmented QRS complex decreases, its initial part changes, and the «notching» on the descending part of the R wave transitions to a «smoothed» appearance. In our opinion, this is a significant change in the ECG signal.

The results of the ECG signal registration of patient A. on a modern digital ECG machine are shown in Figures 2a and 2b. When exporting the recorded signal to machines providing synchronous recordings of twelve standard leads, we did not aim to register the same fragment under different filtering conditions. Figure 2a shows the ECG signal recording with optimal filtering, meeting the recommendations [1]. The fragmented QRS complex in lead II is close to the original, and its amplitude corresponds to that shown in Figures 1c and 1d, exceeding the amplitude in Figure 1b and 1d. With «non-optimal» filters turned on (Fig. 2b), the fragmentation and amplitude of such QRS complexes decrease significantly, with the following pattern observed: the smaller the amplitude of the QRS complex, the greater the reduction. This is clearly seen in lead III.

The result of importing the ECG signal into a widely used domestic computer ECG machine is presented in fragments saved in PDF format. It should be noted that we could not record the ECG with all filters turned off, and the personnel operating this machine confirmed that they never turn off the filters. We had to register fragments with the

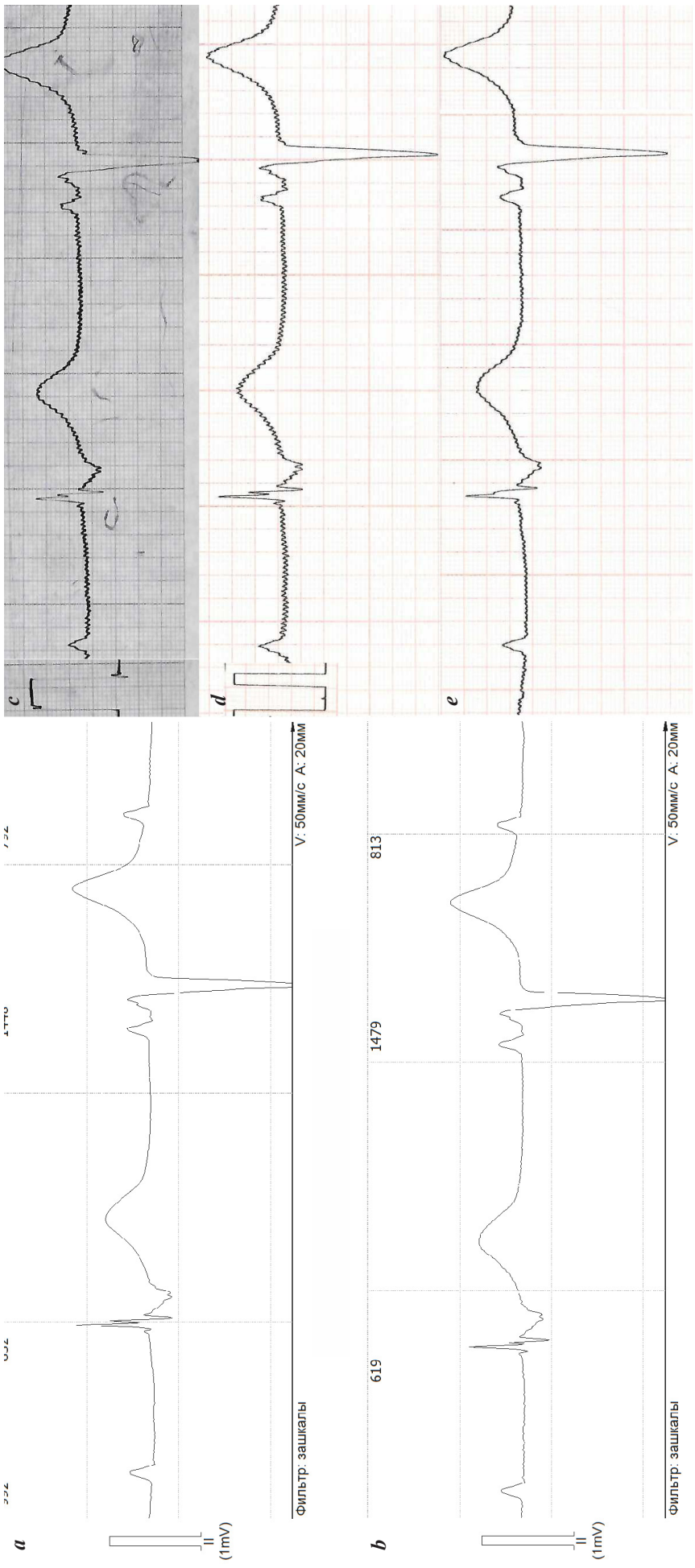

Fig. 1. Results of registering the same ECG signal fragment from patient A by different devices: a - original ECG signal recorded using the Holter monitor «Cardiotechnika», b - ECG signal output in «patient format» and recorded by another Holter monitor «Cardiotechnika», c - the same signal recorded on a single-channel thermoprint analog ECG machine «Salyut» from 1974, d - results of registration on a three-channel digital electrocardiograph Siemens-31S with filters off, e - consequences of signal filtering. Explanations in the text.

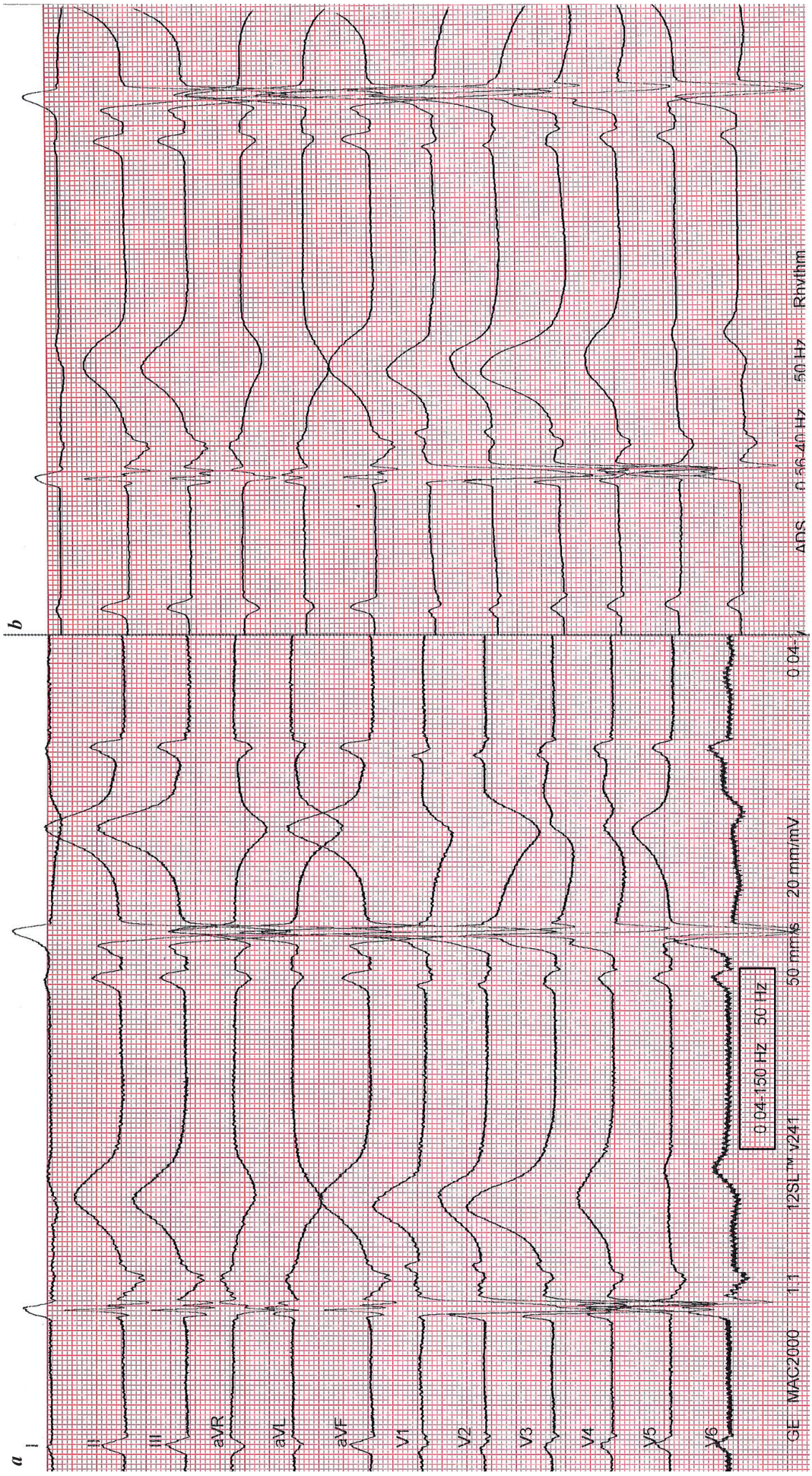

Fig. 2. Results of ECG signal registration from patient A on a modern digital ECG machine: a - with «optimal» filtering with a passband of 0.05-150 Hz, b - when using other filters. Explanations in the text.

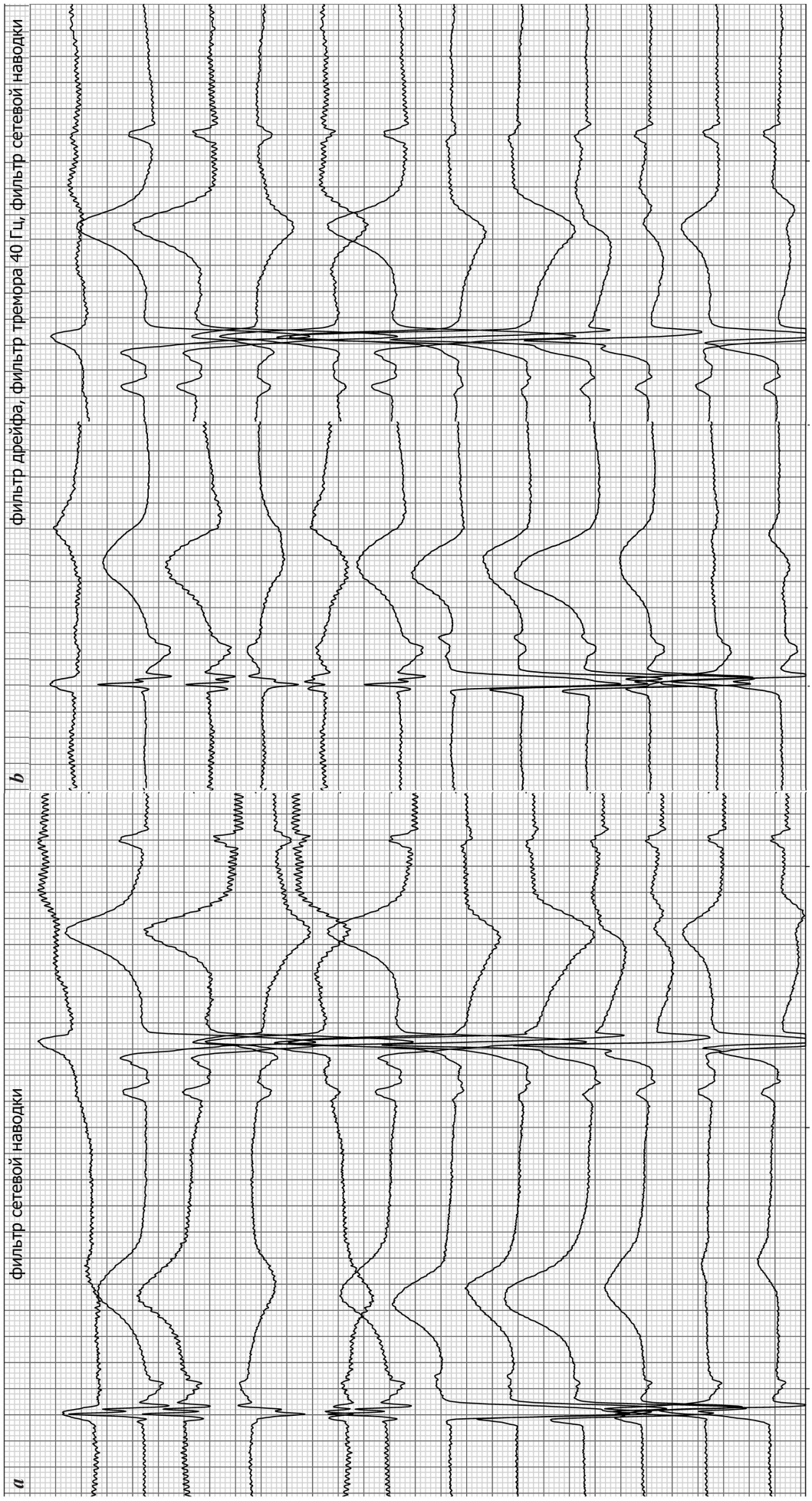

Fig. 3. Results of ECG signal registration from patient A on a widely used domestic computer electrocardiograph: a - using only the network noise filter, b - with various filters in use. Explanations in the text.

network interference filter turned on. Its operation deserves further study, as the amplitude of the remaining network interference varies significantly over time. The amplitude of the QRS complex in lead II with the network filter turned on (Fig. 3a) corresponds to that of the original complex (Fig. 1a), which is likely due to the high sampling frequency, allowing the complete depiction of the waves. The machine transmits the fragmentation of the QRS complex well, but for reasons not fully understood, there is a marked decrease in the amplitude of the retrogradely conducted P waves following the fragmented QRS complex. This phenomenon certainly requires confirmation in other similar complexes and further study. After all filters are turned on (Figure 3b), the amplitude of the fragmented QRS complexes significantly decreases, their configuration changes, and the shape of the T waves also changes.

CONCLUSION

The comparison of the registration features of the same ECG signal by different devices demonstrated significant differences, which were primarily attributed to the nature of the filters used. In the framework of this pilot study, we only examined the possibility of such a comparison, focusing solely on the high-frequency components of the ECG (specifically the QRS complexes with pronounced fragmentation). It is evident that the nature of the registration of other ECG elements, including by other devices, requires further separate study.

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