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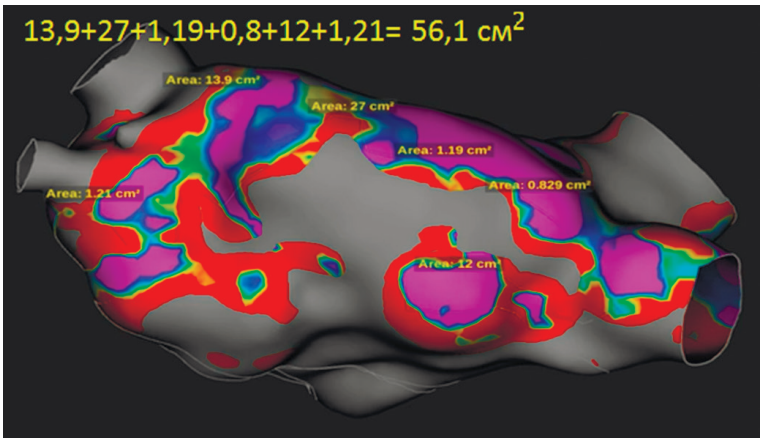

Figure from the article by E.V.Dedukh, M.V.Yashkov, I.A.Taymasova. E.A.Artyukhina, A.Sh.Revishvili

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CONTENT

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LEFT ATRIAL POSTERIOR WALL ISOLATION IN PERSISTENT ATRIAL FIBRILLATION DOES NOT INFLUENCE THE EFFICACY OF CATHETER ABLATION: A PILOT STUDY

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Aim. To study the role of left atrial posterior wall (LAPW) isolation in increasing the clinical efficacy of radiofrequency ablation (RFA) in patients with persistent atrial fibrillation (PeAF) during electrophysiological studies.

Methods. A single-center randomized prospective study. From February 2020 to February 2021, 35 procedures were performed on patients with PeAF. Patients were randomized into two groups - pulmonary vein isolation (PVI) plus LAPW isolation according to the “box lesion” scheme (the first group) and the PVI-only group (the second group). If it was impossible to achieve LAPW isolation, “debulking” was performed. After 3 months, regardless of the clinical status, EPS and RFA of the reconnection zones were performed.

Results. The full study protocol study was completed by 30 patients - 14 in the first group and 16 in the second group. The characteristics of the patients in the groups did not differ statistically. The duration of the primary and redo procedures, as well as the RFA time during the primary procedure in the first group is significantly longer than in the second group. Pulmonary veins were isolated in all patients participating in the study. In the first group, LAPW isolation was achieved only in 21.4% of cases (3 patients), in the remaining 78.6% of cases (11 patients) “debulking” was performed. PVI in the first group was maintained in 78.6% of cases (11 patients), and in the second group in 56.2% (9 patients), the difference was not statistically significant (p=0.209). In the first group, LAPW isolation was maintained in 28.6% of patients (4 patients). All patients with reconnection underwent RFA with the restoration of the conduction block. In the midterm (440±82.1 days) of follow-up, the sinus rhythm was preserved in the first group in 11 patients (78.5%), and in the second group in 13 (81.2%) patients. There was no statistically significant difference between the groups (OR 0.846 95% CI 0.141-5.070, p=0.641).

Conclusions. In our study, LAPW isolation in addition to PVI in patients with PeAF did not improve the efficacy of treatment with a significantly longer duration of procedure and RFA time.

Keywords: persistent atrial fibrillation; radiofrequency ablation; left atrial posterior wall isolation; reconnection; electrophysiological study

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Interventional treatment of patients with persistent atrial fibrillation (AF) is currently an unresolved problem because, despite the development of catheter technologies, the efficacy of radiofrequency ablation (RFA) in this type of AF is about 50% [1]. Elimination of the triggering mechanisms by pulmonary vein (PV) isolation (PVI) is the «gold standard» in the treatment of AF [2]. The role of additional influences in the left atrium (LA) in the persistent form of AF remains unclear. The study STAR AF II showed no benefit of additional interventions in patients with persistent AF compared to patients who received PV RFA [3]. At the same time, a number of meta-analyses indicate improved efficacy of interventional treatment of AF when procedures are performed outside the pulmonary veins, including isolation of the posterior wall of the left atrium (PWLA) [4, 5]. According to its electroanatomical properties, PWLA can be both a trigger and a substrate supporting AF [6, 7]. Thus, PWLA isolation, in addition to PVI, may improve the results of RFA in the persistent form of AF. It is quite difficult to achieve permanent isolation of PWLA; restoration of conduction is seen in more than 50% of patients [8]. A planned intracardiac electrophysiological examination (IC EPE) 3 months after RFA makes it possible to detect gaps in conduction, even if they are not accompanied by the clinical picture of arrhythmia recurrence, and to restore conduction block in a timely manner [9].

Purpose of the study: to investigate the role of left atrial posterior wall isolation in improving the clinical efficacy of radiofrequency ablation in patients with persistent

atrial fibrillation during routine intracardiac electrophysiological examinations.

MATERIAL AND METHODS

A single-center, randomised, prospective study. From February 2020 to February 2021, 506 RFAs were performed for atrial fibrillation. Of this number, 35 patients were selected. The characteristics of the patients are presented in Table 1. All patients signed voluntary informed consent. The study was approved by the institution's ethics committee and conducted in accordance with Good Clinical Practice.

Inclusion criteria: the patient has a persistent form of AF (definition of a persistent form from the expert agreement [10]). At the time of surgery, the patient may have sinus rhythm; AF is symptomatic, antiarrhythmic therapy is ineffective (at least one IC or class III drug) or there is intolerance to it; intake of warfarin with international normalised ratio targets (2.0-3.0) or direct oral anticoagulants; no pathology from the valve system of the heart; signed patient consent form; opportunity for dynamic follow-up; age 40 to 70 years.

Exclusion criteria: paroxysmal form of AF; typical or atypical atrial flutter; repeated RFA procedures; LA diameter > 55 mm according to echocardiography (EchoCG); left ventricular ejection fraction less than 45%; reversible causes of AF (electrolyte balance disorders, thyroid diseases, respiratory failure against chronic obstructive pulmonary disease); any open cardiac surgery within the last three months; left atrial auricular thrombosis confirmed by transesophageal EchoCG; myocardial infarction within the previous two months; contraindications to anticoagulant therapy.

All patients underwent the following examinations before surgery: general clinical tests, coagulogram, coronarography for men over 40 and women over 50 (which is the standard examination before PVI, accepted in our clinic), EchoCG to determine the volume of LA, transesophageal EchoCG to exclude thrombosis of LA auricle.

Patients were randomised into two groups in a 1:1 ratio using a random number generator. Randomisation was performed before the start of the procedure. In one group of patients, only PVI was performed. In the other group, PVI was supplemented with PWLA isolation according to the «box lesion» scheme - a line along the LA roof (roof line) and a line connecting the lower pole of the isolated pulmonary veins (floor line).

The surgeries were performed under intravenous sedation with dexmedetomidine and fentanyl. Transseptal puncture was performed under the control of fluoroscopy twice, and 2 unguided intraductal injectors were inserted into the LA cavity. The esophagus was then contrasted by swallowing 10 ml of Omnipack water-soluble contrast agent (GE HEALTHCARE IRELAND). Activated clotting time was maintained above 300 seconds by intravenous injection of heparin throughout the procedure. The anatomical map of LA was constructed using the CARTO 3 3D mapping system (Biosense Webster Johnson & Johnson, USA). The position of the esophagus was noted on PWLA, using a comparison of radiographic and anatomical mapping data. RFA was performed using EZ Steer Nav SmartTouch bi-directional irrigated electrodes (Biosense Webster Johnson & Johnson, USA). A Stockert RF energy generator (Biosense Webster Johnson & Johnson, USA) was used in power control mode, irrigation rate 30 ml/min, power 40 W, if the patient complained of chest pain the power was reduced to 30 W. When acting on the LA posterior wall in the projection of the esophagus, a power of 30 W was used, and the duration of irradiation at one point did not exceed 10 seconds. The Visitag module of the CARTO 3 system was used to visualise the points of RF energy application with the following parameters: catheter tip displacement level 2.5 mm, clamping force over 4 g at least 35% of the time, ablation index values of no more than 300 at the posterior wall and 450 at the LA anterior wall The distance between the points was no more than 6 mm.

Input block was determined by the disappearance of PV adhesions. The output unit was verified for each pulmonary vein by stimulation with 10 mA current and 1 ms pulse duration from a LASSO catheter (10 or 20 pole) (Biosense Webster Johnson & Johnson, USA). Isolation of PWLA was considered to be achieved if ectopic activity of PWLA itself and/or the presence of «local seizures» without conduction to the atrial myocardium during PWLA stimulation were determined (Fig. 1). If it was not possible to isolate the posterior wall after performing a box lesion set, «debulking» (removal of PWLA potentials - massive RFA exposures to PWLA targeting any registered signal that deviated from the criteria for scar tissue (signal amplitude greater than 0.1 mV) was performed until electrical «silence» was achieved. External cardioversion was performed in case of persisting AF.

Table 1.

Characteristics of patients by group

	Total (n=35)	PVI+PW (n=14)	PVI (n=16)	P
Age, years	57.7±8.3	56.5±9.2	58.8±7.6	0.459
Male gender, n (%)	24 (80)	12 (85.7)	12 (75)	0.481
Body mass index, kg/m^2	29.4±3.5	30.2±3.3	28.7±3.7	0.250
LVEF, %	59.2±6.7	57.1±6.4	61.0±6.5	0.110
LA volume, ml	96.7±21.3	99.9±20.1	93.8±22.6	0.442
LA diameter, mm	42.0±3.8	42.1±3.2	41.9±4.46	0.887
Arrhythmic history, months	57.7±48.2	48.6±32.6	65.8±58.6	0.340
Diabetes mellitus, n (%)	2 (6.6)	2 (14.3)	0 (0)	0.126
Arterial hypertension, n (%)	26 (86.6)	13 (92.8)	13 (81.2)	0.146

Note: hereinafter PVI - isolation of pulmonary venous ostium, PW - posterior wall, P - significance of differences between PVI+PW and PVI groups, LVEF - left ventricular ejection fraction, LA - left atrium.

All patients were treated with antiarrhythmic drugs for 4 weeks after surgery, and anticoagulant therapy was continued in all patients. After 3 months, an IC EPE procedure (regardless of clinical status) was routinely performed to check the consistency of the inlet and outlet block in each pulmonary vein and the LA posterior wall, and repeated RFA at the reconnection sites if necessary.

Patients were monitored remotely due to the epidemiological situation. A telephone survey was conducted with the provision of ECG daily monitoring data 6 and 12 months after the first surgery. Medical record data were also provided, including any ECGs if the patient had been hospitalised or treated as an outpatient during the observation period. Recurrence of arrhythmia was considered as any recorded paroxysm of AF or atrial tachycardia lasting more than 30 seconds. The primary end point was no arrhythmia during the follow-up period. The secondary endpoint was the preservation of conduction block in the pulmonary veins and PWLA.

Statistical analysis of the results was performed using the system software package IBM® SPSS® Statistics (Version 20, 2011). For normal distribution, results were expressed as arithmetic mean ± standard deviation (M±SD) with 95% confidence interval (95% CI). For asymmetric distributions, results were expressed as median and interquartile range. Frequencies and fractions (in %) were used to describe qualitative data, with 95% CI calculated by the Wilson method. Pearson's χ^2 criterion was used for comparison. Performance was compared using a 2-sided log-rank test accompanied by Kaplan-Meier estimates. The critical level of statistical significance for testing statistical hypotheses was taken as 0.05.

RESULTS

A total of 35 patients were selected who underwent the primary procedure. The group of posterior wall isolation and PVI (group 1) included 18 patients; the group of only PVI (group 2) included 17 patients. Four patients refused to undergo IC EPE due to the absence of arrhythmia episodes (three patients from the first group and one from the second group) and were excluded from the study. One patient from the posterior wall isolation group could not be contacted after repeated surgery and was also excluded from the study. Thus, the total number was 30 people (14 in the first group and 16 in the second group) (Fig. 2). The characteristics of the patients by group are shown in table 1 and did not differ statistically according to the main indices - weight, sex, age, duration of history, LA volume and ejection fraction, and the presence of concomitant pathology.

Procedure characteristics

The duration of the primary intervention and the time of RFA was significantly longer than that of the repeat intervention in the entire patient cohort. As the use of X-rays was only required in the interatrial septal puncture phase, the time of fluoroscopy was not statistically different between the primary and repeat procedures. The data are presented in Table 2. Comparison of the main indices of the procedures performed between the groups showed that the duration of primary and repeat surgeries and the time of RFA for the primary procedure were significantly longer in the first group than in the second.

In the PWLA isolation group, 85.7% (12 patients) had AF at the time of primary surgery, and 14.3% (2 patients) were operated on against sinus rhythm. In the second group, AF at the time of surgery was noted in 87.5% of cases (14 patients), sinus rhythm in 12.5% (2 patients). Spontaneous recovery of sinus rhythm during RFA was not observed in any case, all patients with AF underwent external electrical cardioversion.

PVs were isolated in all patients participating in the study. There were no anatomical features of pulmonary veins entering LA. In the first group, only in 21.4% of cases (3 patients) it was possible to achieve «true» isolation of PWLA, confirmed by the presence of local seizures during stimulation from the LASSO catheter. Spontaneous ectopic activity of the posterior wall was not observed. In the remaining 78.6% of cases (11 patients) «debulking» was performed before obtaining electrical silence of the posterior wall.

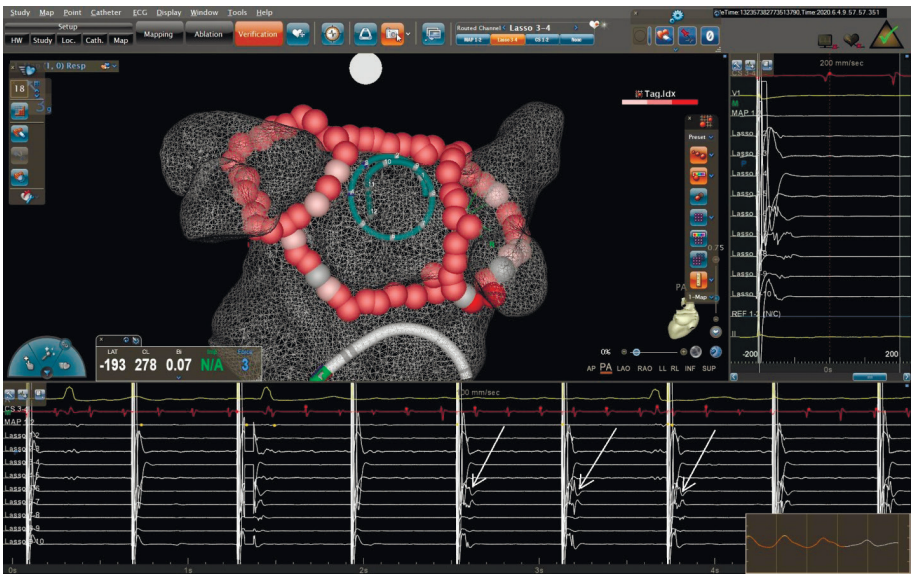

Fig. 1. Isolation of the posterior wall of the left atrium. Electrograms recorded during pacing with the Lasso catheter placed at the posterior wall of the left atrium show local captures indicated by white arrows, while atrial fibrillation persists on electrograms from the coronary sinus (red curve). This phenomenon indicates electrical isolation of the posterior wall of the left atrium.

No life-threatening complications were recorded during the study. There were 2 complications related to vascular access during the primary procedure - false femoral artery aneurysm (PWLA isolation group) and arteriovenous junction (PVI group). Against a background of conservative treatment (compression), the complications receded without the need for surgical treatment. There were no complications during repeated interventions.

Echocardiographic data

Left ventricular ejection fraction and LA diameter did not change significantly 3 months after primary surgery in the two groups. LA volume in the PWLA isolation group tended to decrease, but the difference did not reach significance (Table 3).

Electrophysiological features

The average duration of IC EPE after the primary procedure was 93 [92;95.5] days. PVI in the first group was maintained in 78.6% of cases (11 patients), in the second group in 56.2% (9 patients), the difference being statistically insignificant (p=0.209). In the group of PWLA isolation, PVI and PWLA isolation was preserved in 3 patients, the remaining 11 patients required additional RFA treatment to eliminate excitation conduction gaps in the previously isolated areas. In the PVI group, RFA was required in 7 patients. The difference between the groups was not statistically significant (p=0.113). Restoration of excitation conduction in all PVs in the posterior LA wall isolation group was observed in one patient, in the left PV manifold in one patient, and in the left upper PV in one patient. In the second group, all pulmonary veins were reconnected in one patient, one case each in the left and right PV manifold, 3 cases in the right lower PV and one in the left lower PV.

The absence of posterior wall electrical activity in the course of repeated intervention was noted in 28.6% of patients (4 patients) - two after «debulking», two after «box lesion». All patients with restoration of excitation conduction in PV were subjected to additional RFA exposure with restoration of PVI. In all patients of the first group it was possible to achieve an isolation of the LA posterior wall without «debulking» during the repeated surgery.

Clinical efficacy

In the first group, sinus rhythm was observed in 11 (78.5%) patients 3 months after primary surgery, and in the second group also in 11 (68.7%) patients, although the difference was not statistically significant (p=0.590). Early recurrence of AF was seen in 8 patients (3 from the posterior wall isolation group and 5 from the PVI group), the persistent form of AF was seen in 2 patients from the first group, and in the remaining patients AF changed to the paroxysmal form. All patients with early recurrence of AF showed restoration of conduction in previously isolated areas. At the same time, 4 patients who participated in the study experienced restoration of conduction of excitation without clinics for recurrent AF.

In the entire cohort of patients, sinus rhythm was preserved in 24 of 30 patients (80%) at mid-term follow-up (440±82.1 days after the initial procedure). In the first group, no arrhythmia was detected in 11 of 14 patients (78.5%), in the second group in 13 of 16 patients (81.2%).

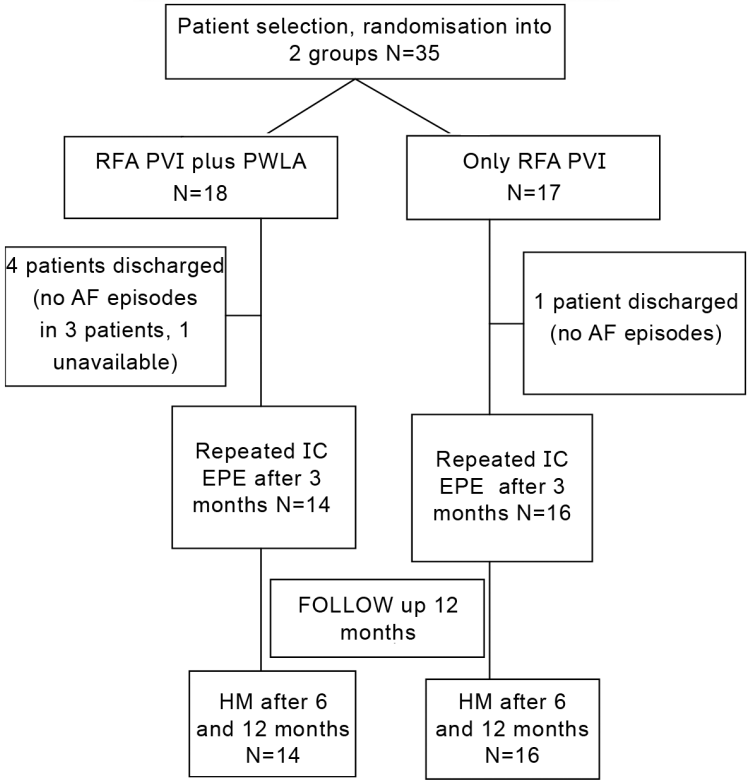

Figure 2. Scheme of the study.

Table 2.

Main characteristics of conducted surgeries by groups

Indicator	Total (n=30)	PVI+PW (n=14)	PVI (n=16)	P
First surgery				
Surgery time, min	107.6±22.9	122.1±20.5	95.0±16.7	0.000
Fluoroscopy time, s	187.6±101.8	176.4±87.9	197.4±114.5	0.580
RFA time, min	32.5±12.1	40.5±11.0	25.6±8.2	0.000
Repeat surgery				
Surgery time, min	59.5±29.4	73.9±32.1	46.9±20.3	0.009
Fluoroscopy time, s	217.6±122.4	251.1±148.9	188.3±88.2	0.165
RFA time, min	6.8±9.5	9.9±11.8	4.2±6.1	0.108

Note: RFA - radiofrequency ablation

Table 3.

LVEF, LA diameter and volume at baseline and 3 months after primary surgery by group

	PVI+PW (n=14)			PVI (n=16)		
	Originally	After 3 months	P	Originally	After 3 months	P
LVEF, %	57.1±6.5	58.1±7.7	0.467	61.0±6.5	62.2±5.6	0.382
LA diameter, mm	42.1±3.2	41.6±3.5	0.336	41.9±4.5	41.4±4.3	0.218
LA volume, cm^3	99.9±20.0	90.9±20.6	0.064	93.8±22.6	91.1±22.4	0.352

There was no statistically significant difference between the groups (odds ratio (OR) 0.846, 95% confidence interval (CI) 0.141-5.070, p=0.641) (Fig. 3).

DISCUSSION

The data on the clinical efficacy of PWLA isolation in patients with AF are inconsistent. Several studies were conducted with 30 to 250 patients, with different inclusion and exclusion criteria, different methods of isolating the posterior wall of LA and with different results.

D.Tamborero et al. conducted a study including 120 patients with paroxysmal, persistent and long-term persistent forms of AF. All patients underwent PVI and mitral isthmus ablation. After that, the patients were divided into 2 groups - the first group additionally underwent RFA of the LA roof, the second group underwent isolation of PWLA. It was possible to achieve conduction block in all created linear RFA lesions in 90% of cases in the first group and 92% in the second group. The follow-up period was 10±4 months. In the first group, cardiac arrhythmias recurred in 27 patients (45%), and in the second group, AF recurred in 27 patients (45%). Twenty-five patients underwent repeated RFA and 84% had restoration of conduction in the previously isolated PV. LA roof conduction block persisted in 31% of cases in the first group, and LA posterior wall isolation in 33% in the second group [11].

J.M.Lee et al., cited data from a study that included 217 patients with a persistent form of AF (73.3% had a long-term persistent form of AF). Two groups were formed - in the first group only PVI was done and in the second group additional damage was done along the upper and lower junction lines between the right and left PV. If this was not sufficient to achieve PWLA isolation, additional RFA influences were performed, directed to the registered potentials along the posterior wall and exceeding the amplitude of 0.1 mV. The follow-up period was 16.2±8.8 months. There was no statistically significant difference in the rate of arrhythmia return between the groups. Sinus rhythm without antiarrhythmic therapy was present in 50.5% of patients in the first group and 55.9% in the second group (p=0.522). The RFA time in the second group was significantly longer than in the first group (5.365±2.358 seconds versus 4.289±1.837 seconds p<0.001) [12]. There was 1 case of atrioesophageal fistula in the PV isolation group 3 weeks after RFA with fatal outcome.

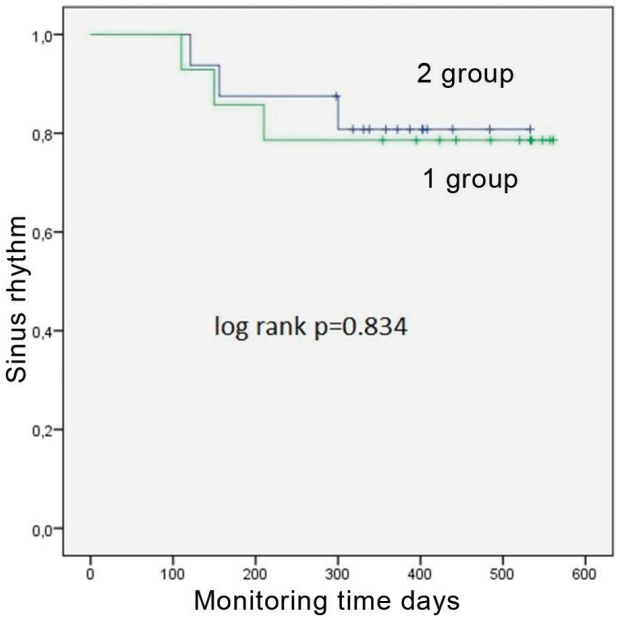

Figure 3. Frequency of sinus rhythm preservation in group 1 (IPVO+PW) and group 2 (IPVO).

The meta-analysis by F. Lupercio et al. included data from 7 studies and 1152 patients. Patients who underwent posterior wall isolation in addition to PVI had a lower rate of recurrent AF (OR 0.55; 95% CI 0.39-0.77) as well as a lower rate of any atrial arrhythmias (OR 0.78; 95% CI 0.63-0.96) [4].

A meta-analysis by A.Thiyagarajah et al. evaluated the acute success of PWLA isolation and the number of complications associated with the procedure, as well as the long-term clinical effect, including the rate of recurrence of arrhythmias and restoration of conduction with PWLA. The final analysis included 17 studies (13 with box lesion posterior wall isolation, 3 with single ring isolation, 1 study with removal of LA posterior wall potentials) with 1643 patients. The incidence of acute success of PWLA isolation was 94.1% (95% CI, 87.2-99.3%). The 12-month freedom from any atrial arrhythmia after intervention was 65.3% overall (95% CI 57.7-73.9%) and 61.9% (54.2-70.8%) for persistent AF. Randomised controlled trials comparing PWLA isolation with PVI (3 trials, 444 patients) had inconsistent results and found no advantage for the PWLA isolation group. Repeat procedures were required in 161 patients, and the rate of restoration of conduction at the LA posterior wall was 63.1% (95% CI, 42.5-82.4%). Fifteen major complications (0.1%) have been reported - 10 cases of hemopericardium requiring drainage, 3 strokes, and 2 atrioesophageal fistulas [8].

As the role of PWLA isolation remains unclear, researchers around the world continue to address this question. There are several randomised multicenter studies investigating the effect of PWLA isolation on the efficacy of treatment of persistent AF. In total, about 1700 patients will participate in these five studies [14]. Perhaps the results can answer the question of who and when to isolate PWLA and in what way.

STAR AF II is a study that questioned the efficacy of extra PV lesions in LA in persistent AF. Patients who received only PVI had similar results in preserving sinus rhythm at follow-up as those who received additional interventions, with a significantly shorter surgery time and duration of RFA. However, the efficiency of the surgery did not exceed 50-55% [3]. In our study, sinus rhythm was preserved in 80% of patients with longer follow-up periods. There may be several explanations for this fact. First, the STAR AF II study did not use clamping force-controlled catheters, which could have affected the permanence of the lesion lines created in LA. Secondly, routine IC EPE allowed identifying patients with restoration of excitation conduction in previously isolated areas, who had no clinics of recurrent AF. Timely reinstatement of the blockade could improve the long-term results.

It should be noted that even with modern technol-

ogies, it is quite difficult to achieve isolation of PWLA, which is related to the anatomical features of the LA structure and the risk of collateral damage when using RFA energy [12]. Only in 21.4% of the patients in our case, isolation of the PWLA could be achieved after performing a series of lesions according to the «box lesion» scheme, and the rest required additional RFA outside the roof and floor lines. This observation suggests the presence of epicardial fibers on PWLA, which must be effectively eliminated to obtain persistent PWLA isolation [15]. Sometimes, however, this may require extensive RFA to be applied to PWLA, potentially increasing the risk of complications, especially esophageal damage. The advent of alternative energy sources such as pulsed field ablation, which have a tropism for cardiomyocytes, reduces the risk of collateral damage and can potentially improve the long-term outcomes of interventional treatment of persistent AF [16]. Thus, in the PersAFOne study (25 patients), when pulsed field ablation technology was used, acute isolation of PVI and PWLA was achieved in all patients participating in the study. When repeated IC EPE was performed 3 months later, PVI was preserved in 96% of cases, and PWLA isolation was confirmed in 100% of patients. At the same time, no patient showed signs of esophageal damage or PV stenosis [17].

The lack of difference in the results of RFA in the isolation of PWLA may be due to the peculiarities of the currently used classification. At the moment, the definition of persistent AF has a rather broad scope. Patients in different clinical situations may have the same diagnosis and receive the same treatment. At the same time, some researchers distinguish an early (up to 3 months) and a late persistent form of AF [17]. It is likely that the distinction of different subtypes of persistent AF will allow a more differentiated approach to determining indications for additional influences outside the pulmonary veins.

CONCLUSION

In our study, isolation of the posterior wall of the left atrium in addition to isolation of the pulmonary vein in patients with persistent AF did not improve treatment efficacy with significantly longer procedure duration and radiofrequency ablation. Permanent isolation of the posterior wall of the left atrium is a difficult task even with modern technology.

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WARFARIN VERSUS NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS: HOW THE DEGREE OF ANTICOAGULATION DIFFERS DURING CATHETER ABLATION OF ATRIAL FIBRILLATION

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Aim. To evaluate intraoperative doses of administered heparin to achieve the target value of activated clotting time (ACT) in patients receiving preoperative anticoagulant therapy with warfarin or one of the non-vitamin K antagonists oral anticoagulants (NOAC).

Materials and methods. The study was of a retrospective. Inclusion criteria: patients with atrial fibrillation (AF) who have indications for catheter ablation in accordance with national clinical guidelines; age 18-75 years; absence of thrombus and the effect of echocontrasting 3-4 stage in the left atrium cavity according to transesophageal echocardiography or computed tomography with contrast enhancement; regular intake of anticoagulants prescribed at least 3 weeks before hospitalization. Exclusion criteria: additional intake of antiplatelet drugs; contraindications to the anticoagulant therapy, including intolerance to the components of drugs; weight more than 100 kg. According to the criteria for inclusion in the study 279 patients were included (211 of them received warfarin and 68 received one of the NOAC). The mean age of the patients was 59.2±8.9 years, the body mass index was 59.2±8.9 kg/m^2. Among them, men accounted for 155 (55,6%), diabetes mellitus was diagnosed in 28 (10%), arterial hypertension - in 224 (80.3%), coronary heart disease - in 103 (36.9%). Paroxysmal AF was observed in 185 (66.3%) of patients, persistent AF - in 77 (27.6%), and long-standing persistent AF - in 17 (6.1%). To ensure maximum comparability of the groups pseudorandomization was performed with the formation of 67 pairs of patients.

Results. A group of patients taking warfarin for preoperative preparation required lower doses of heparin to achieve the target ACT and amounted to 14.8±5.1 thousand ME compared to 17.9±4.4 thousand ME in the NOAC group (p=0.0001). Despite the lower dose of heparin the ACT level in the warfarin group was significantly higher than in patients taking NOAC (441.5±203.4 sec. and 345.4±148.8 sec. accordingly, p=0.0001).

Conclusions. A significantly lower dose of heparin was required in the warfarin group to achieve the target ACT (>300) than in the group of NOAC, while the maximum ACT value was higher. Thus, with the standard starting dose of heparin, the target anticoagulation was achieved faster in patients receiving warfarin.

Keywords: atrial fibrillation, catheter ablation, direct oral anticoagulants, indirect anticoagulants, activated platelet time

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Catheter ablation (CA) for atrial fibrillation (AF) has become an effective alternative to drug therapy and complex open-heart surgery in recent years [1-3]. Considering the high risk of thromboembolic complications (TE complication) caused by left atrial surgery (LA), radiofrequency ablation (RFA) should be performed against a background of mandatory anticoagulant therapy [4, 5].

The procedure of anticoagulation before, during and after CA is carefully prescribed in the guidelines of the Russian Society of Cardiology and ESC [1, 3]. For preoperative preparation, the recommendations allow the use of both warfarin with a target international normalised ratio (INR) of 2.0-3.0 and non-vitamin K antagonist oral anticoagulants (NOACs). Intraoperatively, all patients should receive intravenous heparin at a dose of 5000-15000 IU (or 90-200 IU/kg) with a target activated clotting time (ACT) of more than 300 s [6], but no standard dose is given in the guidelines.

There is evidence that preoperative preparation for NOACs requires a higher dose of heparin to achieve the target ACT [7]. Thus, there is a discrepancy between the standard initial intraoperative heparin dose regardless of the anticoagulant used for preoperative preparation. This topic is inadequately covered and requires further investigation.

Purpose of the study: To evaluate the intraoperative heparin dose administered to achieve the target value ACT

in patients receiving preoperative anticoagulant therapy with warfarin or one of the NOACs.

MATERIALS AND METHODS

The study was retrospective. A total of 492 patients who had undergone RFA for AF at our centre in 2020 were studied. 279 patients were included in the study.

Inclusion criteria:

- Patients with AF with indications for CA according to national clinical guidelines;
- Age 18-75 years;
- Absence of thrombus and grade 3-4 echocontrast in the LA cavity according to transoesophageal echocardiography (EchoCG) or absence of thrombus according to contrast-enhanced computed tomography (CT);
- Regular use of anticoagulants prescribed at least 3 weeks prior to hospitalisation;

Exclusion criteria:

- Additional intake of antiplatelet drugs;
- Contraindications to anticoagulant therapy, including intolerance to components of the medication;
- Weight of more than 100 kg.

The clinical and demographic characteristics of the patients included in the study are listed in Table 1. All patients were examined before surgery: general clinical tests, coagulogram, coronarography for men over 40 and women over 50 (this is the standard examination before RFA of AF in our clinic), EchoCG, transoesophageal EchoCG or CT with contrast enhancement to exclude a thrombus in the cavity LA.

Anticoagulant therapy was administered for at least 3 weeks prior to catheter ablation of AF. Patients taking warfarin achieved and maintained INR at a therapeutic level of 2.0-3.0 at least 3 weeks before hospitalisation. NOACs were discontinued 12 hours before surgery in all patients in our study. Patients taking warfarin did not discontinue the drug before surgery. The surgeries were performed under intravenous sedation with dexedemetomidine and fentanyl. Transseptal puncture (TSP) was performed twice under fluoroscopic control, and 2 unguided intravesicles were injected into the cavity LA. Intraoperatively, all patients received a heparin loading dose of 10,000 units (Republican Unitary Enterprise Belmedpreparaty, Republic of Belarus) in the preoperative period, regardless of anticoagulant therapy, according to TSP, and then a bolus infusion was administered until ACT time values above 300 s were reached. The heparin dose was 15.6±5.1 thousand IU. The first measurement of ACT level was performed every 10 min after the loading dose until the ACT target values≥300 s were reached, then every 30 min. The maximum value of ACT reached 418.1±197.3 s. Heparin solution was also continuously flushed through the infusion device at a rate of 250 r/h for intravenous tubing.

After pulmonary vein angiography, an anatomical map of LA was created using the CARTO 3 3D Mapping System (BiosenseWebster, Johnson & Johnson, USA). RFA was performed using EZ SteerNav and EZ SteerNav SF bidirectionally irrigated electrodes (BiosenseWebster, Johnson & Johnson, USA) without clamp force control. A Stockert RF energy generator (BiosenseWebster, Johnson

Table 1.

Clinical and demographic characteristics of patients who received warfarin or one of the NOACs

	Total (n=279)	Warfarin (n=211)	NOACs (n=68)	P	Warfarin* (n=67)	NOACs* (n=67)	P
Age, years	59.2±8.9	58.7±8.9	60.9±8.6	0.047	58.7±8.9	60.1±8.3	0.077
Male gender, n (%)	155 (55.6)	124 (59.1)	31 (44.9)	0.038	38 (56.7)	30 (44.8)	0.100
BMI, kg/m^2	29.5±3.9	29.3±3.8	29.8±4.1	0.377	29.8±3.9	29.8±4.0	0.387
Diabetes mellitus, n (%)	28 (10.0)	18 (8.5)	10 (14.7)	0.164	6 (8.9)	10 (14.7)	0.204
Arterial hypertension, n (%)	224 (80.3)	161 (76.3)	63 (92.6)	0.003	56 (83.6)	62 (92.5)	0.126
CHD, n (%)	103 (36.9)	73 (34.8)	30 (43.4)	0.408	32 (47.8)	30 (44.8)	0.473
Paroxysmal AF, n (%)	185 (66.3)	136 (64.8)	49 (71.0)	0.590	45 (67.1)	47 (71.1)	0.692
Persistent AF, n (%)	77 (27.6)	60 (28.6)	17 (24.6)		18 (26.9)	17 (25.4)	
LS AF, n (%)	17 (6.1)	14 (6.6)	3 (4.4)		4 (6.0)	3 (4.5)	
CHA_2DS_2-VASc (points)	1.92±1.23	1.85±1.25	2.16±1.13	0.042	1.94±1.24	2.02±1.12	0.143
Creatinine, μmol/l	96.6±20.1	97.9±19.1	92.6±22.3	0.080	94.3±17.1	92.5±22.3	0.112
Creatinine clearance, ml/min	68.5±15.8	68.1±15.7	69.6±15.8	0.483	66.9±17.7	69.5±15.9	0.454
Hemoglobin, g/l	142.9±13.5	143.5±13.5	141.3±13.3	0.255	144.1±13.6	141.2±13.4	0.299
Operation time, min	98.4±33.1	100.1±35.1	93.5±25.6	0.160	99.2±32.3	93.7±25.4	0.365
Complications, n (%)	8 (2.9)	5 (2.4)	3 (4.4)	0.413	2 (3.0)	3 (4.4)	0.434
Hemopericardium, n	4	3	1		1	1	
Arterio-venous junction, n	2	1	1		1	1	
Pulsating hematoma, n	2	1	1		0	1	

Note: NOACs, non-vitamin-K-dependent oral anticoagulants; *, after pseudorandomisation; P, significance of differences between groups; BMI, body mass index; CHD, coronary heart disease; AF, atrial fibrillation; LS, long-standing; CHA_2DS_2-VASc, ischemic stroke and systemic thromboembolism risk prediction scale for AF.

& Johnson, USA) was used in energy control mode. After ablation was completed and the introducers were removed from the LA cavity, 50 mg protamine sulfate (Ellara LLC, Pokrov city) was injected intravenously. A Z-shaped suture was placed at the puncture site in the groyne.

In the postoperative period, haemodynamics and electrocardiography were monitored with bedside monitors for 3 hours, and ultrasound examination of the pleural cavities and pericardium was performed. If haemorrhagic complications could be excluded, anticoagulant therapy was resumed in the postoperative period 4-6 hours after ablation and continued for at least 8 weeks.

Warfarin as an oral anticoagulant was taken by 211 of the 279 patients and 68 were taking one of the NOACs. The clinical and demographic characteristics of the patients are shown in Table 1. The patient groups differed on the basis of four parameters (age, sex, presence of arterial hypertension and CHA_2DS_2-VASc score). To exclude systematic errors and maximise group comparability, pseudorandomisation was performed (propensity score matching) using the 1:1 nearest neighbour method. The following 13 covariates were used (age, sex, body mass index, presence of diabetes mellitus, arterial hypertension and ischaemic heart disease, type of AF, CHA_2DS_2-VASc score, creatinine level and clearance, haemoglobin, time of surgery, presence of complications)..

Statistical analysis

All clinical data of the patients were taken from the electronic medical record («Medialog 7.10 B0119»). The results were statistically analysed using IBM® SPSS® StatisticsVersion 23 (23.0). All quantitative variables were checked for their distribution type using the Kolmogorov-Smirnov criterion, graphically using quantile diagrams and skewness and kurtosis indices. If the distribution was symmetrical, the results are reported as arithmetic mean and standard deviation (M±SD). If the distribution was not symmetrical, the values are represented by the median (Me) and the interquartile range as 25th and 75th percentiles. The Mann-Whitney test was used for the analysis. Frequencies and fractions (percentages) calculated by the Wilson method were used to describe qualitative data. Qualitative variables were compared using Pearson's χ^2 test. The critical significance level was set at ≤0.05.

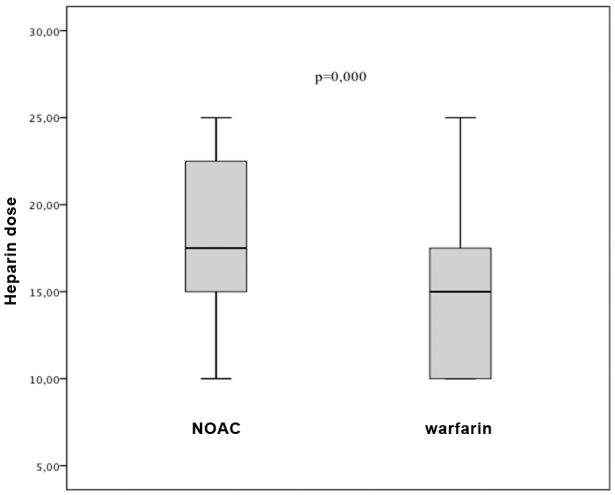

Fig. 1. Mean heparin dose to achieve target activated platelet time (ACT) in groups of patients treated with warfarin or one of the non-vitamin-K-dependent oral anticoagulants (NOACs).

RESULTS

After pseudorandomisation, the warfarin group (n=67 patients) and the NOACs group (n=67 patients) were comparable at baseline. The data are shown in table 1. INR was significantly higher in the warfarin group (2.36±0.82 versus 1.21±0.22 in the NOACs group, p=0.000), which is meaningful. Target INR was achieved in 49 (73.1%) patients treated with warfarin. Heparin doses to reach the target ACT were significantly higher in the NOACs group (17.9±4.4 thousand IU vs. 14.8±5.1 thousand IU in the warfarin group, p=0.0001). At the same time, the maximum value of ACT was higher in the warfarin group (441.5±203.4 s vs. 345.4+148.8 in the NOACs group, p=0.0001). The data are shown in figures 1 and 2.

The following drugs were used in the NOACs group: apixaban in 16 patients at a dose of 10 mg daily, rivaroxaban in 40 patients at a dose of 20 mg daily and dabigatran in 11 patients at a dose of 300 mg daily. The dose of heparin to achieve the target ACT did not differ by type of NOACs (16.6±4.6, 18.7±4.3, 16.8±4.3; p=0.594), nor did the maximum ACT value during surgery (335.1±39.1; 359.1±188.6; 309.5±37.3; p=0.175). The number of intraoperative complications related to anticoagulation therapy (haemopericardium, arteriovenous junction, pulsatile haematoma) was comparable in the warfarin and NOACs groups (3.0% and 4.4%, p=0.434). There were no strokes and transient ischaemic attacks in the postoperative period.

DISCUSSION

CA for AF has become an effective alternative to drug therapy and complex open-heart surgery in recent years [1-3, 8-10]. All patients with AF during paroxysm have some risk of TE complications [11, 12]. In addition, even in these patients, the catheter procedure increases the risk of TE complications caused by TSP and insertion of introducers into LA and radiofrequency damage to the atrial endothelium during ablation [13-15]. In addition, the atrial tissue may be anaesthetised for several weeks or months after ablation, leading to disruption of normal LA contraction and increased risk of thrombosis [16]. However, the prothrombotic state after the procedure is reversible. Therefore, patients with AF are at increased risk of thromboembolism during, immediately after and for several days or months after CA [17-20].

Therefore, cerebrovascular complications associated with CA for AF are relatively rare, usually occur either during the procedure or within the first 24 h after AF and have a benign course. In our study, there were also no cases of stroke or transient ischaemic attack in either group. Previous ischaemic stroke, mechanical heart valve and CHA_2DS_2-VASc≥3 risk of thromboembolic complications are independent predictors of such complications [19]. Consequently, careful monitoring of patients' anticoagulation levels before, during and after CA is crucial for AF to prevent the occurrence of thromboembolism.

At the same time, low anticoagulation levels contribute to some of the most common complications of the

procedure, including haemopericardium, cardiac tamponade and vascular complications. Therefore, care must be taken to achieve optimal, safe coagulation levels as soon as possible throughout the procedure. A number of authors also report that the incidence of AF ablation complications correlates directly with higher CHA_2DS_2-VASc scores, inversely with increasing operator experience and independently of the type of anticoagulant therapy (assessed both individually by drug and by class as a whole) [21, 22]. In our study, we obtained similar data, such that the number of intraoperative complications, such as haemopericardium, arteriovenous transition and pulsatile haematoma, was comparable in the warfarin and NOAC groups (3.0% and 4.4%, p=0.434).

There have been recent changes in the approach to anticoagulant therapy before, during and after catheter ablation. This is also due to the advent of NOACs, whose effective and safe use in patients with non-valvular AF has been demonstrated in the ARISTOTLE (apixaban), RELY (dabigatran), ROCKET-AF (rivaroxaban) trials [23, 24].

Many patients who underwent CA for AF are at high risk for TE complications (CHA2DS2VASc≥2 points), so they are prescribed anticoagulant therapy with warfarin under INR control with achievement and maintenance of a therapeutic INR of 2.0-3.0 or a direct thrombin inhibitor (dabigatran) or factor Xa (rivaroscaban, apixaban). In the case of preparation for CA, anticoagulant therapy is prescribed at least 3 weeks before the procedure, regardless of the risk of TE complications [1, 2, 5]. The mean CHA_2DS_2-VASc score in the patients in our study was 1.92±1.23, so anticoagulant therapy was administered as an outpatient more than 3 weeks before the planned hospitalisation.

A number of authors have also reported the need to perform a transoesophageal EchoCG or contrast-enhanced CT prior to the procedure to detect thrombus or spontaneous echo-contrast effect of the LA cavity regardless of the risk of TE complications, which is also included in the local protocol of patient examination prior to CA in our hospital. As the incidence of thrombus or echocontrast effects varies between 1.6% and 2.1% despite continuous anticoagulant therapy, it is directly proportional to the risk of TE complications on the CHA_2DS_2-VASc scale and the form of AF (persistent or long persistent), although not always [25, 26].

Thanks to a prospective, open-label, randomised, multicentre COMPARE study published in 2014 that found no differences in the risk of TE and haemorrhagic complications with catheter ablation of AF on a background of continuous warfarin therapy, many centres, including ours, have abandoned «bridge therapy» prior to catheter ablation of AF (i.e. discontinuing warfarin and switching to low-molecular-weight heparins) [4].

Unlike warfarin, NOACs have a faster onset of action, a shorter half-life, no association with food intake and a more predictable response to the prescribed dose. Several meta-analyses have shown NOACs to be similarly effective and safe compared with warfarin (CA) [7, 27, 28-31]. However, most of these studies omitted one or two doses of NOACs before CA for AF procedures. Based on the results of the RE-CIRCUIT (direct comparison of the performance of AF ablation in patients receiving continuous dabigatran and warfarin) and Venture- AF (comparison of the performance of AF ablation in patients receiving continuous rivaroxaban and warfarin) trials, the data are now considered sufficient to provide a class I recommendation for the implementation of CA for AF with continuous dabigatran (evidence level A) or rivaroxaban (evidence level A) and a class IIa recommendation for other Ha factor inhibitors for which no specific clinical trials have currently been conducted or are ongoing (as in the case of apixaban). Resumption of anticoagulant therapy is recommended 4-6 hours after ablation, provided that haemorrhagic complications are excluded.

All patients in our study who received NOACs were discontinued 12 hours before the procedure CA. Patients receiving warfarin did not discontinue the drug before the procedure. Therapy was resumed 4-6 hours after surgery, after haemorrhagic complications had been ruled out.

Optimal intraoperative anticoagulation with unfractionated heparin to achieve and maintain a target value ACT of 300 seconds or more (class I recommendation) also plays an important role in minimising haemorrhagic and TE complications. A number of researchers have observed that thrombi can form at the atrial septum and/or catheter almost immediately after TSP despite preoperative anticoagulant therapy and that early administration of heparin significantly reduces this risk. Therefore, in AF ablation procedures, it is recommended that heparin be administered before or immediately after TSP and that it be adjusted to achieve and maintain ACT target values of more than 300 seconds [7-9]. A meta-analysis of studies involving more than 7,000 patients also showed a reduced risk of TE complications without an increased risk of bleeding when the target ACT of more than 300 seconds was achieved during AF ablation [32]. ACT should be monitored at 10-15 minute intervals until therapeutic anticoagulation is achieved and then at 15-30 minute intervals throughout the procedure. Heparinised saline should be administered continuously through each intravenous line to further reduce the risk of thrombosis. The heparin infusion can be stopped after all catheters have been removed from

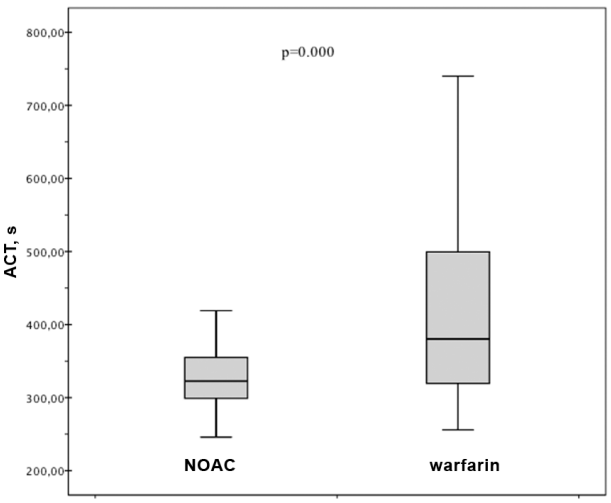

Fig. 2. Maximum activated platelet time (ACT) values in the groups of patients treated with warfarin or one of the non-vitamin-K-dependent oral anticoagulants (NOACs).

LA. At the end of surgery, it is possible to administer protamine to inactivate the effect of heparin (recommendation class IIA) [1].

A number of authors have found that patients receiving warfarin require lower doses of heparin and achieve their ACT goals more quickly than patients receiving NOACs [7, 32]. A survey of different author groups also found a wide variability in heparin loading protocols before ablation. The initial heparin bolus for patients taking warfarin was 50 U/kg, 75 U/kg for patients not taking an anticoagulant prior to CA for AF and 120 U/kg for patients taking one of the NOACs. Thus, a patient weighing 80-100 kg received an initial bolus of 4.0-5.0 thousand IU when using warfarin, 6.0-7.5 thousand IU without an anticoagulant preparation and 9.6-12.0 thousand IU before taking NOACs. The use of higher doses of heparin preoperatively with NOACs than in patients without anticoagulant treatment is quite surprising.

In our observational series, all patients received the first dose of heparin 10,000 IU, regardless of the anticoagulant administered. At the same time, in the warfarin group, the dose of heparin to reach the target value ACT (> 300) was significantly lower than in the NOACs group (14.8±5.1 thousand IU and 17.9±4.4 thousand IU, p=0.0001), and the maximum ACT value was higher (441.5±205.4 and 345.4±148.8, p=0.0001).

To understand and suspect the cause of this phenomenon, it is necessary to know the scheme of the coagulation cascade and the mechanism of action of each drug on the coagulation steps [33]. The coagulation cascade can be activated either internally or externally, leading to thrombin activation and subsequent fibrin formation.

Anticoagulants are divided into two groups: direct-acting anticoagulants (unfractionated heparin, low molecular weight heparins, directly activated X (Xa) factor inhibitors rivaroxaban and apixaban, direct-acting thrombin inhibitor dabigatran) and indirect-acting (warfarin).

Unfractionated heparin inhibits the activity of the factors IX, X, XI, XII, thrombin (IIa). Unlike warfarin, which blocks the formation of several clotting factors (factors II, VII, IX and X), NOACs block the activity of a single clotting step. Apixaban and rivaroxaban inhibit the clotting of factor Xa, while dabigatran is a direct inhibitor of thrombin.

NOACs are also characterised by a faster onset of action (apixaban and rivaroxaban reach maximum blood concentrations within 2to 4 hours and dabigatran - 0.5to 2 hours) and a shorter elimination half-life (for apixaban 12 hours, dabigatran 12to 17 hours, rivaroxaban 5to 13 hours). At the beginning of warfarin therapy, the clotting process is not blocked immediately because there is a «reserve» of circulating prothrombin and related clotting factors. The maximum effect of the drug occurs on the 3-5th day after starting the prescription and ends 3-5 days after stopping the drug.

As shown in the scheme of the coagulation cascade, the simultaneous interaction of heparin and NOACs blocks the activity of a common coagulation step. Thus, the interaction of direct inhibitors of clotting factor Xa and unfractionated heparin impairs the activity of factors IX, X, XI, XII, thrombin (IIa). The interaction of a direct thrombin inhibitor with unfractionated heparin also influences the activity of the factors IX, X, XI, XII, thrombin (IIa). In the case of an interaction between warfarin and unfractionated heparin, more factors are eliminated from the clotting process: II, VII, IX, X, XI, XII, which in turn can lead to a stronger hypocoagulation effect. And since warfarin initially already inhibits several clotting factors that are also affected by unfractionated heparin, a lower dose of heparin is required.

Another reason for the higher need for intraoperative heparin and the lower ACT levels in patients taking NOACs could be a shorter half-life of this group of drugs and the usual skipping of the dose on the eve of surgery. In our opinion, patients taking warfarin or any of the NOACs for preoperative preparation before CA for AF should receive different initial doses of heparin intraoperatively. In addition, the heparin dose should be higher in patients taking NOACs in the preclinical phase. Determining the optimal starting dose of heparin requires further study. A limitation of our study is its retrospective observational nature.

CONCLUSION

In our observational series, the warfarin group required a significantly lower dose of heparin to reach the target ACT (> 300) than the NOACs group, while the maximum ACT was higher. Thus, with a standard starting dose of heparin, target anticoagulation was reached faster in patients treated with warfarin.

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DIFFERENT RESPONSE CRITERIA TO CARDIAC RESYNCHRONIZATION THERAPY IN PATIENTS WITH CONGESTIVE HEART FAILURE

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Aim. To investigate the agreement among different response criteria to cardiac resynchronization therapy (CRT) and long-term mortality in patients with congestive heart failure (CHF).

Methods. The study enrolled 141 patients (men 77.3%; women 22.7%) with CHF (65.2% ischemic and 34.8% non-ischemic etiology). Mean age was 58.6 [53.0;66.0] years. All patients had NYHA II-IV, left ventricular ejection fraction (LVEF) ≤35%; QRS ≥130 мs and/or left bundle branch block. Mean follow-up period was 45.0±34.2 months. Response to CRT was defined according to dynamics of NYHA functional class, LVEF, and left-ventricular end-systolic volume (LVESV).

Results. Moderate agreement was found among LVEF and LVESV (Cohen's k coefficient 0.591±0.068) while we did not find the agreement among echocardiographic criteria and NYHA. Long-term mortality had moderate negative correlation with LVESV (r=-0.486; p<0.001), weak negative correlation with LVEF (r=-0.297; p<0.001), no significant correlation with NYHA functional class was found (r=-0.102; p=0.298). The correlation among long-term mortality and LVESV was significantly stronger when compared with long-term mortality and NYHA correlation (p<0.001), and no significant differences were found when compared with long-term-mortality and LVEF correlation (p=0.086).

Conclusion. Agreement between different criteria to define response to CRT is poor. The strongest correlation with long-term mortality was found for LVESV. This inconsistency among different response criteria severely limits the ability to generalize results over multiple CRT studies.

Key words: survival; mortality; response criteria; cardiac resynchronization therapy; congestive heart failure; echocardiography

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Cardiac resynchronization therapy (CRT) is an effective treatment for patients with congestive heart failure (CHF) with reduced ejection fraction and prolonged QRS duration. Large multi-center clinical trials have confirmed that CRT can improve cardiac function, exercise capacity and quality of life in patients with CHF. CRT reduces mortality and hospitalization and can also improve the prognosis in CHF patients [1, 2]. About 30% patients do not respond adequately to CRT and search of new selection criteria and respond predictors is one of the most important questions of CRT implantation [3-7]. In most trials, prognostic models for CRT response were based on baseline clinical and functional parameters. Meanwhile, there is a lack of consensus on the definition of response to CRT and in what period after implantation it should be assessed. clinical and echocardiographic response criteria were used [8, 9].

A joint position statement from the Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology (ESC) calls to stop the current binary approach of CRT response and calls for the response to be individualized for every patient [10]**.** Thus, it worth to compare the agreement of different response criteria to CRT in real clinical practice, and to analyze the relationship between different response criteria and long-term mortality.

Aim. To investigate the agreement among different response criteria to CRT and long-term mortality in patients with CHF.

MATERIAL AND METHODS

This study enrolled 141 patients from local database of implanted CRT devices (mean age 58.6 [53.0;66.0] years, 77.3% men) with CHF (92 patients with ischemic and 49 with non-ischemic etiology) [11]. Main criteria for CRT implantation were New York heart association (NYHA)

functional class II-IV, reduced left ventricular ejection fraction (LVEF) <35%, QRS ≥ 130 ms, and left bundle branch block. Combined devices with defibrillator function (CRT-D) were implanted in 64.5% of patients. The device implantation was effective in all patients and occurred without complications. All patients received medical treatment according to the current guidelines [1].Clinical characteristics of the study participants are shown in Table 1.

At baseline, after 1 month, 3 months, and every 6 months after implantation we evaluated clinical, electrocardiographic, and echocardiographic parameters. Standard echocardiography was performed using a commercially available system Philips IE 33.

The study was conducted in accordance with the ethical standards of the Local Institutional Review Board and with the 1964 Helsinki declaration and its later amendments. This project was approved by the Local Bioethics Committee. All patients gave their written informed consent before the study.

Mean follow-up period was 45.0±34.2 months. Response to CRT was evaluated retrospectively according to the best dynamics of NYHA functional class, LVEF, left ventricle end-systolic volume (LVESV). According to dynamics of these parameters patients were divided in 4 groups: non-responders (increase of NYHA functional class, decrease of LVEF, increase of LVESV); non-progressors (no changes of NYHA, increase of LVEF <5%, decrease of LVESV <15%); responders (1 grade decrease of NYHA, increase of LVEF 5-9%, decrease of LVESV 15-29%); superresponders (2 grade decrease of NYHA, increase of LVEF ≥10%, decrease of LVESV ≥30%)

Statistical analysis was performed using SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL, USA). In case of normal distribution results were expressed as the mean value ± standard deviation (mean±SD), in case of not normal distribution as median and interquartile range (Me [25%;75%])]). The χ^2 or Fisher's exact test were used to compare categorical variables. Continuous variables were compared using Student's t test for normally distributed variables or the Mann–Whitney test for non-normally distributed variables. The Cohen ***κ***-coefficient was used to assess agreement between the different response criteria. Cohen κ-coefficient <0.2 was defined as the absence of agreement, from 0.21 to 0.39 as minimal agreement, 0.40 – 0.59 – poor agreement, from 0.6 to 0.79 – moderate, from 0.8 to 0.9 – strong agreement, > 0.9 – almost ideal agreement [13]. To assess the relationship between the response to CRT and all-cause mortality a correlation analysis was performed with the calculation of the Kendall correlation coefficient. P<0.05 was significant.

RESULTS

According to dynamics of NYHA functional class 67 patients (47.5%) were responders, 15 patients (10.6%) - superresponders, 56 patients (39.7%) were non-progressors, and 3 patients (2.1%) – non-responders. According to dynamics of LVEF 57 patients (40.4%) were identified as superresponders, 33 patients (23.4%) were responders, 36 (25.5%) and 15 (10.6%) patients were identified as non-progressors and non-responders. When assessing the response to CRT according to dynamics of LVESV 55 patients (35.5%) were superresponders, 28 patients (19.9%) responders. 49 patients (34.8%) demonstrated decrease of LVESV 0-15% and were identified as non-progressors, in 14 patients (9.9%) LVESV increased when compared to baseline values (Fig. 1).

The lowest percentage of non-responders (2.1%) and at the same time the lowest percentage of superresponders (10.6%) were identified when assessing the response according to the dynamics of NYHA, and the largest percentage of superresponders (40.4%) when assessing response based on LVEF dynamics.

Fifty-five patients (39%) died during the observation period. The percentage of CRT-D devices did not

Table 1.
Clinical characteristics of the study participants (n=141)

Parameters	N (%)
Number of patients, n	141
Mean age, years	58.6 [53.0;66.0]
Male/female, n (%)	109 (77.3)/32 (22.7)
Non-ischemic etiology, n (%)	49 (34.8%)
Ischemic etiology, n (%)	92 (65.2 %)
Diabetes, n (%)	25 (17.7%)
Myocardial infarction, n (%)	64 (45.4%)
Atrial fibrillation, n (%)	34 (24.1%)
Radiofrequency ablation, n (%)	15 (10.6%)
Arterial hypertension, n (%)	102 (72.3%)
Left bundle branch block, %	111 (78.7%)
QRS, ms	172.87±26.3
QRS ≥150 ms	112 (79.4%)
QRS 130-149 ms	29 (20.6%)
LVEF, %	31 [27;33]
LVESV, ml	168.6 [142.0;207.1]
Left ventricular end-diastolic volume, ml	239.0 [209.0;289.0]
NYHA II, n (%)	59 (41.8%)
NYHA III, n (%)	62 (44.0%)
NYHA IV, n (%)	20 (14.2%)
ACEI/ARB (%)	136 (96.5%)
β-blocker, n (%)	128 (90.8%)
Diuretic, n (%)	119 (84.4%)
Statins, n (%)	84 (59.6%)
Digoxin, n (%)	39 (27.7%)
Spironolactone, n (%)	120 (85.1%)
Warfarin, n (%)	43 (30.5%)
Platelet inhibitor, n (%)	88 (62.4%)
Antiarrhythmic drugs, n (%)	24 (17.0%)
Targeted vein, n (%)	115 (81.6%)

Note thereafter: LVEF - left ventricular ejection fraction; LVESV - left ventricular end-systolic volume NYHA - New York Heart Association; ACEI - angiotensin-converting enzyme inhibitors; ARB - angiotensin II receptor blockers

differ between died and survived patients (56.4% vs 69.8% respectively: p=0.105). The rate of implantation of a left ventricular lead into the target vein also did not differ between deceased and survived patients (75% vs 86%; p=0.118). Among the deceased patients, the number of responders+superresponders was 16 (29.1%) when assessing by the decrease of LVESV, 29 (51.8%) when assessing by the decrease of NYHA class and 28 patients (50%) on LVEF assessment. Among the surviving patients, there was not a single non-responder when assessing the response according to the dynamics of LVESV and NYHA functional class. Kaplan-Meier curves are shown in Fig. 2.

Of 141patients, 118 (83.7%) showed a positive response according to at least 1 criteria, whereas 93 patients (66%) were classified as a non-responder by at least 1 criteria. Similarly, 48 patients (34.0%) showed a positive response by 3 criteria, whereas only 36 patients (25.5%) showed a positive response by 3 criteria and were alive during follow-up period.

The Cohen *κ*-coefficient demonstrated the absence of agreement between echocardiographic criteria and NYHA (κ-coefficient <0.2), and poor agreement between response defined by LVESV and LVEF (κ-coefficient 0.5) (Table 2).

Correlation analysis showed a significant moderate negative correlation of all-cause mortality with the response assessed by the dynamics of LVESV and a poor negative correlation with the response assessed by the dynamics of LVEF (Table 3).

Comparison of correlation coefficients showed a significant difference in the strength of the relationship between mortality and LVESV and NYHA (p<0.001), and no significant differences in the correlation coefficients of NYHA - LVEF (p=0.057) and LVEF - LVESV (p=0.086).

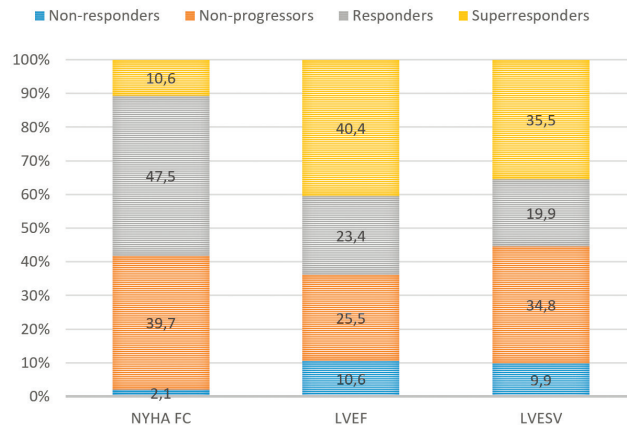

Fig. 1. Distribution of response to CRT using different criteria: dynamics of NYHA, LVEF, and LVESV.

DISCUSSION

The definition of response to CRT varies across clinical trials. Numerous variables including clinical and functional parameters, event-based, imaging, or composite outcomes have been used to describe response to CRT. Results of MIRACLE, MUSTIC SR, and MIRACLE ICD trials demonstrated that CRT could improve exercise capacity, quality of life, NYHA class and these criteria were used to evaluate the efficacy of CRT [14-16]. In other studies, echocardiographic parameters of reverse remodeling` (LVESV, LVEF) were used to define the response [17]. In several large multicenter studies hospitalization for CHF, total mortality, and cardiovascular mortality were used as a measure of the effect of CRT [18,19].

However, the agreement between echocardiographic and clinical criteria for defining a response to CRT is low. When 11 pairs of most cited response criteria were evaluated the agreement between response criteria was strong in only 7.6% of response criteria pairs [8, 9]. Yu C.M. et all did not find the agreement between the decrease of LVESV, improvement of NYHA class, increase in exercise tolerance, and improvement in the quality of life after CRT [20]. In a recent study by Bleeker et al. authors compared a decline in NYHA class (clinical response) with a 15% decrease in LVESV echo response) and concluded that the agreement of 76% [21]. In the MIRACLE trial, correlation between the change in left ventricular end-diastolic volume and change in NYHA class after 6 months of CRT was weak (r=0.13), and the correlation between the change in distance walked in 6 minutes and change in LVEF was weak (r=0.15) [14]. In addition, patients with reduction in LVESV 0-14% demonstrate improvement in clinical status and LVEF and survival rates compared to subjects with reduction in LVESV 15-30% [6]. The main conclusion that should be drawn from our study is similar: the agreement between echocardiographic and clinical criteria for defin-

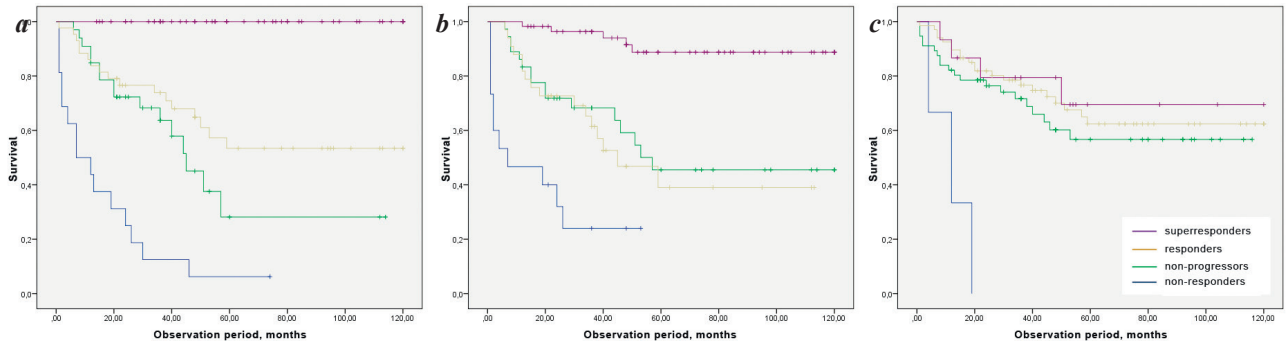

Fig. 2. Kaplan-Meier curves for groups with different response to CRT defined by: a - LVESV: Log Rank test: non-responders vs all groups p<0.001; non-progressors vs responders p=0.167; superresponders vs all groups p<0.001. b - LVEF: Log Rank test: non-responders vs all groups p<0.05; non-progressors vs responders p=0.280; superresponders vs all groups p<0.001. c - NYHA: Log Rank test: non-responders vs all groups p<0.05; non-progressors vs responders p=0.386; superresponders vs non-progressors p=0.381; superresponders vs responders p=0.748.

ing a positive response to CRT is only slightly better than that expected by chance alone.

Previous studies have reported different rates of CRT response when different definitions of response were used within the same population. For example, the PROSPECT study reported that 56% of patients were echocardiographic responders (decrease of LVESV ≥15%), whereas 69% of patients were clinical responders (improvement in the clinical composite score) [17]. Thus, different measures of CRT response can lead to incorrect management of patients in clinical practice and inadequate interpretation of the results of studies aimed at finding predictors of response to CRT.

We found a comparable percentage of patients with a positive response to CRT (responders+superresponders) using different criteria, however, according to our data, there was poor or no agreement between the criteria. The number of superresponders when assessing by echocardiographic criteria was significantly higher in comparison with the assessment of NYHA, and the lowest percentage of non-responders was found when we used dynamics of NYHA as a response criterion.

Whether death should be considered a nonresponse to CRT is an area in which there is inconsistency. There are at least 3 different methods that authors have used to incorporate death into response criteria: cardiovascular death, death due to worsening of CHF, and death due to any cause. Although inclusion of all-cause mortality as a criteria for nonresponse may not be appropriate, a patient who dies of worsening of CHF should, objectively, be classified as a non-responder. Regardless, there is no consistent method for incorporating mortality into the definition of response to CRT, and this needs to be standardized.

We considered all-cause mortality as an endpoint. None of the survived patients was non-responders when using NYHA class or LVESV as a response criteria. At the same time, about half of the deceased patients were responders or superresponsors when assessing the dynamics of LVEF (50%) and NYHA (51.8%). In recent studies with a large population of heart failure patients treated with CRT the reduction in LVESV demonstrated to be a better predictor of long-term survival than improvement in the clinical status [22-25], that was confirmed in our study. Nakai T. et al concluded that the functional response definition (NYHA) is associated with a higher response rate and better clinical outcomes than that of the echocardiographic response definition, and therefore it is reasonable to use the functional definition to assess CRT response [26]. Potentially this result may be explained by high percentage (70%) of patients who had NYHA III at baseline in the study of Nakai T. el al, while only 14% of patients had NYHA II. In our study, 42% of patients had NYHA II, that means they had less severity of CHF. In addition, the follow up period in the study of Nakai T. et al was 6 months. Previously CRT has been shown to have early effect during first year on clinical response (NYHA), but long-term effect on reverse remodeling [6, 27].

In our study combined CRT-D devices were implanted in 64.5% of patients and 35.5% of patients received CRT-P. Some recent large observational studies highlighted the importance of CHF etiology in the assessment of potential benefits of CRT-D over CRT-P. CRT-D was associated with a significant risk reduction in all-cause mortality compared with CRT-P in patients with ischemic cardiomyopathy [28]. Data from the DANISH trial illustrate that a strategy for routine implantation of CRT-D versus CRT-P for patients with a non-ischemic etiology does not improve overall long-term survival [29]. Recent CRT guidelines indicate the addition of cardioverter-defibrillator to CRT should be considered, especially in younger patients with a good survival prognosis, ischemic etiology, and a favorable comorbidity profile or presence of myocardial fibrosis. Moreover, the benefit of the implantable cardioverter-defibrillator is governed by the balance between the risk of sudden cardiac death and the risk of death from other causes, as well as comorbidities [1, 2, 30]. A joint position statement from the HFA, EHRA, and EACVI of the ESC indicates that a process of shared decision-making should guide the choice between CRT-P and CRT-D between patients and clinicians, considering both medical facts and patient values [10]. It should be noted that most part of CRT-P devices was implanted before 2012. Subsequently, CRT-D devices were implanted for all CHF patients, except for isolated cases. More than 80% of CRT-P devices were implanted in patients with non-ischemic etiology of CHF with NYHA III/IV.

CRT is one of the most effective therapies for CHF resulting in improved quality of life, beneficial reverse remodeling and reductions in heart failure hospitalization rates and all-cause mortality. Mechanisms of the positive effect of CRT may differ among cases that limits the ability to compare the results of different studies and makes difficulties in real clinical practice. Numerous variables including functional, event-based, imaging, or composite outcomes have been used to describe response to CRT. The importance of certain metrics might differ according to the stakeholders, such as patients, doctors, payers, or industry. Indeed, the size and shape of the ventricle is irrelevant for patients complaining of exercise intolerance. For a patient with CHF and NYHA II the most significant effect will be a slowdown in the progression of CHF, and such a patient will not experience a significant improvement in NYHA. For a patient with coronary artery disease and prior myocardial infarction an improvement in prognosis will be much more important measure than a decrease in LVESV.

Table 2.

Agreement among the response criteria

Criteria for assessment of CRT response	LVEF	NYHA
LVESV	0.591±0.068*	0.192±0.083
LVEF	-	0.168±0.083

Table 3.

Agreement among response criteria and all-cause mortality

Criteria for assessment of CRT response	LVESV	LVEF	NYHA
Total mortality	r=-0,486 p<0,001	r=-0,297 p<0,001	r=-0,102 p=0,298

The aim of CRT may also differ among cases. No consensus exists on how or when to measure response to CRT. It is still not clear what magnitude of change constitutes response «predictors of response». Most of predictors are based on results of observational studies, and due to a lack of control data, cannot determine the relation between the clinical and functional effect of CRT and outcome benefit (risk reduction). On the other hand, according to Cleland J.G. et al. for many doctors and patients' acute improvement in quality of live and improvement of exercise tolerance is more clear and measurable effect rather than the disease outcome [31].

Thus, due to the individual clinical and hemodynamic characteristics of CRT response and due to the low agreement between different response criteria the need for an integrated approach to assessing the effectiveness of CRT becomes obvious. In real clinical practice, the effect of CRT should be evaluated by one isolated criteria.

STUDY LIMITATIONS

The study had a retrospective design, and the number of patients was relatively low. A significant limitation of the study is that the evaluation of the response to CRT was carried out not at a fixed specific time after implantation, but during the whole observation period for each individual patient that could significantly affect the results obtained.

We did not analyze the intra- and interobserver variability of echocardiographic criteria, and therefore the limitation of the study is the probable errors in the evaluation of echocardiographic criteria.

Only the most used criteria for evaluating response to CRT were evaluated in the study. It was previously shown that the levels of inflammatory mediators and markers of myocardial fibrosis have a significant relationship with the effects of CRT, as well as speckle tracking echocardiography with an assessment of two- and three-dimensional strain can also be used to predict the response to CRT [32, 33]. However, in the current study the levels of biochemical markers, parameters of speckle-tracking echocardiography were not evaluated. Additionally, we did not assess the severity of the functional and clinical response to CRT in groups with different etiology of CHF.

CONCLUSION

Agreement between different criteria to define response to CRT is poor. The strongest correlation with long-term mortality was found for LVESV. This inconsistency among different response criteria severely limits the ability to generalize results over multiple CRT studies.

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ALGORITHM FOR DETERMINING THE FIBROSIS STAGE USING HIGH-DENSITY MAPPING

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Aims. To develop an algorithm for assessing the stage of fibrosis based on high-density endocardial mapping. To study the effect of the stage of left atrial (LA) fibrosis on the results of atrial fibrillation (AF) catheter ablation.

Methods. The study included 64 patients with paroxysmal or persistent AF, who underwent high-density LA mapping and catheter ablation. After the intervention procedure, we analyzed the electroanatomical maps of the left atrium, assessed the prevalence of low-voltage areas according to the developed algorithm. Patients were divided into 4 groups depending on the prevalence of areas of low voltage based on the Utah score.

Results. The follow-up period was 14.5 ± 6.7 months. AF recurrence developed in 18 (28.1%) patients after the ablation procedure. AF recurrence after ablation was more frequent in patients with a low-voltage area of more than 20% than in patients with a low-voltage left atrial area of less than 20%, 6 (15.4%) versus 12 (48%), p=0.02. A logistic regression analysis was performed to identify AF recurrence predictors in the postoperative period. As a result, only widespread areas of low-amplitude activity were an independent predictor of AF recurrence after the pulmonary veins isolation, this predictive model was significant (p=0.026). Significant statistical differences between groups I, II and III,I V are the ejection fractions and the duration of the P-wave. Patients with low-voltage regions have lower left ventricular ejection fraction (62.8±6.9% versus 58.1±5.7%, p=0.01), and longer P-wave duration (84.7±8,2 ms versus 101.5±11.0 ms, p=0.01).

Conclusion. LA high-density mapping before AF ablation makes it possible to determine the prevalence of low-voltage areas. After regression analysis, it was proved that common low-voltage areas are an independent predictor of AF recurrence after pulmonary vein isolation. Patients with low-voltage areas of more than 20% of the LA surface have longer P-wave duration and lower left ventricular ejection fraction.

Key words: high-density mapping; atrial fibrillation; catheter ablation; left atrial fibrosis

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Catheter ablation is a surgical treatment for patients with atrial fibrillation (AF). The main target of catheter ablation in AF is the elimination of arrhythmia triggers localized in the pulmonary veins [1]. Electrical and structural atrial remodeling are the main determinants of the pathogenesis and progression of AF [2]. Histological analysis of the structure of the atrial myocardium in patients with AF revealed multiple accumulations of fibroblasts and diffuse dissemination of collagen fibers [3].

A multicenter prospective DECAAF study showed that areas of left atrial (LA) fibrosis identified by magnetic resonance imaging (MRI) were independent predictors of AF recurrent after catheter ablation [4]. Some studies have shown that areas of accumulation of gadolinium-containing contrast agent are characterized by areas of low-amplitude activity (0.38±0.28 mV) compared with the intact atrial myocardium, where the amplitude of the bipolar signal is higher (1.38±1.23 mV) [5, 6]. However, these and other previous studies analyzed electroanatomical maps constructed using 20-pole circular or ablation catheters [5, 6].

The purpose of the study was to develop an algorithm for assessing the stage of fibrosis according to high-density endocardial mapping, to study the effect of the stage of LA fibrosis on the results of AF catheter ablation.

MATERIAL AND METHODS

The study included 64 patients with paroxysmal or persistent AF, who underwent high-density LA mapping and AF catheter ablation. We analyzed the clinical characteristics of the patients included in the study (Table 1). All patients underwent preoperative echocardiography, computed tomography of the LA, transesophageal echocardiography, clinical blood count, and gastroscopy. In the presence of risk factors for coronary heart disease and/or a clinical presentation of it, patients underwent coronary

angiography at the preoperative stage. If hemodynamically significant narrowing of the coronary arteries was detected, patients underwent myocardial revascularization, and these patients were excluded from the study.

Inclusion Criteria:

• Age over 18;
• AF recorded on the electrocardiogram (ECG);
• Indications for catheter ablation;
• Signed informed consent form.

Exclusion Criteria:

• Pregnancy or planned pregnancy within the terms of the clinical study;
• Contraindications to the catheter procedure (patients with acute and subacute myocardial infarction, as well as those with decompensated heart failure, patients with decompensated concomitant diseases, etc.).
• Previous interventional treatment of cardiac arrhythmias or any cardiac surgery;
• With implantable devices.
• Valvular heart disease, requiring surgical correction;
• Presence of signs of a fragmented or floating thrombus in the LA.

This study was approved by the local ethics committee. All patients signed an informed consent prior to enrollment in the study.

High Density Mapping

Patients included in the study underwent LA mapping using a basket catheter, which contains 8 splines with 8 electrodes on each (the distance between the electrodes is 2 mm).

Mapping was performed with a uniform distribution of annotated points using a filling threshold of 1 to 3 mm, voltage maps contained at least 10,000 points. Low-voltage areas were defined as areas with a bipolar signal of less than 0.2 mV, and transitional areas - from 0.2 to 0.5 mV; an endocardium with a bipolar signal of more than 0.5 mV was considered intact.

In low voltage areas, the maximum number of points was annotated for a more accurate assessment of structural changes. The stability of the catheter was limited to fluctuations of 3 mm. To avoid annotating incorrect mapping points due to poor contact of the mapping electrode with the tissue, we set the filtering of the distance between the projection of the electrode and the geometric surface of the model to 2 mm. The signals were filtered with a frequency from 30 to 400 Hz. The automatic mapping function made it possible to avoid manual verification of all endograms on the obtained voltage maps.

Algorithm for determining the stage of LA fibrosis

The evaluation of the propagation stage of low-voltage regions was carried out as follows. After constructing a high-density voltage map containing more than 10,000 mapping points, the atria were divided by one plane into 2 parts using the Reset Clipping Plane tool (Fig. 1). Next, the total surface area was measured. The area of each half of the atrium was measured sequentially. After that, the obtained results were summarized. Using the "Area measurement" tool, the area of each area was alternately measured, where the signal amplitude was less than 0.2 mV, the results were summarized (Fig. 2).

According to the formula S of low-voltage sections / S of the total area * 100% (where S is the area), the area of low-voltage sections was measured. Subsequently, the patients were divided into 4 groups.

Table 1.

Clinical characteristics of patients

	I group (n=20)	II group (n=19)	III group (n=8)	IV group (n=17)
Age, years	63 [50.5-68.5]	60 [51-64]	56 [42-62.5]	66 [56-70]
Persistent AF, n (%)	6 (30.0)	7 (36.8)	3 (37.5)	9 (52.9)
Paroxysmal AF, n (%)	14 (70.0)	12 (63.2)	5 (62.5)	8 (47.1)
Duration of arrhythmia history, years	3 [2-5]	5 [3-12]	6.5 [4.5-10.5]	6 [2-7]
Volume of the left atrium, ml	133.9±25.7	139.8±29.7	144.2±37.3	161.1±56.1
Left ventricular ejection fraction, %	64.3±6.5	61.2±7.2	60.4±4.9	56.9±5.8
AF recurrence, n (%)	2 (10)	4 (21)	2 (25)	10 (59)
Low-voltage areas, %	6,6±2.4	13.6±2.7	24.0±2.2	54.5±16.9
P-wave duration, ms	84.2±8.1	85.4±8.4	91.4±6.7	106.2±9.3
Diabetes mellitus, n (%)	3 (15)	5 (26)	1 (13)	4 (24)
Arterial hypertension, n (%)	13 (65)	10 (53)	5 (63)	11 (65)
Postponed coronavirus infection, n (%)	6 (30)	6 (32)	4 (50)	8 (47)
Radiofrequency ablation, n (%)	15 (75)	14 (74)	8 (100)	16 (94)
Cryoablation, n (%)	5 (25)	5 (26)	0	1 (6)
Sotalol + lappaconitine hydrobromide, n (%)	4 (20.0)	3 (15.8)	2 (25.0)	3 (17.6)
Amiodarone, n (%)	7 (35.0	6 (31.6)	3 (37.5)	4 (23.6)
Propafenone, n (%)	3 (15.0	3 (15.8)	0	1 (5.9)
Beta blockers, n (%)	6 (30.0)	7(36.8)	3 (37.5)	9 (52.9)

Note thereafter: AF - atrial fibrillation.

By the Utah gadolinium MRI fibrosis staging scale used in the DECAAF study, in our work we divided fibrosis grades in a similar way:
Stage 1 - with total low-voltage areas of less than 10%;
Stage 2 - with total low-voltage areas of 10-20%;
Stage 3 - with total low-voltage areas of 20-30%;
Stage 4 - with total low-voltage areas of more than 30%.

Catheter treatment

Catheter ablation was performed under intravenous sedation. The ablation procedure was preceded by transesophageal echocardiography performed to exclude thrombosis of the LA appendage.

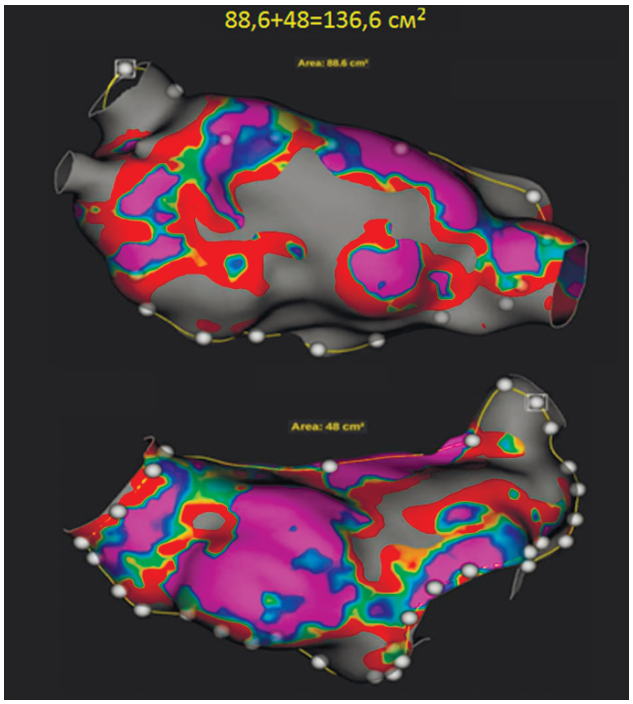

Fig. 1. Electroanatomical voltage map of the left atrium. Using the «Reset Clipping Plane» tool. The surface area of the two halves of the atrium was calculated and the total area was determined to be 136.6 cm³. Areas where the signal amplitude is higher than 0.5 mV are colored in purple; red - signal amplitude from 0.5 to 0.2 mV; gray - signal amplitude less than 0.2 mV.

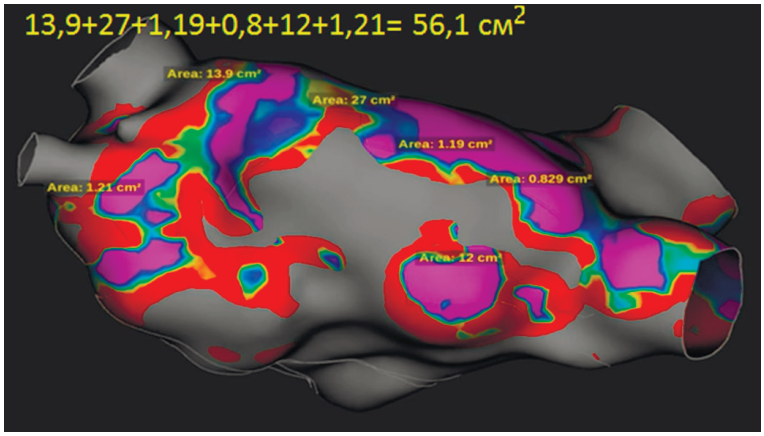

Fig. 2. Electroanatomical voltage map of the LA. Using the «Area measurement» tool. The total low-voltage area was determined to be 56.1 cm³. Areas where the signal amplitude is higher than 0.5 mV are colored in purple; red - signal amplitude from 0.5 to 0.2 mV; gray - signal amplitude less than 0.2 mV.

In the operating room, punctures of the femoral and subclavian veins were performed according to the Seldinger technique. A 10-pole diagnostic electrode was positioned in the coronary sinus. All patients underwent transseptal puncture under fluoroscopic control. Patients underwent catheter isolation of the pulmonary veins using cryoballoon ablation or radiofrequency ablation.

Radiofrequency exposures were carried out point by point. Radiofrequency energy during ablation was limited to 34 W and 44°C, irrigation of the catheter tip during exposure was 30 ml/min. During ablation on the posterior wall of the LA, the power did not exceed 32 W, the duration of exposure did not exceed 10 seconds at each point.

During the cryo-procedure, the cryoballoon was positioned in each pulmonary vein sequentially until complete occlusion, then a cryo-exposure was performed for 180 seconds at a temperature not lower than -60°C, but not higher than -40 °C.

The impact was carried out until the complete electrical disconnection of the antrum of the pulmonary veins from the LA, when it was not possible to register the potentials of the pulmonary veins along the antrum or inside the veins using a mapping catheter.

Intraoperatively, heparin was administered intravenously to patients at a calculated dosage of 100 units per kg. During mapping and interventional treatment, activated clotting time was monitored, the target values of which ranged from 250 to 300 seconds.

The revision of the veins was performed using a multipolar circular catheter to verify the residual potentials of the pulmonary veins, if necessary, further ablation was performed to eliminate them. Additional extrapulmonary ablation lines were not performed.

In order to detect recurrence of AF, patients were invited for follow-up examinations 3, 6, and 12 months after surgical treatment. At the control examination, ECG registration and daily ECG monitoring were performed. Also, when symptoms appeared outside the follow-up examinations, an ECG or 24-hour ECG monitoring was recommended. Registration of AF paroxysm lasting more than 30 seconds was taken into account as a recurrence of AF in the postoperative period.

Statistical analysis

Statistical analysis was performed using STATISTICA 10 software. All continuous variables were tested for normal distribution using the Shapiro-Wilk test. Normally distributed continuous variables are presented as mean ± standard deviation. Non-normally distributed continuous variables are presented as the median [interquartile range]. For qualitative variables, absolute frequencies and percentages of the total are shown. Comparisons between groups were made using the Mann-Whitney test. Box plots are provided to illustrate the significance of differences between groups. In order to identify predictors and the significance of the binary classification model, a logistic regression analysis was carried out, where R2 McF is the McFadden determination coefficient, illustrating the quality of the binary

model. For all statistical tests, a two-sided significance level p=0.05 was used.

RESULTS

Low-voltage areas in the LA of high-density mapping were observed in all patients in the range from 4 to 88%. Comparison of baseline clinical characteristics is shown in Table 1.

All continuous variables except for the variables "age" and "duration of arrhythmia history" have a normal distribution (p>0.05). The continuous variables "age" and " duration of arrhythmia history" have a non-normal distribution (p<0.05) and are presented as the median [interquartile range].

When analyzing the results obtained, the patients were divided into 4 groups according to the low-voltage area. The distribution was carried out by the Utah scale. The first group included 20 patients with a low-voltage area - 6.6±2.4%, in the second group - 19 patients, with a low-voltage area - 13.6±2.7%, in the third group - 8 patients, with a low-voltage area - 24±2.2%, the fourth group included 17 patients, low-voltage area - 54.5±16.9%.

All groups included patients with persistent and paroxysmal AF. In the group I - 6 patients with persistent AF and 14 with paroxysmal, in group II - 7 patients were diagnosed with persistent AF and 12 patients were diagnosed with paroxysmal AF, in group III there were 3 patients with persistent AF and 5 patients with paroxysmal AF, in group IV, most of the patients had persistent AF - 9 people, and 8 patients had paroxysmal AF.

In the preoperative and postoperative periods, patients took antiarrhythmic therapy (Table 1). All patients with paroxysmal AF continued to receive similar antiarrhythmic therapy after surgical treatment. Patients with persistent AF in the preoperative period received drugs of the beta-blocker group, after surgical treatment, patients were prescribed amiodarone as antiarrhythmic therapy.

In groups I and II, there is a smaller volume of LA and a higher left ventricular ejection fraction than in patients of groups III and IV.

In patients with low-voltage areas less than 10%, the volume of LA, determined according to the data of computed tomography, was 133.9±25.7 ml, in patients of group II - 139.8±29.7 ml, in patients of group III - 144 .2±37.3 ml, in patients of group IV - 161.1±56.1 ml.

In patients with a low-voltage area of less than 10%, the left ventricular ejection fraction, determined according to transthoracic echocardiography, was 64.3±6.5%, in patients of group II - 61.2±7.2%, in patients of group III - 60 .4±4.9%, in patients of group IV - 56.9±5.8%.

The comorbidities of the patients included in the study were also analyzed. Three (15%) patients from group I, 5 (26%) patients from group II, 1 (13%) patient from group III and 4 (24%) patients from group IV had diabetes mellitus.

Arterial hypertension was present in more than half of the patients in each group. In group I, 13 (65%) patients suffered from high blood pressure, in group II - 10 (53%) patients, in group III - 5 (63%) patients, in group IV - 11 (65%) patients.

In 2020, the world was hit by a pandemic of a new coronavirus infection. A total of 24 (37.5%) patients from our study had a new coronavirus infection, the distribution by group is presented in Table 1.

The choice of ablation technique was made after evaluation of computed tomography data of the LA and pulmonary veins. Pulmonary vein isolation was achieved in all patients. No complications associated with ablation procedures have been reported. Before and after catheter ablation, an LA voltage map was constructed in all patients. The number of mapping points averaged 14190±6179, mapping time averaged 19.7±7.8 minutes.

During the follow-up period of 14.5±6.7 months, AF recurrence was registered in 18 (28.1%) patients after the ablation procedure. The frequency of AF recurrence after ablation was lower in patients of groups I and II than in patients of groups III and IV. In 6 (15.4%) patients from

Table 2.

Comparison table of patients depending on the total low voltage areas

	I, II group	III, IV group	p
Age, years	61 [51-67]	63 [51-68]	0.57
Women/men	16 / 23	10 / 15	0.94
Body mass index, kg/m2	28.8±5.1	28.2±3.5	0.93
Duration of arrhythmia history, years	4 [2-6]	6 [3-8]	0.16
Left ventricular ejection fraction, %	62.8±6.9	58.1±5.7	0.01
Volume of the left atrium, ml	138.9±31.9	154.3±49.5	0.35
P-wave duration, ms	84.7±8.2	101.5±11.0	0.01
Diabetes mellitus, n (%)	8 (21%)	5 (20%)	0.97
Arterial hypertension, n (%)	23 (59%)	16 (64%)	0.69
Postponed coronavirus infection, n (%)	12 (31 %)	12 (48 %)	0.17

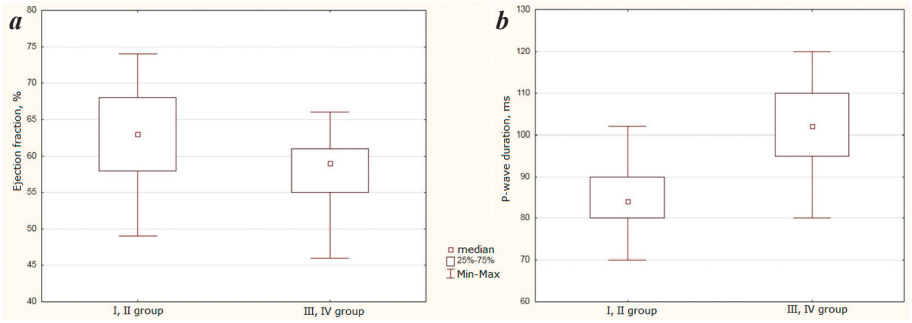

Fig. 3. Box plot illustrating the LV ejection fraction, % (a) and P-wave duration, ms (b) in groups with a low-voltage area of less than 20% (groups I and II) and more than 20% (groups III and IV).

groups I, II and in 12 (48%) patients from groups III, IV, recurrence of atrial fibrillation was recorded after catheter treatment (p=0.02).

To obtain statistical significance, patients were grouped, stages I, II of fibrosis and III, IV stages of fibrosis were analyzed. The results of the comparative evaluation are presented in Table 2.

Significant statistical differences were obtained in terms of ejection fraction and P-wave duration. Patients with a low-voltage areas have a lower left ventricular ejection fraction (62.8±6.9% vs. 58.1±5.7%, p=0.01 (Fig. 3a) and longer P-wave duration 84.7±8.2 ms vs 101.5±11.0 ms, p=0.01) (Fig. 3b).

Logistic regression analysis was performed to identify predictors of AF recurrence in the postoperative period. As a result, only low-voltage areas were an independent predictor of AF recurrence after isolation of pulmonary vein ostia, and this predictive model was significant (p=0.026). Determination coefficient R2 McF= 0.162.

DISCUSSION

This is the first domestic study that used high-density mapping (> 10,000 points) to assess the stage of fibrosis in patients with paroxysmal and persistent AF. Past studies have characterized the LA substrate according to electroanatomical mapping data, but only with 54-158 mapping points [5, 6].

In 2005, a study by Verma A. described the effect of the presence of areas of fibrosis in the left atrium on the results of primary pulmonary vein isolation [7]. The results of amplitude mapping of 700 patients were analyzed. Low voltage areas were defined where the bipolar signal was less than 0.5 mV, as described in previous studies [8,9]. The low voltage areas in this study were calculated manually by summing the area of the rectangular areas with low voltage activity. Mapping was performed with a 20-pole circular catheter, most of the mapping points were annotated manually. As a result of this study, low-voltage areas were an independent predictor of failure of radiofrequency pulmonary vein isolation. In our study, we used automatic mapping to automatically annotate points that meet the selection criteria, and we also used a multi-pole basket catheter to reduce mapping time and annotate more points (more than 10,000). The high-density mapping study also found a direct relationship between low-voltage areas and recurrence of AF in the postoperative period.

Masuda M. et al. demonstrated a direct relationship between the induction of atrial fibrillation after isolation of pulmonary veins in patients with low voltage areas. A total of 147 patients were analyzed. The majority of patients with low-voltage areas have been induced atrial tachyarrhythmias after antral isolation of the pulmonary veins. AF was induced in 70% of patients with low-voltage areas versus 16% of patients without low-voltage areas (p=0.0001); perimitral macroreentry atrial tachycardia - in 18% versus 0% (p=0.0001) [10]. This study proves the importance of voltage mapping prior to AF catheter treatment. We evaluated the occurrence of AF in the late postoperative periods in our study. It was also found that in patients with low-voltage areas (groups III and IV), AF occurs more often in the long-term period.

Today there is no consensus on the threshold values of the bipolar amplitude of fibrosis areas. Kapa et al. proposed voltage limits of 0.2-0.45 mV for “abnormal” tissues [11]. Harrison et al. based on histological data, MRI with gadolinium-containing contrast agent, and LA amplitude mapping data, pigs reported mean bipolar signal values of 0.3-0.6 mV [12]. Jadidi et al. demonstrated that electrograms in areas of accumulation of gadolinium-containing contrast agent have an average bipolar value of 0.63-0.8 mV [13]. Given the inconsistency of the results of modern studies, we decided to use the most common thresholds in the literature from 0.2 to 0.5 mV.

In 2019, a study was conducted in Spain evaluating the effectiveness of high-density mapping in predicting AF recurrence after catheter ablation. Ninety eight patients were analyzed, 40.8% of whom had persistent AF. Arrhythmia recurrence after a year of observation developed in 29 (29.6%) patients. When conducting regression analysis in this study, the only most significant predictor of arrhythmia recurrence after AF catheter treatment was also obtained - this is structural remodeling of the LA myocardium. In this study, it was evaluated using the MATLAB software [14]. However, this study included patients who had previously undergone AF catheter treatment, which could also influence the recurrence of AF or its absence in the long-term period. In our study, catheter ablation of the pulmonary veins was performed for the first time in all patients. Also, in the presented study, LA fibrosis was not quantified, the analysis was carried out on the basis of data obtained in the MATLAB software, the mean value of the bipolar signal (Vm) and the slope of the scatterplot (Vslope) were estimated. In our study, low-voltage areas were quantified using the algorithm we developed.

Study limitations

The study is relatively small and conducted at a single center, but is powerful enough to show a primary outcome. The area of the left atrial appendage was not always fully mapped due to the size of the mapping catheter and the risk of perforation.

CONCLUSION

High-density mapping of the left atrium before interventional treatment of atrial fibrillation allows to determine the stage of fibrosis. Regression analysis proved that low-voltage regions are an independent predictor of atrial fibrillation recurrence after pulmonary vein isolation. Patients with low-voltage areas greater than 20% have a longer P-wave duration and a lower left ventricular ejection fraction.

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A CASE OF SUCCESSFUL RADIOFREQUENCY ABLATION OF ECTOPIC VENTRICULAR ACTIVITY WITH PARA-HISIAN ORIGIN BY ACCESS FROM THE RIGHT CORONARY SINUS OF VALSALVA

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A clinical case of successful radiofrequency ablation of ventricular tachycardia with para-Hisian localization of the substrate by access from the right coronary sinus of Valsalva is presented.

Key words: radiofrequency ablation; aortic sinus of Valsalva; ventricular tachycardia; premature ventricular contractions.

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Premature ventricular contractions (PVCs) are common heart rhythm disorders occurring in patients without any structural heart disease. There are several mechanisms responsible for PVCs development: abnormal automaticity, triggered activity and re-entry. Despite the absence of clinical manifestation in several patients, high PVC burden can lead to the development of PVC-induced cardiomyopathy followed by worsening of systolic and diastolic functions of the left ventricle (LV) and affecting quality of life [1].

Radiofrequency catheter ablation (RFA) is considered an effective method for treating patients with PVCs and ventricular tachycardias (VT). According to Latchamsetty et al. (2015) reports, acute effect of PVC ablation procedures was achieved in 84% of patients, medium-term effectiveness (follow-up time 20.2±21.7 months) was 71% and 85% in combination and without antiarrhythmic drug therapy respectively [2].

The substrate of some arrhythmias may be inaccessible from the endocardial surface of right chambers, and that is precisely why retrograde arterial approach via sinuses of Valsalva is preferred in such cases, especially when the origin of arrhythmia is localized in para-Hisian region [3]. According to different literature, in adults the incidence of PVCs and ventricular tachycardias originating from the aortic sinuses varies between 16.6-18%. Furthermore, ventricular arrhythmias more often originate from the left sinus of Valsalva [4].

The aortic root comprises the sinuses of Valsalva, valvar leaflets and fibrous interleaflet triangles. This region is of particular interest to electrophysiologists, because it takes central position in the heart and anyway contacts atrial and/or ventricular myocardium, this circumstance makes it possible to eliminate some types of arrhythmias by access from the aortic sinuses located at the base of the aortic root. The right sinus of Valsalva (RSV) is commonly located directly posteriorly and downwards from the right ventricular outflow tract (RVOT). From this spatial relationship it follows that the electrogram in the RSV region has a large ventricular component reflecting the activation of the adjacent relatively thick posterior wall of the infundibulum of the RVOT. In the area of the fibrous interleaflet triangle between non-coronary and right sinuses of Valsalva the central fibrous body is located. The penetrating bundle of His is located here, and more distally, the beginning of its left bundle branch. The compact portion of the atrioventricular node is placed posteriorly and downwards from the commissure between non-coronary and right sinuses of Valsalva. Awareness of these anatomical relationships is of significant importance for safe RFA in the area of RSV [5].

Considering possible complications of RFA in this area (coronary vascular or leaflet injury, conduction disturbances, systemic embolisms and transient ischemic attacks), it is necessary to follow certain rules and have a sufficient experience in carrying out such procedures, as well as use available methods of visualization to assure safety of mapping and RFA [5, 6].

This article presents a clinical case of successful catheter ablation of ventricular ectopic activity by access from the RSV.

A 65-year-old patient was admitted with dyspnea during exercise, palpitations and general weakness. The

patient has been observed for arrhythmia for the last four years. From Holter monitoring data, up to 30000 monomorphic PVCs were registered per day, in this connection the patient received antiarrhythmic drug therapy (I and II classes according to Vaughan-Williams classification). On the background of treatment, no significant clinical effect was observed, and the patient was recommended to perform RFA of arrhythmogenic foci in one of the cardiovascular surgical hospitals. According to the patient's operative notes from the medical institution in which the patient previously underwent RFA, the origin of PVCs was in para-Hisian region. RFA was accompanied by the appearance of rapid junctional rhythm with a transient atrioventricular block, and therefore the procedure was discontinued. It was decided to refrain from further ablation due to the high risk of atrioventricular block. With the same complaints, the patient was hospitalized for a repeat catheter ablation.

Physical examination: heart tones are attenuated, there are no murmurs, heart rate 68 b.p.m., blood pressure 130/85 mmHg. Radial artery pulse is symmetrical, arrhythmic, of satisfactory filling. Height - 177 cm, body weight - 88 kg, body mass index - 28.09 kg/m^2.

Coronary angiography data: proximal stenosis of anterior interventricular branch of left coronary artery (CA) (up to 30%), the remaining arteries without angiographically significant stenosis.

According to 12-lead Holter monitor data, 22651 monomorphic PVCs were registered per 24 hours, including couplets and triplets. Preoperative analysis of QRS-morphology on algorithm proposed by K. Park et al. (2012) allowed to suggest the origin of PVC in His bundle [7].

Transthoracic echocardiography data: LV end-diastolic volume 174.2 ml, LV ejection fraction 49.5%, LV end-systolic diameter 4.4 cm, LV end-diastolic diameter 5.9 cm, LV posterior wall hypokinesia; moderate mitral and tricuspid regurgitation. Aorta: ascending part 42 mm, the walls are indurated, the valve at the level of the fibrous ring is 26 mm, regurgitation is minimal. Interventricular septal thickness is 12 mm.

Medication: amiodarone 200 mg/day, aspirin 75 mg/day, indapamide 1.5 mg/day, atorvastatin 20 mg/day, ramipril 10 mg/day.

Based on complaints, anamnesis, objective examination, as well as the results of additional methods of medical examination, the patient was diagnosed with "Cardiac arrhythmia. PVCs, 4B grade (B. Lown). Paroxysmal ventricular tachycardia. RFA of PVCs with para-Hisian origin

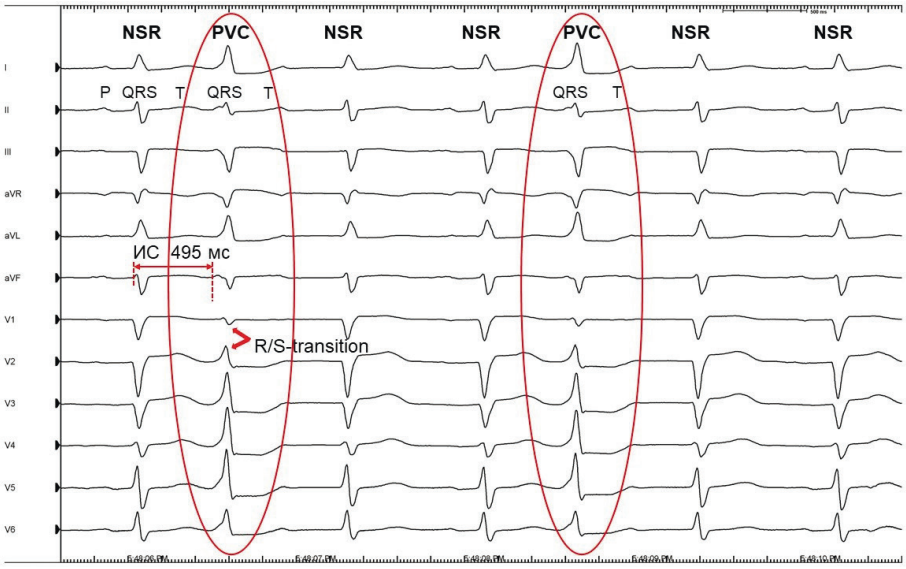

Fig. 1. ECG (50 mm/sec, 10 mm/mV). Sinus rhythm, rate 72-75 bpm, single monomorphic premature ventricular complexes (circled) with coupling interval (CI) 495 ms, left anterior fascicular block, PQ interval extension to 230 ms. From top to bottom: I, II, III - standard limb leads (bipolar), aVR, aVL, aVF - augmented limb leads (unipolar), V1-V6 - precordial leads (unipolar). PVC - premature ventricular complex; NSR - normal sinus rhythm.

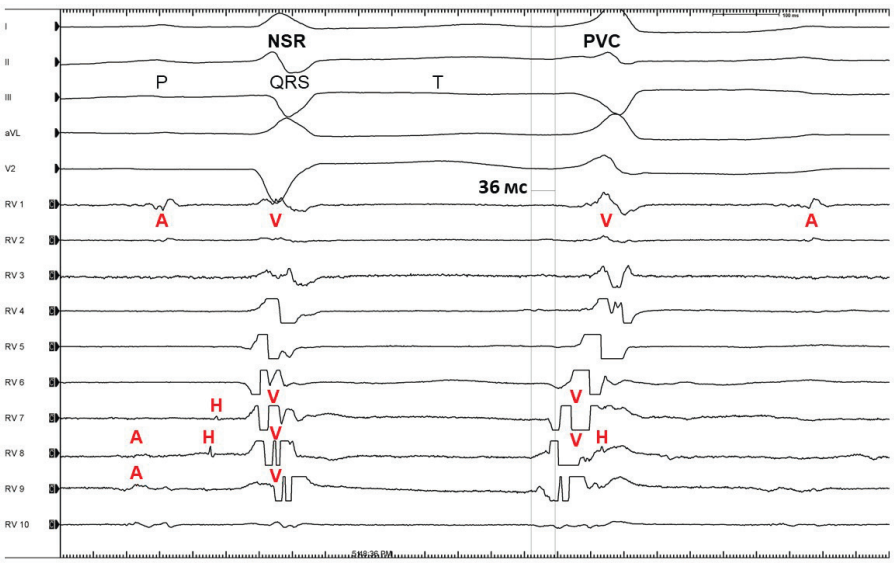

Fig. 2. Bipolar electrograms obtained during right ventricular outflow tract mapping (200 mm/sec). The earliest site of ventricular activation (-36 ms ahead of the referent - R-wave in lead II) is recorded on electrograms from channels RV 8-9; on these and adjacent channels the spike of His-bundle (H) is also noted. From top to bottom: I, II, III, aVL, V2 ECG leads; electrograms recorded from a 20-pole diagnostic electrode placed in right ventricular outflow tract (RV 1-10). NSR - normal sinus rhythm; PVC - premature ventricular complex; A - atrial activation; H - His bundle activation; V - ventricular activation.

in 2017. Arterial hypertension, grade 3, very high cardiovascular risk".

Surgery

The patient was taken to the electrophysiological laboratory in sinus rhythm, heart rate 70-75 bpm, left anterior fascicular block, PQ interval extension to 230 ms, frequent PVCs, presumably from the para-Hisian region (according to the algorithm, proposed by K. Park et al., 2012) (Fig. 1). [7].

The right femoral vein was punctured three times under combined anesthesia. A diagnostic 10-pole catheter was placed in the coronary sinus. A diagnostic 20-pole catheter, as well as an irrigated ablation catheter Celsius Thermocool (Biosense Webster) were positioned in RVOT. The "earliest" activation site is registered close to the His-bundle (Fig. 2). When mapping this area, the earliest site was -37 ms ahead of the referent (R-wave in lead II).

Due to high risks of RFA in the His bundle, it was decided to continue mapping in the aortic root. A puncture of the right femoral artery was performed, heparin was instantly injected (100 I.U. per 1 kg of body weight). An irrigated ablation catheter was delivered to the aortic root. When mapping this region, the "earliest" site (-40 ms ahead of the aforementioned referent) was registered in RSV (Fig. 3). Pace-mapping in this area had not succeeded due to the lack of ventricular myocardium "capture".

A puncture of left femoral artery was performed. A Judkins-type angiographic catheter was delivered to the aortic root. A multi-projection coronary angiography of the left and right CA was performed, a safe position of ablation catheter from the ostia and trunks of the CA was verified (Fig. 4 A, B, C, E). Under continuous angiographic control, irrigated RFA was carried out in this site for 2 minutes at 40-42 ºC and 35 W. The disappearance of PVCs was noted at the 3rd second of the first RFA, in the next 45 minutes of observation a stable sinus rhythm without PVCs had been recorded. During the entire procedure, there were no ST-segment displacements and T-wave morphology abnormal changes. At the end of the procedure, coronary angiography was performed (no signs of thermal damage to the coronary arteries) and, then, echocardiography, decannulation and hemostasis. The patient was transferred to the department with sinus rhythm.

A normal sinus rhythm without PVCs was recorded before patient's discharge. (Fig. 5). In the early postoperative period, a control Holter monitoring was performed: 16 supraventricular extrasystoles, 4 single monomorphic PVCs of another morphology. The patient was discharged with a significant improvement in well-being.

DISCUSSION

In catheter treatment of supraventricular and ventricular arrhythmias retrograde arterial approach is an effective and save alternative to venous access. There are several electrocardiographic indicators in the arsenal of cardiologists and cardiovascular surgeons that allow to assume at the preoperative analysis that one of the sinuses of Valsalva would be the best access for PVC/VT ablation. VT and PVCs from the region of the Valsalva sinuses have similar features on ECG to those from the upper-septal part of RVOT. Nevertheless, the former usually show an early R/S transition in leads V1-V3, whereas for the latter the R/S transition occurs in lead V3 or later [8]. In the presented case report, the R/S transition was determined between leads V1 and V2.

Several quantitative ECG-indexes have also been proposed, which make it possible to distinguish the PVC/VT originating from the sinuses of Valsalva from other idiopathic ventricular arrhythmias. For example, R-wave duration index, which is defined as a ratio of R-wave duration (measured from the onset of the QRS complex to the transition point between the R-wave and the isoelectric line) to the total QRS duration in lead V1. Values ≥50% for PVC/VT with left bundle branch block morphology and an inferior axis suggest the Valsalva sinuses origin [9]. In the presented case report the value of this indicator amounted 53%. (Fig. 4 D)

The benefit of retrograde arterial approach to eliminate PVC/VT is evidenced, first, by the results of activation mapping in the right ventricle: if the "earliest" ventricular activation is detected in the area of His bundle, the access from the Valsalva sinuses may be effective

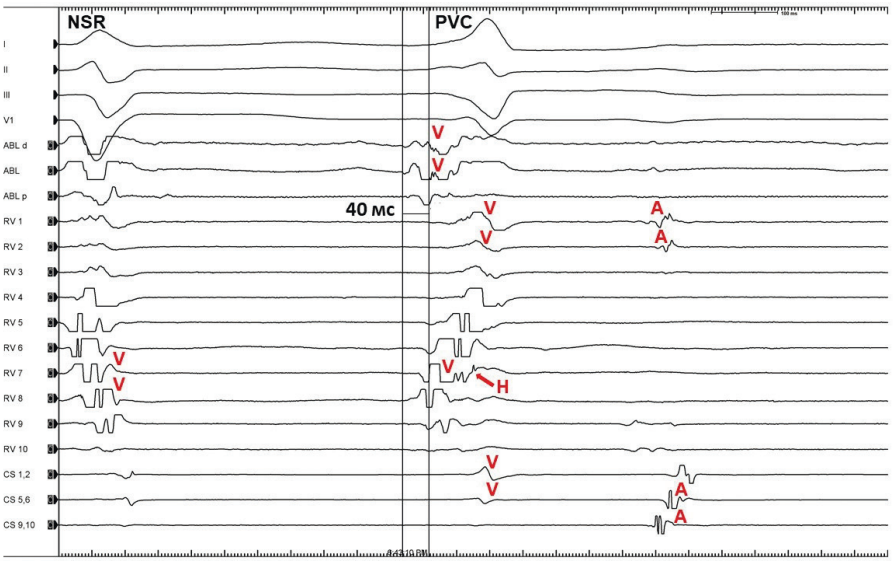

Fig. 3. Activation mapping within right sinus of Valsalva (200 mm/sec). The "earliest" activation is recorded on the ablation electrode (-40 ms ahead of the referent - R-wave in lead II). From top to bottom: I, II, III, V1 ECG leads; electrograms recorded from the ablation catheter (ABL); electrograms recorded from a 20-pole diagnostic electrode placed in right ventricular outflow tract (RV 1-10); electrograms recorded from a diagnostic electrode in coronary sinus. NSR - normal sinus rhythm; PVC - premature ventricular complex; A - atrial activation; H - His bundle activation; V - ventricular activation.

[4]. Additional validity for the arterial access choice in the presented case report was the previous episode of unsuccessful ablation in para-Hisian region by access from the RVOT.

Prior to RFA it's recommended to examine the aortic root to visualize the peculiarities of anatomy, CA ostia localization, as well as to establish anomalies of the CA, if any. Coronary angiography is the gold standard. It should be performed during and after RFA, to exclude possible subclinical injury of CA. In some cases, electroanatomic mapping with non-fluoroscopic navigation is useful, which also allows you to model detailed anatomy of cardiac structures with high accuracy and, as a result, safely perform manipulations in the aortic root. An alternative method of intraoperative diagnostics is intracardiac echocardiography, which allows you to control the distance between the tip of the electrode and the ostia of CA, and also makes it possible to visualize atherosclerotic areas and calcification of the aorta [4]. Besides, the use of intracardiac echocardiography is reasonable if there are any relative contraindications to coronary angiography (contrast-induced nephropathy, etc.). According to Al Ahmar M. et al. (2021) research, in 95% of cases, monitoring of the safety of RFA in the Valsalva sinuses was performed under control of intracardiac echocardiography, only in 5% of cases there was a necessity of coronary angiography to visualize the CA [6].

Conventional, irrigated radiofrequency electrodes or cryoenergy sources can be used for ablation in the sinuses of Valsalva. Each of the listed electrodes has its own advantages and disadvantages. Conventional electrodes are widely available and effective, acceptable for most ablation procedures, but, on the other hand, they promote coagulation at the tip of the electrode. There are observations demonstrating a greater risk of cerebral microembolism associated with RFA using conventional electrode [10]. In this regard, irrigated electrodes have significant advantages: greater lesion depth (compared to conventional and cryoelectrodes), counteraction to coagulum formation and reduction of the risk of thromboembolism. Cryoablation doesn't destroy elastic fibers in the tunica media, this is an obvious advantage in the context of reducing the severity of the inflammatory reaction provided by macrophages [9].

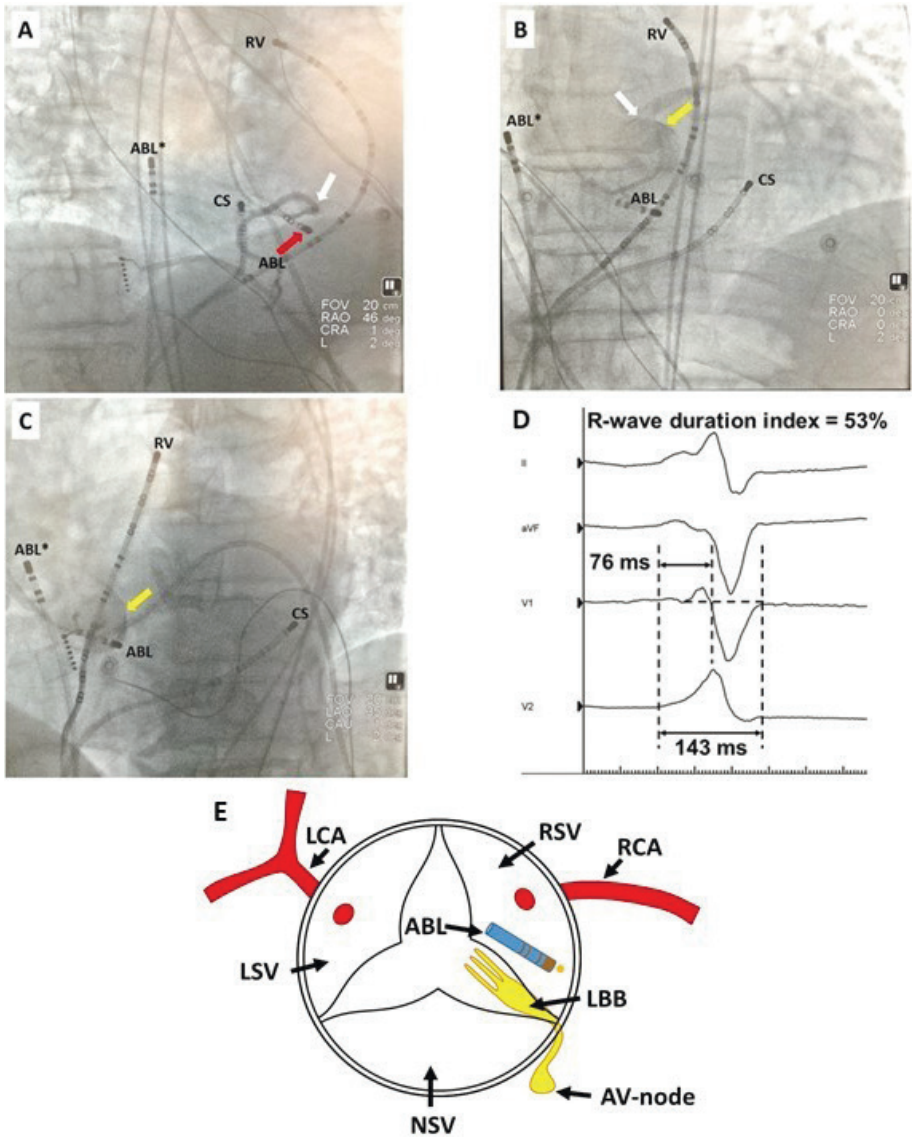

Fig. 4. The position of the ablation catheter at the effective site of ablation on intraoperative radiographs: A - right anterior oblique view (RAO 46 deg.), the white arrow indicates the ostium of the right coronary artery, the red arrow indicates the tip of ablation catheter placed in the "earliest" site of ventricular activation; B - antero-posterior view, the white arrow indicates the ostium of the left coronary artery, the yellow arrow indicates the bottom of the left sinus of Valsalva; C - left anterior oblique view (LAO 35 deg.), the yellow arrow indicates the boundary of the right sinus of Valsalva. D - R-wave duration index, calculated for premature ventricular complex; from top to bottom: II, aVF, V1 u V2 ECG leads. E - schematic representation of the position of the ablation catheter at the effective site of RFA. Indications on radiographs: CS - 10-pole diagnostic electrode placed in coronary sinus; RV - 20-pole diagnostic electrode placed in right ventricular outflow tract; ABL - ablation catheter delivered via retrograde arterial approach; ABL* - ablation catheter passed via the right femoral vein into the "right" cardiac chambers. Indications on the operation diagram: LCA - left coronary artery; RCA - right coronary artery; LSV - left sinus of Valsalva; RSV - right sinus of Valsalva; NSV - non-coronary sinus of Valsalva; LBB - left bundle branch; ABL - the position of the ablation catheter.

The literature highlights the experience of using various parameters of RFA by access from RSV: 1) assessment of paced QRS morphology during pace-mapping: the similarity of paced QRS morphology with the native PVC in 11 of 12 ECG leads is desirable [11]; 2) the number of RFA: 1-3 RFA are sufficient for successful ablation of supraventricular arrhythmias, whereas for PVC/VT there could be more (2-6); 3) duration of exposure: it is generally accepted to stop RFA in the absence of an effect within 10 seconds from the onset [4].RFA in the sinuses of Valsalva often causes anxiety among electrophysiologists due to possible complications. Let's focus on them in more detail.

In some cases, the optimal ablation point is closely adjacent to the ostium of the CA, so ablation in the right and left coronary sinuses is associated with a significant risk of spasm, injury, or occlusion of the CA. Therefore, it is generally accepted among electrophysiologists that these vessels should be visualized before RFA is performed. If it is not possible to ensure a stable position of the electrode, it is proposed to protect the coronary artery by cannulating it with a Judkins catheter (5F) [10]. Most researchers are of the opinion that RFA is safe at a distance of more than 1.0 cm from the ostia of the coronary arteries. If the arrhythmogenic focus is localized too close to the ostium of the CA, then the risk of injury exceeds the benefit of RFA in this area, and alternative approaches should be considered. It is possible to verify the absence of CA stenosis when performing an exercise stress testing after 6 months after RFA [6].

Certain attention is required for cerebral and peripheral thromboembolism during the procedure or in the immediate postoperative period caused by aortic wall damage. Therefore, adequate antithrombotic therapy is necessary during and after RFA [10].

It is important to take into account, that there is a central fibrous body behind the fibrous interleaflet triangle between the right coronary and non-coronary sinuses of Valsalva, through which the penetrating bundle of His passes. For this reason, RFA in the two mentioned sinuses of Valsalva may be complicated by a violation of atrioventricular conduction up to complete block [4]. The appearance of an accelerated junctional rhythm during RFA in these sinuses should be followed by an immediate cessation of energy delivery [4, 11]. ECG monitoring of the integrity of atrioventricular conduction after RFA is necessary before patient's discharge and after 6 months of follow-up. At the same time, the risk of atrioventricular junction injury is much less frequent than if one uses access from the right chambers. So, Wei et al. (2018) report successful RFA of PVC/VT substrate in para-Hisian region in 13 out of 14 patients by access from RSV, only in 1 patient the RFA was accompanied by the appearance of an accelerated junctional rhythm, and therefore energy delivery was discontinued. [11].

The thermal effect of RFA in RSV may be accompanied by a vagal reaction caused by the penetration of energy into the adjacent epicardial fat pad. The fat pad contains autonomous fibers and parasympathetic ganglia, their irritation or injury potentiates Bezold-Jarish response (bradycardia, hypotension, hypopnea) [12].

CONCLUSION

Among all ventricular arrhythmias that have a substrate in the aortic root area, only about 9% originate from the right sinus of Valsalva. Radiofrequency ablation by access from the right sinus of Valsalva shows high efficiency in the treatment of ventricular arrhythmias with para-Hisian localization of the substrate. Fundamentally important for reproducing this access is understanding of cardiac anatomy, especially the structural relationships between the aortic root, ventricular outflow tracts, coronary arteries and conduction system. At the same time, access from the right sinus of Valsalva leaves the question of the commensurability, on the one hand, of greater safety of the cardiac conduction system elements, and, on the other hand, the risk of coronary arteries injury. Currently available visualization methods (angiography, intracardiac echocardiography), as well as navigation systems for electroanatomic mapping, pretty much allow monitoring the safety of lesions in this area.

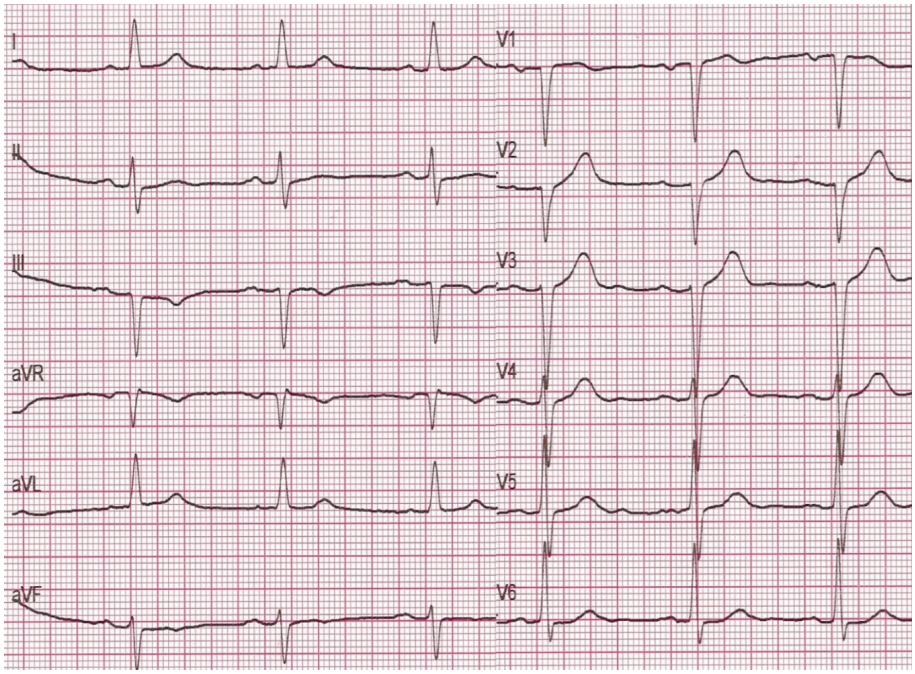

Fig. 5. ECG before patient's discharge (25 mm/sec). Sinus rhythm, rate 54 bpm, left anterior fascicular block, PQ interval extension to 230 ms. I, II, III - standard limb leads (bipolar), aVR, aVL, aVF - augmented limb leads (unipolar), V1-V6 - precordial leads (unipolar).

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LEFT ATRIAL APPENDAGE CLOSURE IN A PATIENT WITH CONTRAINDICATIONS FOR TRANSESOPHAGEAL ECHOCARDIOGRAPHY: A CASE REPORT

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We present a case of successful intracardiac echocardiography guided left atrial appendage catheter closure in a patient with esophageal varices using deflectable delivery sheath to improve ICE-catheter stability.

Keywords: intracardiac echocardiography; Amplatzer Amulet; atrial fibrillation; thromboembolic complications; left atrial appendage occlusion; hepatic cirrhosis; oesophageal varices

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Ischemic stroke is one of the most common complications of atrial fibrillation (AF), and its prevention is paramount in patients with AF [1]. Direct oral anticoagulants (OACs) are the first-line treatment in such patients, but their applicability has some difficulties.

In particular, their use is limited in patients with hepatic cirrhosis. Edoxaban and rivaroxaban are contraindicated in patients with Child-Pugh class B hepatic cirrhosis, and none of the available OACs is recommended for patients with class C hepatic cirrhosis [2].

Catheter-based left atrial appendage occlusion (LAAO) is a safe and effective alternative to lifelong anticoagulation for patients with AF, especially for those with contraindications to OACs. Initially, LAAO was an alternative for patients with contraindications to OACs or with high bleeding risk [3]. Several studies showed LAAO non-inferiority to OACs. It has IIb class of recommendations for patients with AF and high thromboembolic risk in the European Soci-

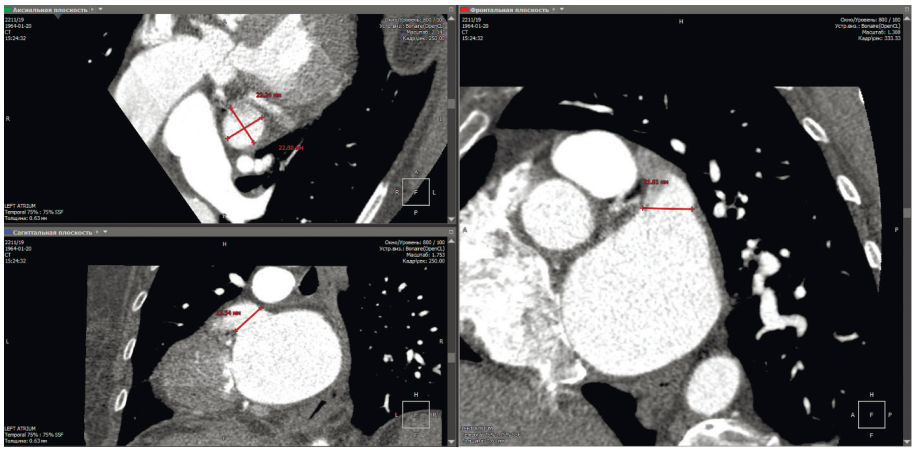

Fig. 1. CT imaging of the left atrium red line is shoing transves dimention of left atrium appendage ostium.

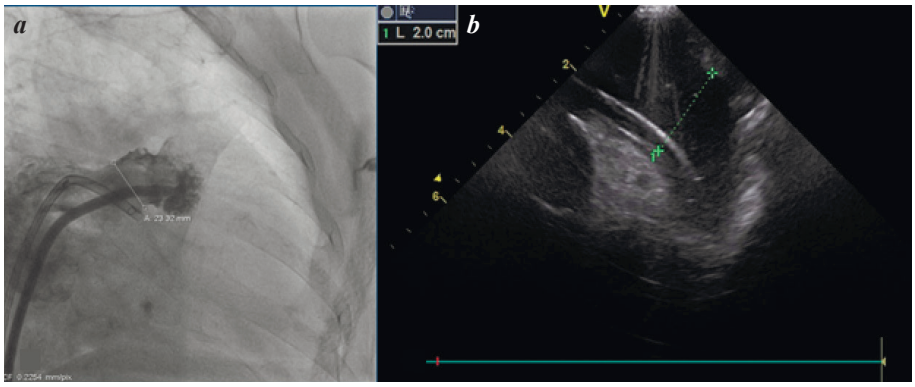

Fig. 2. Ostium of the left atrium appendage measured by angiography (a) ICE visualization of left atrium appendage with transvese size of left atrium appendage ostium (b).

ety of Cardiology [1] and Russian national guidelines[4] for AF treatment. This method is commonly used in Russia as a sole procedure [5,6] or combined with pulmonary vein ablation [7,8].

Intraprocedural transesophageal echocardiography (TEE) is the gold standard to assess LAA anatomy, perform linear dimensions, evaluate delivery sheath position, and criteria of implantation success during LAAO. However, esophageal varices are a relative contraindication to perform TEE due to the high risk of esophageal bleeding [9]. Many patients with liver cirrhosis are diagnosed with such condition, which increases their bleeding risk [10]. Intracardiac echocardiography (ICE) is an alternative to TEE [11], but its performance can be challenging depending on LAA anatomy.

A 55-year-old female patient with permanent AF and high risk of thromboembolic and hemorrhagic events (CHA_2DS_2-VASc score 5, HAS-BLED score 3), Child-Pugh B hepatic cirrhosis, and esophageal varices (grade II of modified Paquet classification) was referred to our center for catheter-based LAA closure procedure.

Her medical history included arterial hypertension, left brachial artery thrombosis, requiring embolectomy, carotid atherosclerosis, gastrointestinal (GI) bleeding on OACs (warfarin, rivaroxaban). In 2018, she was diagnosed with Child-Pugh class B hepatic cirrhosis and grade II esophageal varices. OAC therapy was discontinued due to the high risk of recurrent GI bleeding with hemoglobin loss down to 5,5 g/dl, and the patient was recommended to undergo endovascular LAAO.

The physical examination did not reveal any remarkable changes: the blood pressure was 135/88 mmHg, heart rate 62 -98 b.p.m., respiratory rate 17, oxygen saturation 100%. Lungs were clear to auscultation without any wheezes and crackles. Endoscopy showed esophageal varices grade II (modified Paquet classification), with maximum strand diameter up to 10 mm in the lower two-thirds of the esophagus.

Preprocedural computer tomography (CT) of the left atrium (LA) revealed an oval shape LAA ostium with 20-23 mm transverse size. There were no signs of LA thrombosis (Fig. 1).

An intracardiac ultrasound catheter (Acuson AcuNav 8Fr, Biosense Webster, USA) was placed in the right atrium (RA) via the left femoral vein. We visualized LAA from the RA and right ventricular outflow tract to exclude LAA thrombosis and, after confirmation, performed transseptal puncture. Angiography of LAA was performed, LAA ostium transverse size was 23 mm (Fig. 2A).

The ultrasound probe was advanced into the LA to improve LAA imaging by ICE. However, we could not achieve optimal LAA visualization due to the instability of the ICE catheter both in the LA cavity and left pulmonary veins. We decided to deliver a steerable sheat into the LA (Agilis 8.5 Fr, St Jude Medical, USA). The delivery sheath was placed into the left superior pulmonary vein (LSPV), and the ICE catheter was advanced via the delivery system to the LA. The catheter remained inside the sheath at the LA level. We visualized the LAA with a minor artifact in the upper part of the sector, which did not affect the imaging quality (Fig. 2B). We measured the LAA ostium transverse size 20-23 mm, which correlated well with fluoroscopy and CT data. Based on measurements, an Amplatzer Amulet 28 mm device was successfully implanted (Fig. 3A and 3B) under ICE guidance. According to ICE data, the device lobe compression was 17%, and more than two-thirds were positioned distal to the left circumflex artery. A separation existed between the device lobe and the disk, and no peri-device leak was observed, indicating an effective LAAO.

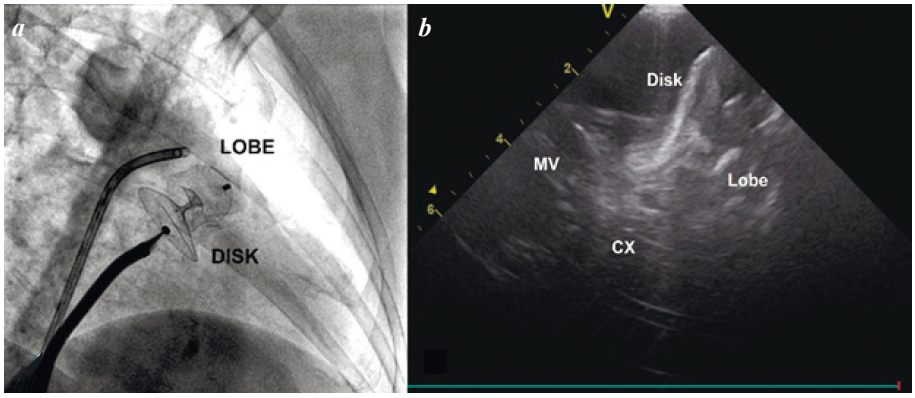

Fig. 3. The visualization of Amplazer Amulet in the atrial appendage by fluroscopy (a) The visualization of Amplazer Amulet in the atrial appendage by intracardiac echocardiography (b). MV - mitral valve, Cx - circumflex artery.

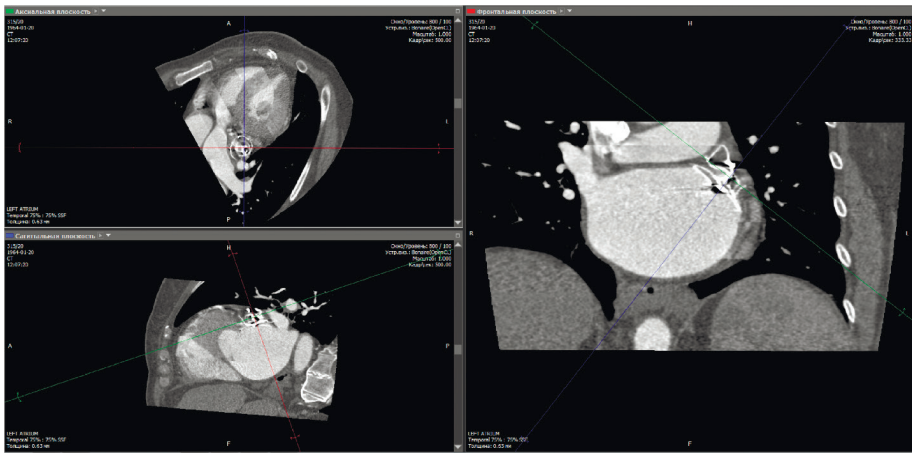

Fig. 4. Postprocedural left atrium computer tomography. Computed tomography scan confirmed the exclusion of left atrium appendage from systemic circulation.

The postoperative period was uneventful. We discharged the patient six days after the intervention on dual antiplatelet therapy (clopidogrel 75 mg/day, acetylsalicylic acid 75 mg/day).

The patient did not report any adverse events or complications during the following three

months. The CT scan in 3 months did not reveal either device thrombosis or any communication between the LAA cavity and the LA (Fig. 4). Antiplatelet therapy was discontinued. The last follow-up visit was in 24 months after the implantation, the patient reported neither complications nor adverse health events at that time.

DISCUSSION

Patients with AF, high risk of LAA thrombosis, and liver cirrhosis are at higher risk of life-threatening thromboembolic and hemorrhagic events. However, data are limited on OAC safety and efficacy in these patients. Neither were enrolled in randomized controlled trials studying OACs effects in AF patients, nor effective and safe international normalized ratio values were determined for them. It is known that continuous OAC therapy is associated with severe GI bleeding in this group of patients [12]. LAAO is an alternative approach to thromboprophylaxis and should be considered even in patients with contraindications to TEE. ICE is a comparable alternative to TEE [13]. Moreover, ICE does not require general anesthesia and may be better tolerated.

However, optimal LA and LAA anatomy visualization may be challenging when using ICE. In our case, catheter positioning in RA, right ventricle outflow tract, coronary sinus was not helpful for LAA anatomy evaluation and measurements, so we decided to advance the ICE catheter into the LA. Fassini et al. [14] in 2014 reported that ultrasound-probe, placed in the LA, improved LAA anatomy visualization. Following this, Masson et al. [15] offered to use a deflectable sheath for further LAA imaging enhancement.

However, we faced another problem while positioning the catheter in LA and LSPV: the instability of the ultrasound probe severely compromised the LAA measurements and real-time evaluation. We used a steerable delivery sheath to gain additional stability. The delivery system was inserted into the LSPV to play the role of a stabilizing 'bridge' and allow the ICE catheter to remain at the LA cavity level. Such position of the ICE catheter helped evaluate LAA anatomy entirely, perform the requiring measurements, and successfully implant the occlusion device. A minor artifact did not compromise the imaging quality.

CONCLUSION

Using a steerable delivery system increases ICE catheter stability and improves ICE-guided LAA anatomy evaluation. The ICE catheter positioning within the delivery sheath does not compromise the LAA imaging quality and should be considered to ensure catheter stability when required.

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LEFT ATRIAL APPENDAGE THROMBOSIS AND FREDERICK'S SYNDROME: A CASE REPORT

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The article presents a clinical case of a young patient living in the Far North for a long time with Frederick's syndrome and diagnosed of the left atrial appendage thrombosis.

Keywords: Frederick syndrome; atrial fibrillation; complete heart block; left atrial appendage thrombus; His pacing

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Frederick's syndrome is a combination of complete atrioventricular (AV) block and atrial fibrillation (AF) or flutter, which is manifested by a complete interruption of the excitation impulses from the atria to the ventricles. In this case, the ventricles are excited by a rhythm driver from the AV junction or the ventricular conduction system, and there is a disordered contraction of individual groups of muscle fibres in the atria [1]. Frederick's syndrome occurs in 0.6-1.5% of patients with AF [1, 2]. On transoesophageal echocardiography (TOE) prior to catheter ablation or cardioversion in AF, the incidence of thrombus in the left atrial appendage (LAA) is 5.1-27.1%, depending on oral anticoagulants, and the risk of thrombus formation remains even with adequate anticoagulant therapy [3]. The aim of this paper is to present the clinical case of a young patient with Frederick's syndrome and proven LAA thrombosis according to the TOE data in the conditions of the far north over a long period of time.

Patient R., 34 years old, was admitted to the Tyumen Cardiology Research Centre in January 2020 complaining of excruciating left chest pain unrelated to physical activity, unstable blood pressure (BP), shortness of breath when ascending to the 4th floor. Past medical history: 13 years of living in the Far North (in Yamalo-Nenets Autonomous District). Medical history: In 2000 and 2012, the patient suffered severe electrical trauma with loss of consciousness on two occasions. Arterial hypertension in the last 7 years with maximum BP increase to 215/110 mm Hg, against a background of constant hypotensive therapy BP values were recorded mainly at the level of 130/90 mm Hg. Every year (1-2 times per year) he had cases of acute respiratory viral infections with an increase in body temperature up to 39-40 °C, he was treated independently as an outpatient. In 2014, after a severe viral infection, the patient noticed «interruptions» in the work of the heart for the first time; he did not seek medical help at that time. Since 2015, a series of electrocardiograms (ECG) as part of screening examinations have constantly registered a rhythm of AF with scarring changes in the left ventricle (LV); no attempts have been made to restore sinus rhythm at the residence. For the last 2 years before the present hospitalisation, the patient had a steady, infrequent pulse of 40 per minute, without clinical manifestations. At the end of December 2019, against a background of psycho-emotional stress, the complaints of excruciating

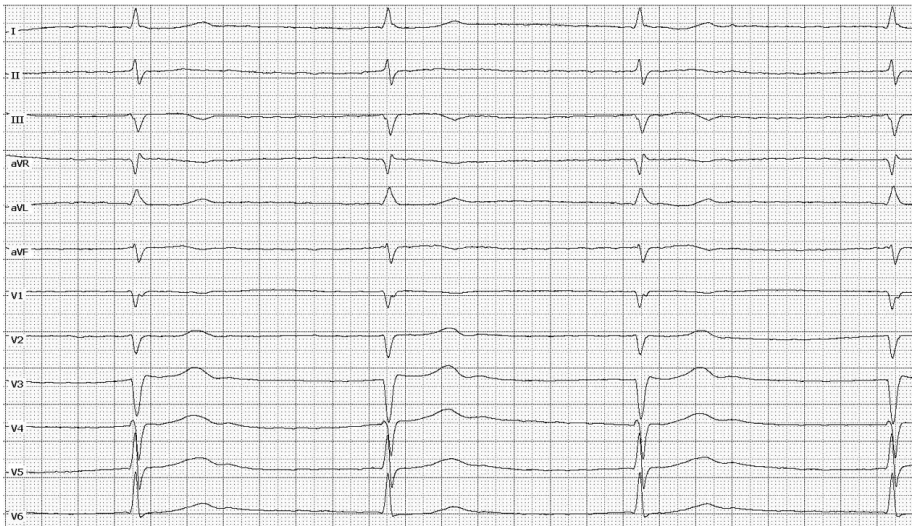

Fig. 1. Patient's ECG on admission (recording rate 50 mm/s, amplitude 10 mm/mV).

pain in the left side of the chest and general weakness appeared. With the diagnosis: coronary heart disease (CHD), unstable angina pectoris, unspecified postinfarction cardiosclerosis, the patient was admitted to the hospital at his place of residence. On admission, ECG and daily ECG monitoring revealed signs of Frederik's syndrome with a ventricular rate of 33-46-77 during the day and 28-35-62 per minute at night. Transthoracic echocardiography (EchoCG) revealed signs of dilatation of the left atrium (LA), right ventricles against a background of satisfactory contractile function of the myocardium LV. The patient underwent coronary angiography which showed a muscular bridge in the middle third of the anterior descending artery which narrowed the arterial lumen by up to 40% in systole. Against the background of medical therapy at the place of residence (losartan 50 mg/day, torasemide 2.5 mg/day, spironolactone 25 mg/day, clopidogrel 75 mg/day, dabigatran 110 mg twice daily, atorvastatin 40 mg/day), the signs of Frederick's syndrome persisted. The patient was transferred to the Tyumen Cardiology Centre for surgical intervention - permanent pacemaker implantation (PM) - via the Centre for Disaster Medicine.

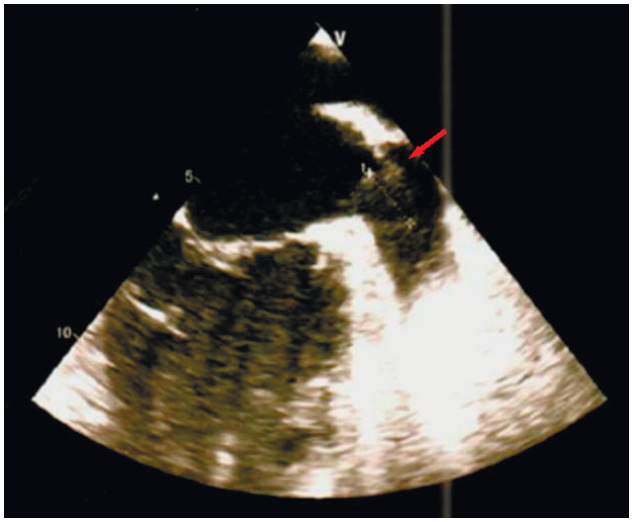

Fig. 2. TOE: soft globular parietal thrombus in LAA (arrow indicates thrombus).

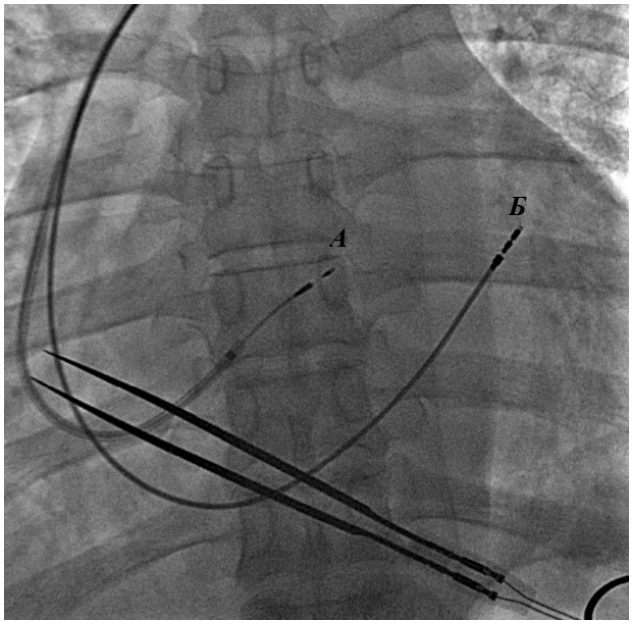

Fig. 3. Location of electrodes in the bundle branch (A) and RV septum (B) in direct projection.

At the time of admission to our centre, the ECG showed Frederick's syndrome with a ventricular contraction rate of 43 per minute combined with blockage of the anterior branch of the left bundle branch, signs of LV scar changes with anterior apical localisation, and signs of right ventricular (RV) strain were observed (Fig. 1).

According to the results of diurnal ECG monitoring, the rhythm of AF (signs of Frederick's syndrome) was constantly observed during the day, the frequency for ventricles during the day varied at the level of 31-43-70 per minute. EchoCG findings: cardiac cavity dilatation, predominantly right sections (LA - volume index 71.1 ml/m^2; right atrium (RA) - volume index 108.8 ml/m^2; RV - diameter index 20.1 mm/m^2, LV end-diastolic volume index 79.4 ml/m^2, LV end-systolic volume index 34 ml/m^2), signs of LV remodelling in the form of eccentric LV hypertrophy (LV myocardial mass index 119.8 g/m^2, relative thickness of LV wall 0.4), moderate mitral regurgitation, moderate tricuspid regurgitation, echo signs of moderate pulmonary hypertension (systolic pulmonary artery pressure 56 mm Hg), preserved LV ejection fraction (55%).The study was based on the results of the study of the patients with a small number of patients. The TOE findings showed a soft spherical parietal thrombus up to 1.5 cm in diameter in LAA, and there was moderate spontaneous echoconstriction with reduced velocity of blood flow in LAA up to 38 cm/s (Fig. 2).

Among hematological parameters, there was an increase in NT-proBNP level up to 815 pg/ml. Against the background of therapy with dabigatran in standard coagulation tests there was a 1.5-fold increase in activated partial thromboplastin time (up to 45.4 s) and 5.5-fold increase in thrombin time (up to 110 s). Other coagulogram parameters, such as D-dimer, prothrombin index, and antithrombin III, were within normal limits. Laboratory data confirmed euthyroidism (thyroid hormone - 1.01 IU/ml, free T4 - 17.8 pmol/l).

Taking into account the clinical and anamnestic data (absence of clinical symptoms typical of CHD, coronarography findings, absence of asynergia and hypokinesia zones on EchoCG), the diagnosis of CHD, previous myocardial infarctions, the final diagnosis was made: principal diagnosis: Arterial Hypertension stage III. Controlled arterial hypertension. Risk of cardiovascular complications 4 (very high). Target BP ≤130/70-79 mmHg. Complications: Rhythm and conduction disorder: Permanent AF, combined with total AV block (Frederick's syndrome). CHA_2DS_2-VASc - 2, HAS-BLED - 0. Secondary dilatation of heart cavities. Moderate pulmonary hypertension. Thrombus in LAA. Chronic heart failure IIA with preserved ejection fraction, NYHA functional class II.

The patient underwent correction of antithrombotic therapy, clopidogrel was cancelled. In view of the deviations in the coagulation indices responding to the effect of dabigatran, treatment with the thrombin inhibitor dabigatran was continued and the dose was increased to the standard dose - 150 mg twice daily.

Taking into account the absolute indications (permanent AV blockade), the patient was implanted with a

Medtronic Adapta DR dual-chamber PM with two endocardial leads: one lead was placed in the region of the bundle branch and connected to the atrial channel of the PM, the second lead was placed in the region of the RV septum to enable safety cardiac pacing and connected to the ventricular channel (Fig. 3, 4).

When programming the PM, the following parameters were determined and set: AAIR mode, lower rate limit - 60 per minute, at the parahysial electrode: stimulation threshold 1.25 V at pulse duration 0.5 ms, amplitude 4.0 V, impedance 549 ohms; at the RV electrode: stimulation threshold 1.25 V at pulse duration 0.4 ms, amplitude 3.5 V, impedance 575 ohms. During ECG recording against a background of hypotensive stimulation, an PM rhythm was recorded with a ventricular rate of 60 ppm, and the width of the QRS complex was 100 ms and did not differ from the QRS complex in spontaneous rhythm (Fig. 4b).

One week after surgery, a repeat EchoCG was performed, which showed a positive trend in the form of a decrease in the size of LA (volume index from 71.1 to 55.7 ml/m^2), the right heart (the volume index of RA from 108.8 to 82, 5 ml/m^2, RV diameter index from 20.1 to 19.1 mm/m^2), decrease in mitral regurgitation to mild and tricuspid regurgitation to moderate, systolic pressure in the pulmonary artery (from 56 to 38 mm Hg), increase in ejection fraction to 57%.

At discharge, the patient was advised to continue the drug therapy chosen in hospital (losartan 50 mg/day, spironolactone 25 mg/day, dabigatran 150 mg twice daily), atorvastatin was discontinued because the diagnosis of CHD was excluded.

After 3 months, the patient was repeatedly hospitalized to our center for dynamic examination and optimization of PM parameters. At admission, the patient had no active complaints. The ECG and daily ECG monitoring recorded an PM rhythm with a frequency of 62 per minute; against a background of physical activity, the rhythm increased up to 98 per minute. EchoCG data showed continued positive dynamics in the form of a further decrease in LA volume index to 49 ml/m^2, RA to 77.3 ml/m^2, mitral and tricuspid regurgitation to grade 1, systolic pulmonary artery pressure to 36 mm Hg, LV myocardial mass index to 106.7 g/m^2. The patient underwent a repeat TOE against a background of continuous dabigatran dosing of 300 mg/day: there was no evidence of thrombosis and spontaneous echocontrast in LAA, there was an increase in velocity indices up to 56 cm/s (Fig. 5). Among hematological parameters, the normalization of NT-proBNP index (101 pg/ml) was noted in the dynamics. When programming the PM parameters, the stimulation threshold at the electrode in the bundle branch area was 1.5 V, and the pulse amplitude was reduced to 3.25 V. The repeated study of the patient one year after PM implantation (ECG, EchoCG, TOE, examination of the PM system, NT-pro BNP index) did not reveal any negative dynamics. During the year, the patient continued to take the prescribed drug therapy in the former doses (losartan, spironolactone, dabigatran). Repeated TOE showed no signs of thrombus in LAA.

DISCUSSION

This clinical case is of interest from several points of view.

Firstly, this case shows a long asymptomatic course in a patient with complete AV block on a background of permanent AF (Frederick's syndrome), which developed due to an unspecified cause and led to the development of arrhythmogenic cardiomyopathy.

In our clinical example, the absence of clinical manifestations of arrhythmia against the background of the subjective sensation of a rhythmic pulse may have led to the incorrect assessment that the patient had sinus rhythm and that timely recognition of Frederick's syndrome was not possible. In addition, the narrow QRS complexes (up to 100 ms) in this patient's ECG indicate the localisation of the rhythm driver in the AV junction and speak for a proximal type of block, which is often not accompanied by a disturbance of the biomechanical cardiac contraction [4]. In the Russian literature, a case was described in which bradycardia was not diagnosed in time against a background of permanent atrial fibrillation (Frederick's syndrome), which led to syncope in one patient and delayed the implantation of an PM [2].

One of the possible causes of concomitant rhythm and conduction disturbances in this patient may be myocarditis. This version can be supported by the history of cardiac arrhythmias associated with repeated viral infections as well as the involvement of all cardiac chambers in the pathological process, while due to the age of the disease we have no confirmation by laboratory and instrumental examination methods of the diagnosis of myocarditis. Another probable cause of arrhythmia could be a repeated electrical trauma accompanied by loss of consciousness. Since the cause of the disease was difficult to determine, the dilatation of the cardiac cavity detected after EchoCG with an elevated NT-proBNP level of up to 815 pg/ml against the background of a persistent bradyarrhythmia

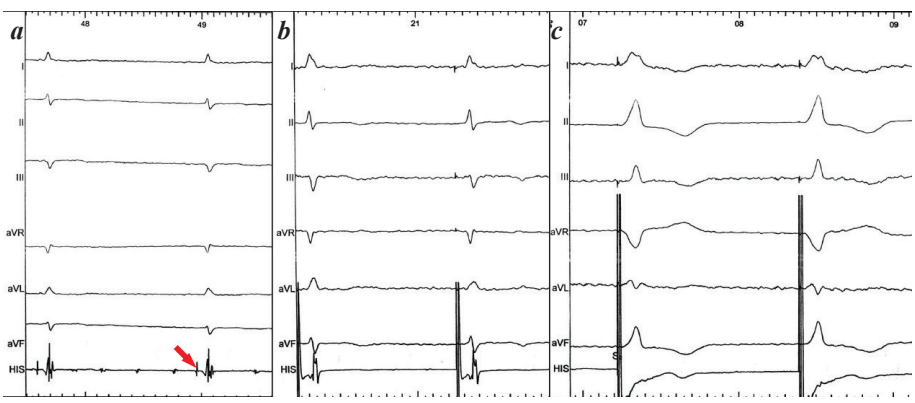

Fig. 4: a - intracardiac endogram of bundle branch area (arrow indicates bundle branch commissure), b - bundle branch stimulation, c - stimulation of RV septal area (endogram recording rate 67 mm/s, amplitude 10 mm/mV).

with a ventricular contraction rate of 40 per minute was considered to be a manifestation of arrhythmogenic cardiomyopathy. The validity of this interpretation is confirmed by the positive dynamics of the EchoCG data and the NT -proBNP level against the background of the continuous operation of the PM during the dynamic observation of the patient.

Besides the asymptomatic course, a long history of AF and AV block obviously plays an important role in the pathogenesis of arrhythmogenic cardiomyopathy. The absence of atrial systole against a background of AF and the presence of AV dyssynchrony with marked slowing of the heart rate is accompanied by a decrease in the atrial and ventricular contribution to LV filling in diastole. This leads to an increase in mitral regurgitation and occlusion pressure in the pulmonary artery, an increase in RV afterload, gradually leading to its dysfunction and enlargement, and dilatation of the fibrous rings of the tricuspid valve [5, 6].

Secondly, in this clinical example, a patient with an absolute indication for permanent PM implantation has opted for bundle branch pacing, which allows near physiological pulse propagation through the cardiac conduction system. It is known that the bundle branch is a part of the AV node whose stimulation leads to functional involvement of the left and right legs of the bundle branch without decrementing [7]. Implantation of an endocardial right ventricular lead in an apical position can lead to the occurrence and significant increase in tricuspid regurgitation [4, 8] with subsequent progression of right ventricular heart failure. Given the evidence of right ventricular dilatation with tricuspid regurgitation of moderate-to-severe on initial EchoCG in our patient, correct selection of the optimal area for intracardiac lead placement is critical to prevent progression of heart failure. PM implantation in the area of the bundle branch provides a normal sequence of ventricular contractions and does not dilate the QRS complex [8], as shown in our example. At the same time, a decrease in the diameter of the fibrous ring of the tricuspid valve against a background of hypotensive stimulation and normalisation of heart rate can be considered a predictor of local hemodynamic improvement (reduction in right ventricular preload). The stimulation of the bundle branch in the patient was thus accompanied by a positive dynamic in the form of a reduction in the size of the cardiac cavity, a normalisation of the LV myocardial mass index, a reduction in regurgitation at AV valves, especially at the tricuspid valve.

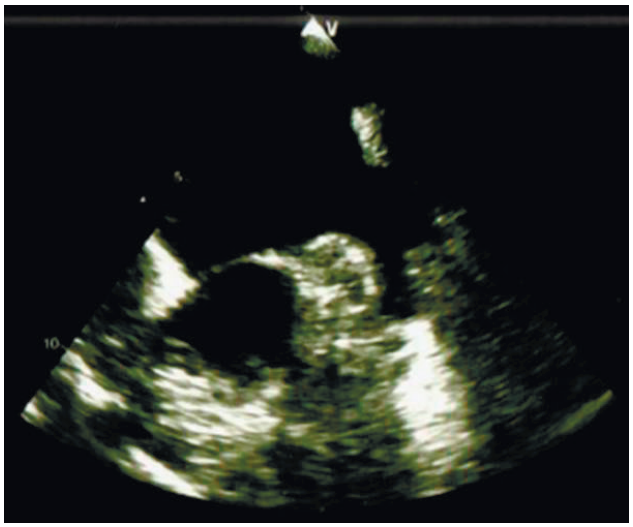

Fig. 5. No signs of thrombosis and spontaneous echocontrasting in LAA according to TOE.

Thirdly, this example shows a rather unusual situation where a soft spherical parietal thrombus was detected in LAA with signs of moderate spontaneous echocontrast and decreased velocity indices in LAA in a young patient with TOE. Possible cause of LAA thrombosis formation, first of all, can be the formation of cardiomyopathy of both atria [5, 6], and ventricles. In our previously published work, left atrial cavity dilatation and the presence of eccentric LV hypertrophy were independent echocardiographic predictors of LAA thrombosis in patients with non-valvular AF [9]. These changes are also observed in our patient and may be involved in the pathogenesis of thrombosis.

Another possible cause of thrombogenesis is an unreasonably low dose of dabigatran. According to the instructions and clinical guidelines, a standard dose of 150 mg 2 times daily should also be taken in combination with clopidogrel; there was no evidence to reduce the dose at the time of hospitalisation [10]. Considering the coagulation indices, we left dabigatran as is, but the dosage was increased to the standard dose of 150 mg twice daily.

One of the possible factors that also contributes to the earlier development and rapid progression of cardiovascular pathology (arterial hypertension) with the formation of thrombosis could be the negative effects of the climatic conditions of the far north. According to literature data, thermoregulatory adaptation to low air temperatures leads not only to vasoconstriction, increased BP, but also to fluid loss, increased blood viscosity without compensatory activation of the fibrinolysis system with subsequent development of hypercoagulation [11]. According to our previous retrospective study [12], in patients living in the far north, the presence of LV hypertrophy is one of the most important predictors of LAA thrombosis, and compared to mid-latitude residents, northerners show LV hypertrophy at an earlier age.

CONCLUSION

The clinical observation presented thus shows the combined effect of several unfavourable pathological factors in a young patient living in the far north, which led to the formation of arrhythmogenic cardiomyopathy, heart failure on a background of complex arrhythmias and the formation of a thrombus in LAA. Properly chosen therapeutic tactics to eliminate chronotropic insufficiency using stimulation of the bundle branch made it possible to achieve a positive dynamic in the form of reversed structural and functional cardiac remodelling and elimination of signs of heart failure, and administration of the standard dose of dabigatran resulted in lysis of the thrombus in LAA. Moreover, one cannot deny the possible additional influence of the unfavourable climatic conditions of living in the far north on the patient's body, which was the basis for the recommendation to change the place of residence to a region with a more favourable climate.

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PACING MANEUVERS FOR SUPRAVENTRICULAR TACHYCARDIA DIFFERENTIAL DIAGNOSIS: VENTRICULAR OVERDRIVE PACING

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The accurate tachycardia mechanism verification is the most important condition for high effectiveness and safety of the supraventricular tachycardia ablation. Ventricular overdrive pacing - is a simple and useful diagnostic maneuver, frequently used in the supraventricular tachycardia diagnosis. The conditions for its performance and interpretation in the standard and rare situations are described in this review.

Key words: supraventricular tachycardia; electrophysiological study; catheter ablation;, AV nodal reentry tachycardia; orthodromic tachycardia; atrial tachycardia; ventricular overdrive pacing

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Catheter ablation is one of the most common and effective treatments for supraventricular tachycardia (SVT). Since the mapping technique and choice of instruments for catheter ablation depend largely on the type of tachycardia, intraoperative diagnosis is of paramount importance. Both the basic parameters of SVT (cycle duration, ventriculo-atrial (VA) interval, etc.) and the responses to different stimulation techniques need to be considered. The choice of pacing technique and the interpretation of the response to it also depend on the initial parameters of the tachycardia. As each stimulation technique has its own advantages and limitations, the electrophysiologist must be confident in its use and interpretation in order to successfully diagnose SVT. This is what this review is about.

This literature review is first dedicated to the differential diagnosis of the three most common types of SVT: atrioventricular nodal recurrent tachycardia (AVNRT), atrioventricular recurrent tachycardia (AVRT) with involvement of an accessory conduction pathway (ACP) and atrial tachycardia (AT). First we will look at «resetting» and «entrainment» as basic electrophysiological phenomena. In the following we will discuss the role of ventricular overdrive pacing (VOP) in determining the diagnosis in most cases.

ELECTROPHYSIOLOGICAL BASIS OF STIMULATION TECHNIQUES

The absolute majority of supraventricular tachycardias develop by the mechanism of re-entry, therefore a significant proportion of pacing techniques are based on two electrophysiological phenomena: «resetting» and «entrainment» of the tachycardia [1, 2]. With the help of these phenomena, it is not only possible to determine the mechanism of the tachycardia, but also to determine the location of the re-entry circuit, to confirm or exclude the presence of ACP and its involvement in the maintenance of the arrhythmia. Before we turn to the specific issues of differential diagnosis of SVT using stimulation techniques, let us briefly describe the electrophysiological basis of resetting and entrainment.

Resetting the tachycardia

When a single electrical stimulus is applied to the re-entry circuit during a tachycardia, two new excitation waves (two excitation fronts) are generated that move in opposite directions from the point of stimulation (Fig. 1a,b). The wave propagating in the direction opposite to the movement of the tachycardia wave is called retrograde [3]. The stimulated wave propagating along the course of the tachycardia wave is called antegrade. After the tachycardia wave and the retrograde wave have collided (Fig. 1c), they disappear and the antegrade excitation front remains the only wave moving in the re-entry circuit. Thus, the antegrade wave becomes a new tachycardia wave, which will then continue to move in a circuit (Fig. 1d). Since the speed of impulse propagation through the myocardium and the length of the ree-ntry circuit remain unchanged, the frequency of tachycardia will remain the same. Since the retrograde stimulated wave stops the tachycardia and the antegrade wave simultaneously triggers a new tachycardia in the same circuit, this technique is called «resetting» the tachycardia. During resetting, all complexes following the resetting extrastimulus appear «shifted» to the left on the ECG (Fig. 1d).

Entrainment

If a series of pulses, rather than a single pulse, is administered during tachycardia in the re-entry circuit, each

subsequent pulse may terminate the tachycardia that was «reset» by the previous pulse and «resetting» the tachycardia anew. In this case, during a series of stimuli in the re-entry circuit, there are constantly three waves of excitation: an antegrade wave, a retrograde wave and a tachycardia wave (or an antegrade wave from the previous impulse) [2]. At the end of the stimulation, the retrograde wave of the last pulse again stops the tachycardia triggered by the previous (penultimate) pulse, while the antegrade wave resets the tachycardia and continues the cycle of re-entry as the next pulse fails to occur. Since the tachycardia wave is constantly overlaid by retrograde and antegrade waves from both sides during a series of impulses and the tachycardia appears accelerated to the pacing frequency, this phenomenon is called «entrainment». In this case the entrainment is a continuous resetting of the tachycardia during a series of stimuli. Simultaneous excitation of the myocardium from two sources (the main tachycardia wave and the retrograde wave) leads to the formation of ECG complexes (QRS, P waves or F waves) with «merging» morphology, i.e. an intermediate morphology between that during tachycardia and that during pacing (Fig. 2a). It should be noted that in order to assess the ECG shape during entrainment, the configuration of the complexes must be known both during tachycardia and during pacing outside tachycardia.

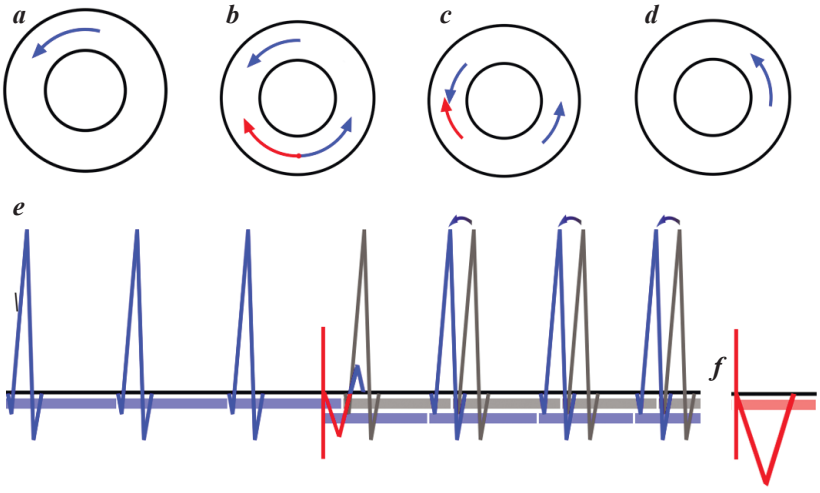

Fig. 1. Schematic representation of the phenomenon of re-entry resetting tachycardia. a) The tachycardia wave propagating in the circuit of re-entry is indicated by the blue arrow. The myocardium outside the arrow is at rest, i.e. it is capable of electrical excitation. b) The extrastimulus applied in the re-entry circuit causes two other excitation waves in addition to the tachycardia wave: antegrade (blue arrow) and retrograde (red arrow). c) The tachycardia wave collides with the retrograde stimulated wave and they cancel each other out. d) The only excitation wave remaining in the re-entry circuit is the antegrade stimulated wave, which becomes a new tachycardia wave that can continue in an endless circular motion. e) Schematic representation of an ECG during a re-entry resetting of tachycardia. A single extrastimulus causes the appearance of a premature complex, which has a confluent morphology (has features of stimulated and spontaneous complexes). The first return tachycardia complex follows the stimulated one at an interval equal to the duration of the tachycardia cycle. Thus, all subsequent complexes (shown in blue) are «shifted to the left» relative to their proper position, which would be observed without «resetting» (shown in gray). f) Schematic representation of the stimulated complex.

Signs of entrainment tachycardia are:

- stable fusion morphology of the complexes, during increasing stimulation with continued tachycardia after termination of stimulation (Stable fusion) (Fig. 2a,c),
- change in the morphology of the complexes during stimulation with gradually increasing frequency with continuation of tachycardia after termination of stimulation (Progressive fusion) (Fig. 2b,d),
- local conduction blockade at the moment of tachycardia termination during increasing stimulation, followed by earlier local activation of this site during the continuation of the series of stimuli,
- change in the morphology of electrograms (EG) and the relative activation time of any part of the circuit of re-entry when the frequency of stimulation changes with continuation of tachycardia after termination of stimulation (Local fusion) [4].

Depending on the presence of signs of confluent excitation on the surface ECG or local ECG, the following main variants of entrainment are distinguished.

- Entrainment with «manifest collision of excitation fronts» (manifest entrainment). During entrainment, the surface ECG has an intermediate morphology between its own and that imposed from stimulation (fusion complexes). The degree of fusion is determined by the volume of myocardium depolarised by the retrograde wave, which depends on the location of the site of stimulation relative to the main circuit of re-entry, the frequency of stimulation and the decremental delay of conduction in the circuit of re-entry. In manifest entrainment, the ECG notes a steady «fusion» with stimulation at a certain frequency and a progressive «fusion» with increasing frequency of stimulation. After termination of stimulation, tachycardia continues, and the last complex accelerated to the stimulation frequency on the ECG already has the morphology of tachycardia without signs of fusion, that is, the same morphology as during tachycardia (Fig. 2a,b) [5].
- Entrainment with a «local collision of fronts». The tachycardia wave (an antegrade wave from the previous pulse) entrains such a small volume of myocardium that it does not cause changes on the surface ECG. In this regard, stimulated complexes are recorded on the ECG, and there is no draining morphology (in contrast to the manifest entrainment). Nevertheless, the collision of fronts in a small area of the myocardium can be recognised with a local intracardiac recording. This requires recording the different morphology and interval from the stimulus to the local excitation at two stimulus series with different frequencies. At a lower frequency, it is possible to find a region in which the St-EG inter-

val is long, and the electrogram will be caused by an antegrade wave from the previous stimulus (Fig. 1a,c). At higher frequency, the St-EG interval will be significantly shorter due to the entrainment of the retrograde wave from the last stimulus (Fig. 1b,d) [4, 5].

• Entrainment with «full retrograde entrainment» If the frequency of stimulation significantly exceeds the frequency of tachycardia or the point of stimulation is far from the circuit of re-entry, the retrograde wave will entrain the entire stimulated chamber (ventricles or atria). In this case, no signs of antegrade activation can be registered neither on surface ECG, nor by intracardiac ECG (Fig. 3a and see Fig. 11b) [5].

• Entrainment with «hidden front collision» (sometimes also called hidden entrainment) is a phenomenon opposite to full retrograde entrainment. The tachycardia is accelerated to the stimulation frequency, but the plum morphology cannot be registered, neither by surface ECG, nor by intracardiac recordings. The morphology of the surface ECG and the sequence of intracardiac activation are the same as during tachycardia. The antegrade front resets the tachycardia, while the retrograde front collides with the main tachycardia front near the point of stimulation and cannot entrain enough myocardial volume to cause changes on the ECG. (Fig. 3b,c) [5].

Post-stimulation interval

If the stimulation point is directly in the re-entry circuit, the time interval between the last stimulus in the series that triggered the tachycardia and the first recurrent local electrogram at that point (post-pacing interval - PPI) corresponds to the duration of the tachycardia cycle. W.Stewenson et al. established that PPI duration equal to tachycardia cycle length (TCL) or exceeding it not more than by 30 ms is a good prognostic factor for detection of points of effective ventricular tachycardia ablation [6]. The use of this criterion has also been described for mapping atrial tachycardia [7]. The longer duration of PPI compared to TCL reflects the remoteness of the stimulation point from the main circuit of re-entry. The further away

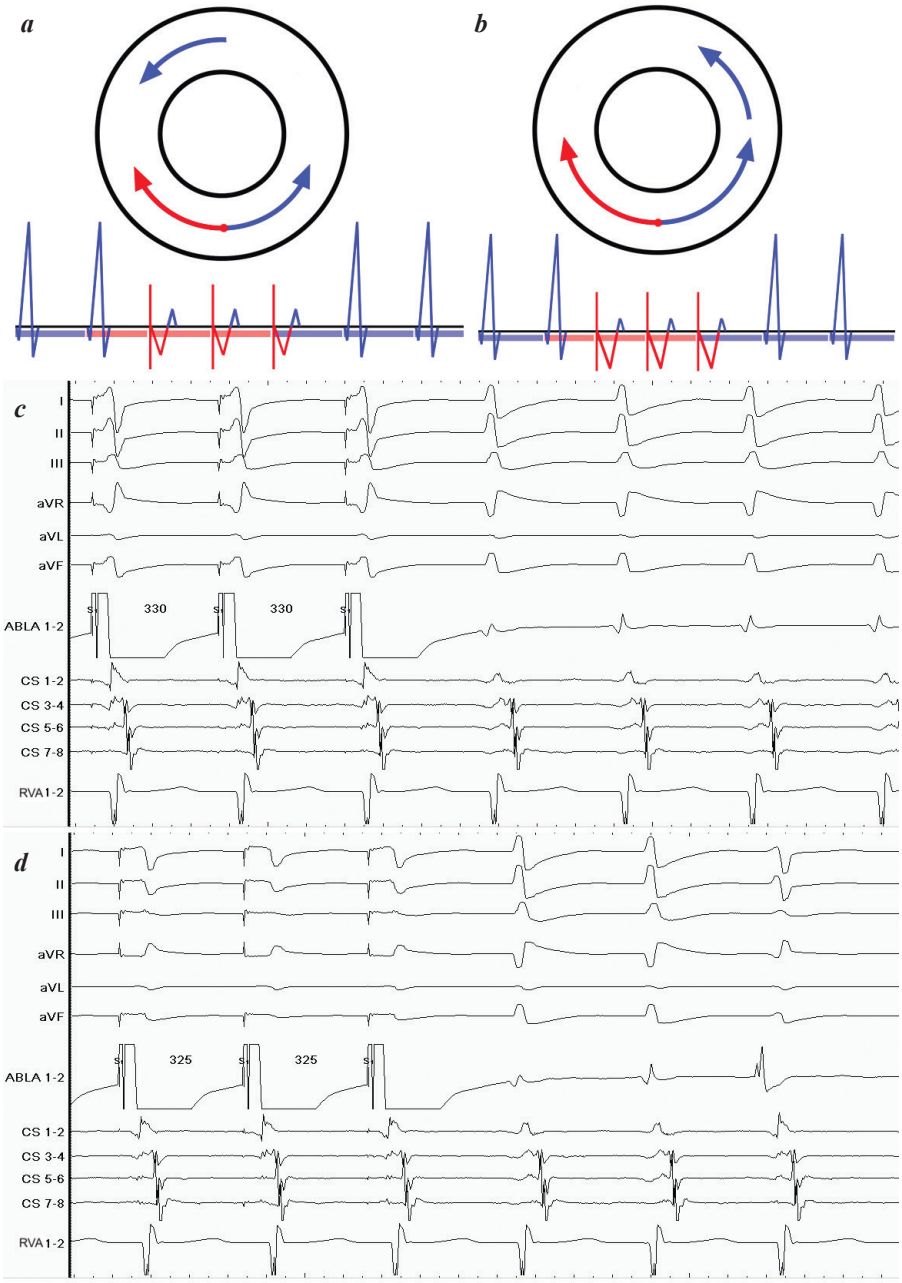

Fig. 2. Schematic representation of the propagation of excitation waves in the tachycardia circuit during entrainment. a) During a series of stimuli with a cycle duration close to the tachycardia cycle, confluent complexes with stable morphology are detected. After termination of pacing, the tachycardia continues. b) With shorter-cycle pacing, the pluminal complexes have a different morphology (due to the greater volume of myocardium captured by the retrograde wave), but the morphology within the pacing is stable. c, d) ECG and EG during ventricular pacing in orthodromic AV re-entry tachycardia. The morphology of the stimulated (merging) QRS complexes changed when the stimulation cycle was shortened from 330 ms to 325 ms. c) At a lower stimulation frequency (stimulation cycle duration of 330 ms), the ventricular myocardium is more strongly entrained by the antegrade excitation wave, the QRS complexes have a shape close to the morphology of QRS during tachycardia (the last 2 complexes). d) At a higher stimulation frequency (cycle duration 325 ms), the retrograde wave started to entrain a slightly larger volume of the ventricular myocardium. Fusion QRS complexes have a morphology less similar to that during tachycardia than in Fig. 2c.

the stimulation point is from the re-entry circuit, the greater the distance the stimulated excitation wave has to travel to reach the re-entry circuit and then return to the stimulation point (after one revolution in the re-entry circuit, which takes the same time as TCL) (Fig. 4).

PRIMARY PARAMETERS FOR EVALUATING SVT

On invasive electrophysiological examination (EPE), SVT is most often tachycardia with narrow QRS complexes and normal H-V interval. Among the parameters presented in Table 1, the first three are the main ones, and their assessment is necessary when analysing any SVT induced during an EPE:

- V:A ratio (quantitative ratio of ventricular to atrial contractions) (Fig. 5);
- V-A interval (from the beginning of the earliest ventricular activation to the beginning of the earliest atrial activation in the bundle branch region);
- atrial activation sequence: concentric (from the interatrial septum to the lateral walls - see Fig. 8a) or eccentric (from the lateral wall of one of the atria to the septum - Fig. 2c,d, Fig. 3c).

If possible, important information about the mechanism of SVT can be obtained by assessing three additional parameters:

- spontaneous termination of SVT with registration of another (not premature) atrial contraction at the end of the paroxysm without changing the atrial activation sequence (Fig. 6);
- with small fluctuations in TCL, changes in the H-H or V-V intervals precede changes in the A-A intervals or, conversely, change after them. In other words, whether fluctuations in the tachycardia cycle are due to changes in the duration of the A-H (A-V) or H-A (V-A) intervals (Fig. 7).
- changes in the V-A interval duration associated with the appearance and termination of functional blockade of one of the legs of the bundle branch.

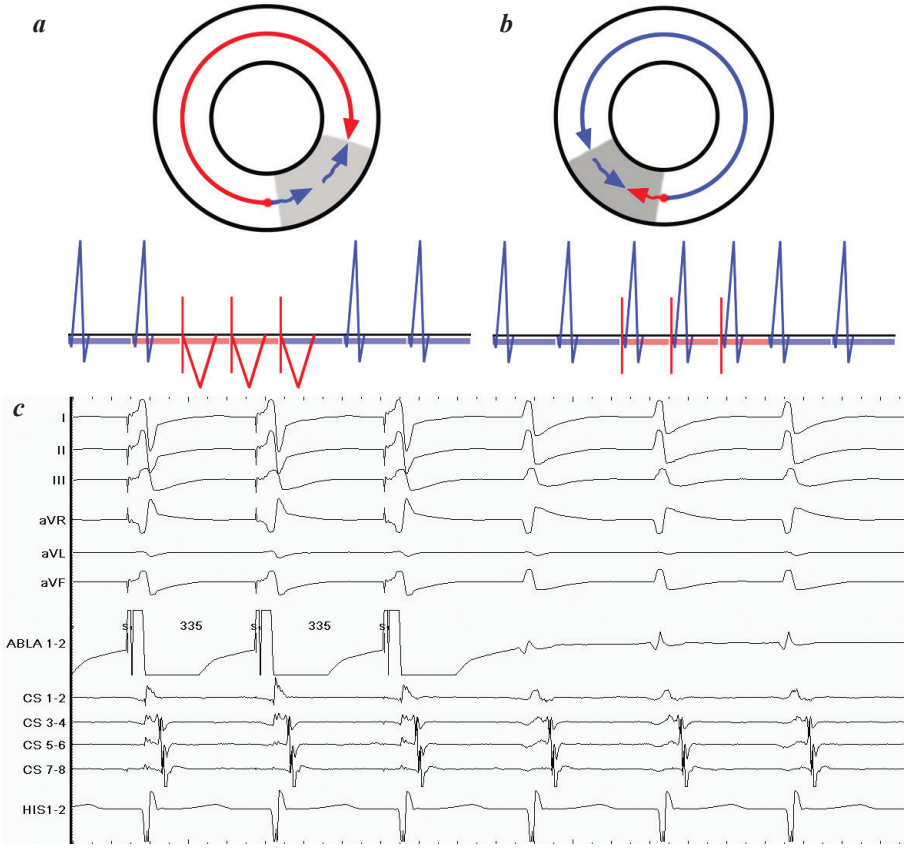

Fig. 3. Schemes depicting rare variants of entrainment. a) Entrainment with full retrograde entrainment. Due to the fact that the stimulation point in the re-entry circuit is in close proximity to the delayed conduction zone, the antegrade excitation wave and the tachycardia wave are significantly delayed in this zone. During this time, the retrograde wave manages to cover in retrograde direction all or almost all of the circuit of re-entry. This leads to the formation of fully stimulated complexes on the ECG without signs of plummeting morphology. Confirmation of the presence of entrainment is the continuation of tachycardia after termination of stimulation. b). The situation is the opposite of that shown in panel a. The delayed-excitation zone is in the path of the retrograde wave. The antegrade wave manages to completely cover the re-entry circuit and form complexes identical to those of tachycardia. Confirmation of tachycardia entrainment is acceleration of tachycardia during stimulation to the stimulation frequency and continuation of tachycardia with the same frequency after termination of stimulation. c) ECG and intracavitary EG in latent entrainment orthodromic AV re-entry tachycardia involving left lateral ACP with ventricular stimulation near the ventricular end of the ACP. The morphology of stimulated (confluent) QRS complexes is almost identical to the morphology of complexes during tachycardia.

In most cases, after evaluation of the listed SVT parameters, the diagnosis is clear and it is possible to perform ablation without additional stimulation techniques. For example, if the V-A interval < 80 ms is registered during SVT in the area of the bundle branch (excludes the possibility of AVRT) and small changes in the H-H interval (or V-V) exactly precede the changes in the A-A interval (excludes the possibility of AT), then the diagnosis of a typical AVNRT (slow-rapid mechanism) can be made and ablation can be performed in the area of the slow pathway of the AV connection.

At the same time, it is not surprising that much attention is paid in the literature to the differential diagnosis of SVT with a ratio of V:A=1:1, a V-A interval duration in the septal area > 80 ms and a concentric (from the centre to the periphery) atrial excitation sequence, since in such a situation any of the SVT types can occur (Fig. 5a). In such

cases, it is absolutely essential to be sure of the diagnosis before proceeding with ablation. In particular, it is critical to differentiate AVNRT from septal AT, or AVRT involving the septal ACP. The latter two mechanisms require mapping and searching for the point of earliest atrial activation. In the case of AVNRT, such tactics will result in exposures in the fast pathway area of the AV junction, where the risk of AV blockade is higher than in the slow pathway area of the AV node (between the coronary sinus mouth and the tricuspid valve ring). It is important to remember that it is easier to choose the right diagnostic technique if the primary parameters are used to narrow down the range of SVT mechanisms to only two possible options (AVNRT and AT or AVRT and AT).

HOW TO QUICKLY RULE OUT ATRIAL TACHYCARDIA?

Since any V-A interval duration and almost any A:V ratio can be recorded in AT, this rhythm disturbance is mentioned in 12 lines of 15 (80%) in Table 1. A quick way to confirm or exclude the diagnosis of AT is a VOP from the right ventricle (RV) with a cycle length 10-30 ms shorter than that of TCL [8]. If, during VOP, the atrial CL accelerates to the CL of the stimulation, and after termination of the stimulation the tachycardia continues and the sequence of spikes represents a «V-A-A-V» type response - this confirms the diagnosis of AT (Fig. 8a). If at the end of stimulation a «V-A-V» type response is recorded, the diagnosis of AT can be excluded, and further differential diagnosis should be made between AVNRT and orthodromic AVRT (see Fig. 10b). The first atrial EG is always the last atrial EG accelerated to the CL of stimulation.

Understanding how VOP confirms or excludes the diagnosis of AT is important to identify specific response variants that can lead to misinterpretation of the result, misdiagnosis, and an adverse outcome of ablation. Let us consider sequentially the options for responding to VOP under each of the SVTs.

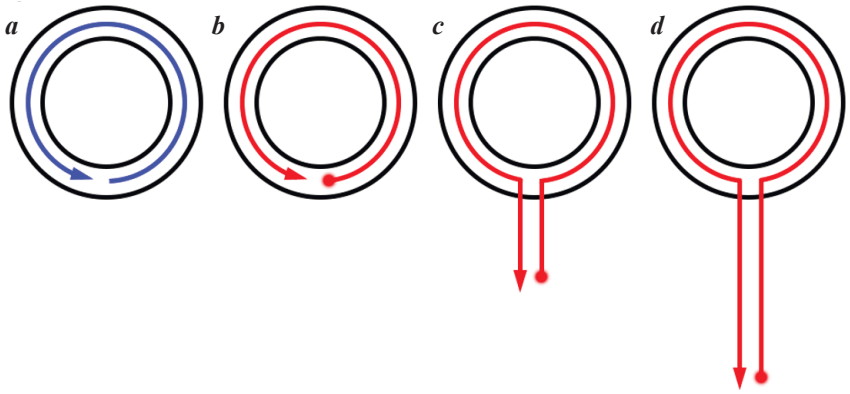

Fig. 4. Schematic depicting the relationship between the duration of the post-pacing interval (PPI) and the distance from the stimulation point during tachycardia entrainment to the circuit of re-entry. a) Tachycardia wave in the circuit of re-entry. b) The stimulation point is on the re-entry circuit: PPI=TCL (0-30 ms). c) The stimulation point is near the re-entry circuit: PPI>TCL (30-60 ms). d) The stimulation point is far from the tachycardia circuit: PPI>>>TCL (>60 ms).

Table 1.

Six basic parameters to be evaluated before selecting a stimulation technique

	Parameter	Note	Mechanism of tachycardia
1.	Ratio of the number of V:A	V=A	AVNRT, AVRT, AT
		V>A ± VA dissociation	oNVRT, oNFRT, AVNRT
		V<A ± AV dissociation	AVNRT, AT
2.	Interval V-A	V-A > 80 ms	aAVNRT, AVRT, AT
		V-A ≤ 80 ms	tAVNRT, AT
		V-A > A-V	aAVNRT, AT, AVRT involving slow-functioning ACP
3.	Atrial activation sequence	Top to bottom	AT
		Concentric	AVNRT, AVRT, AT
		Eccentric	AVRT, AT*
4.	Spontaneous cessation	Last «spike» is A	AVRNT, AVRT
		Last «spike» is V	AVNRT, AVRT, AT
5.	H-H interval changes precede A-A changes	Yes	AVRNT, AVRT
		No	AVNRT, AVRT, AT
6.	V-A interval is increased by more than 30 ms in the development of functional bundle branch block	Yes	AVRT with ACP involvement - on the side of the blocked bundle branch (ipsilateral block)
		No	AVNRT, AVRT, AT

Note: AVNRT - atrioventricular nodal reciprocal tachycardia; AVRT - atrioventricular reciprocal tachycardia; AT - atrial tachycardia; tAVNRT - typical AVNRT; aAVNRT - atypical AVNRT; oNVRT - orthodromic nodo-ventricular reciprocal tachycardia; oNFRT - orthodromic nodo-fascicular reciprocal tachycardia; * - most likely, AVNRT involving left atrial node exit - rare, but AVNRT and AVRT are theoretically possible.

Atrial tachycardia

When VOP is performed during AT, any excitation wave conducted retrogradely to the atria will accelerate the arrhythmia (in a triggered tachycardia mechanism) or inhibit it (in an automatic tachycardia mechanism) or enter the re-entry cycle (entrainment) if AT has a reciprocal mechanism. The last retrogradely conducted excitation wave (responsible for the atrium EG, which we consider the first response to the termination of VOP) cannot return antegradely to the ventricles as an echo response, because the heart's excitation conduction system is still in the refractory phase at this point - it has just conducted the same wave from the ventricles to the atria. Even in the presence of a double AV junction or a bystander accessory pathway, re-entry of the excitation wave that has just come retrogradely from the ventricles into the atria is impossible, as these pathways will simultaneously depolarise parallel to each other in the retrograde direction and will be in the refractory phase for some time (Fig. 9a-c). If AT is not stopped as a result of the series of stimuli, the next atrial EG (i.e., the second atrial EG after the termination of VOP) will be the result of the continuation of AT. Now the cardiac conduction system is out of refractory state, and the next after the atrial EG will be the bundle branch EG (H), followed by the ventricular EG (V2) (Fig. 9d). Thus, the response to the VOP will be «St-V-A-A-H-V», or simply «V-A-A-A-V» (Figs. 8, 9).

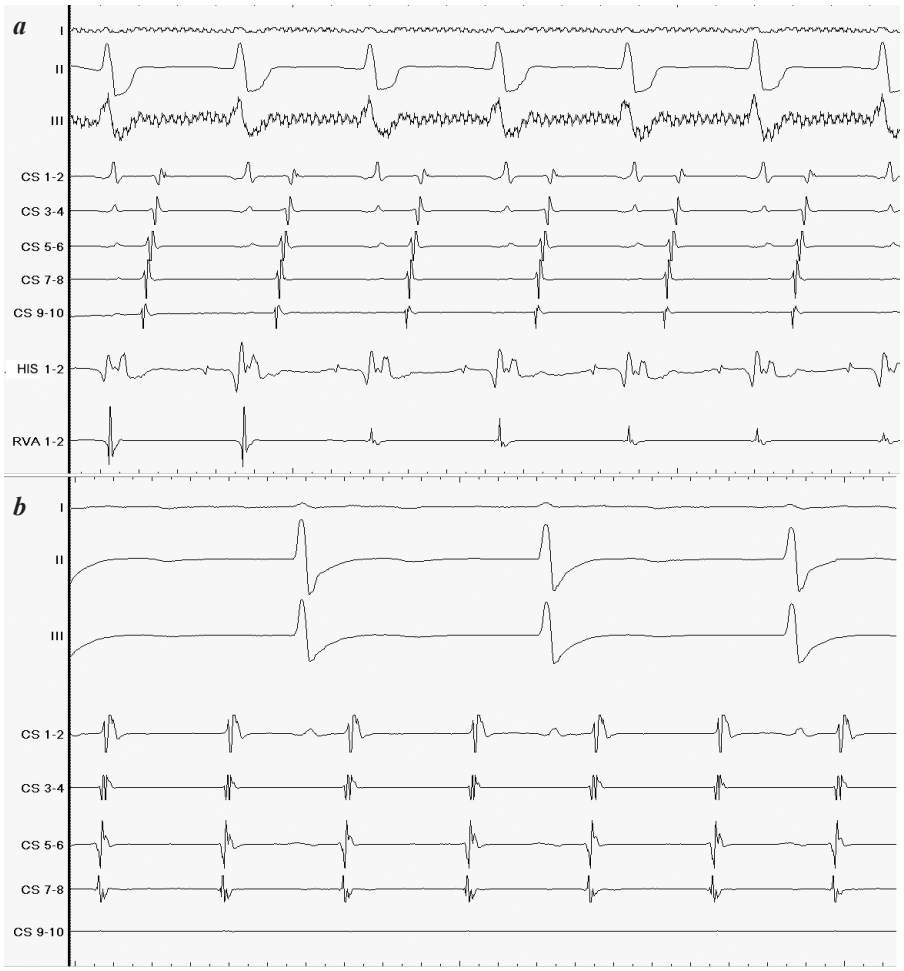

Fig. 5. Examples of ECG and electrograms of patients with tachycardia with narrow complexes and V:A ratio of 1:1 (a), 2:1 (b).

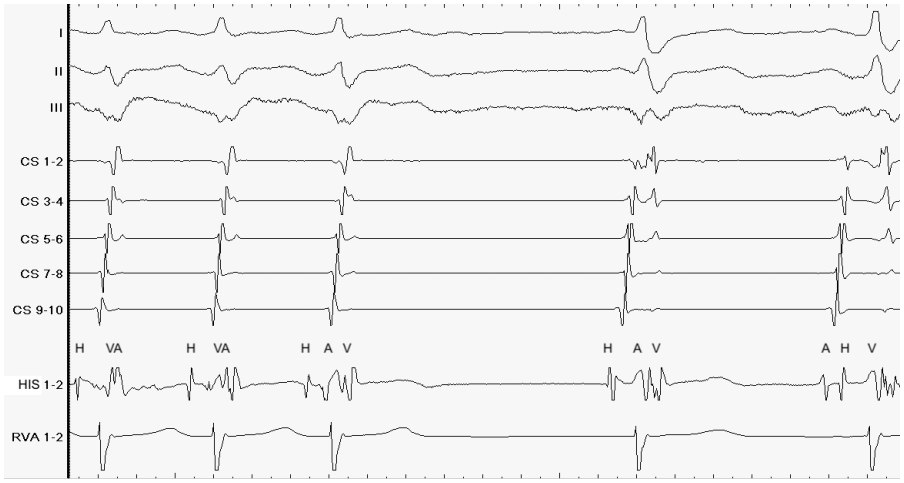

Fig. 6. Capping of AVRT when the next pulse through AV node to ventricles is stopped. At the end of the paroxysm, the H-A sequence is recorded.

Orthodromic AV re-entry tachycardia

In orthodromic AVRT, VOP causes the appearance of two waves of excitation propagating in opposite directions along the circuit of re-entry, and leads to entrainment of tachycardia. The antegrade wave induces atrial excitation through the ACP, so that the sequence of atrial activation coincides with the sequence during AVRT. The retrograde wave propagates through the ventricular myocardium and cardiac conduction system towards the AV node, meeting a tachycardia wave (after the first stimulus) or an antegrade wave of the previous stimulus (after the subsequent stimuli) on its way (Figure 10a). This is how tachycardia entrainment occurs - the tachycardia is resets- «turned on» or «immersed» in a series of stimuli. The best confirmation of entrainment is the registration of confluent QRS complexes (manifest entrainment) during VOP, which combine the morphology of stimulated ventricular complexes and narrow complexes registered during AVRT. If during a series of stimuli an acceleration of atrial activation was observed before the CL

stimulation and the tachycardia continues after the termination of the VOP, then even in the absence of signs of fusion excitation in the ECG, it can be assumed that an entry into the tachycardia circuit has taken place (in this case we speak of entrainment with local collision of the excitation fronts). At the termination of pacing, the last imposed wave will propagate retrograde through the ACP to the atria (thus registering the first atrial EG in response to the VOP), traverse a full circuit of tachycardia in the antegrade direction, without encountering a retrograde wave in the absence of the next stimulus, and leading to the registration of successive bundle branch (H) and ventricular (V) EGs, representing the response to VOP of the «St-V-A-H-V» or simply «V-A-V» type (Fig. 10b).

AV nodal re-entry tachycardia

The situation is similar when the AVNRT entrainment is carried out with the help of VOP. The only difference is that a single stimulated wave of excitation must completely cover the ventricles and pass through the conduction system to the AV node. Then the antegrade wave, having introduced in «fast» way of AV connection, will restart AVNRT and also will accelerate an atrial rhythm to CL stimulation. At the same time, the retrograde wave will enter the «slow» pathway of the AV junction and collide there with the antegrade wave from the previous stimulus (Fig. 11a). The last stimulated wave delivered to the atria in the retrograde direction will result in registration of the first (and the only) atrial EG in response to the VOP, passing through a circuit of tachycardia. Then it will return to the ventricles through the «slow» AV junction pathway and a bundle branch without encountering a retrograde wave (due to the absence of the next impulse). Thus, the response to the VOP «St-V-A-H-V», or simply «V-A-V», is recorded (Fig. 11b). It should be noted that during the AVNRT entrainment, the collision of the retrograde excitation wave and the antegrade wave from the previous stimulus occurs within the «slow» pathway of the AV node. Accordingly, the morphology of the QRS complex is always stimulated and cannot be confluent. Therefore, in AVNRT, entrainment is al-

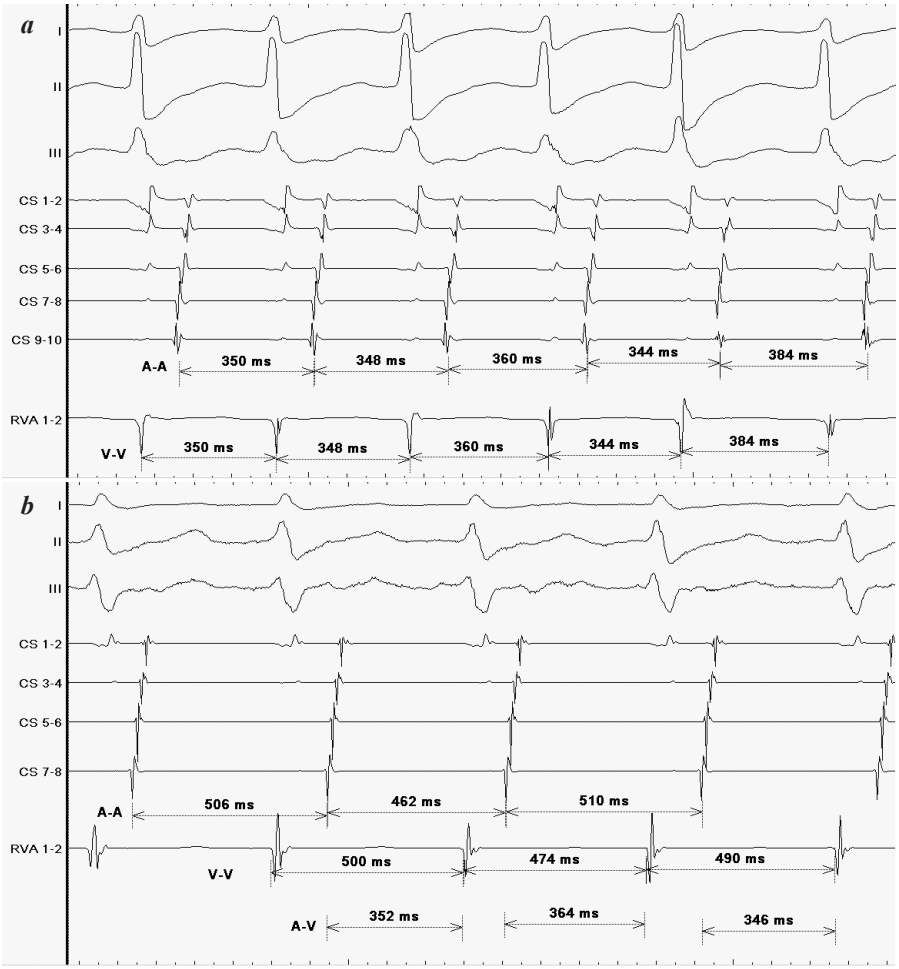

Fig. 7. Changes in the duration of the SVT cycle, allowing for a differential diagnosis. a) Cycle fluctuations in AVRT. Changes in the duration of VV intervals precede changes in AA intervals. b) Cycle fluctuations in AT. Changes in AA intervals precede changes in VV. The duration of the VV intervals does not fully correspond to the duration of AA due to the decremental conduction through the AV node: the shortening of the preceding AA leads to the lengthening of the following AV and vice versa, the lengthening of the preceding AA leads to the shortening of the AV interval.

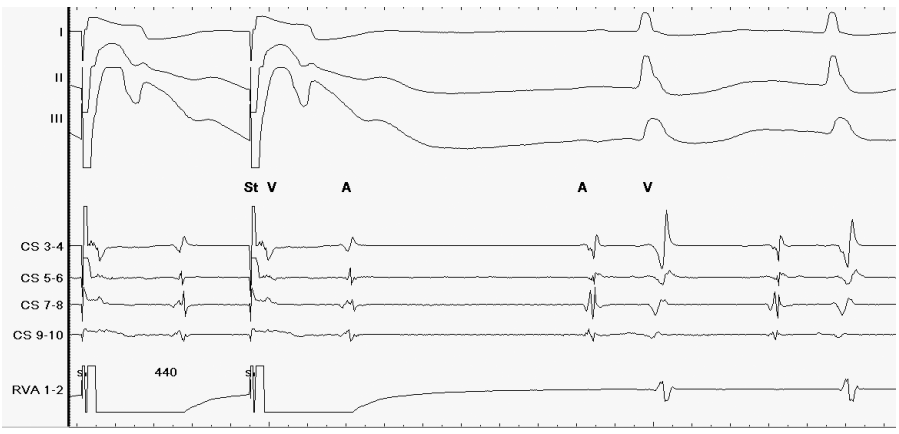

Fig. 8. Entrainment of SVT with the help of VOP. A V-A-A-V response is pathognomonic for atrial tachycardia.

ways characterised by complete retrograde ventricular entrainment and is never manifest neither by surface ECG nor by local EG data.

Thus, a «V-A-V» response to VOP is a sign of entrainment in AVRT or AVNRT and excludes the presence of AT. On the other hand, a «V-A-A-V» type response confirms the presence of AT, excluding the possibility of AVNRT or AVRT. The main disadvantage of this technique is that in 50-80% of cases atrial acceleration to ventricular stimulation rate is impossible. In other words, the atria continue to be excited at the frequency of tachycardia and the ventricles continue to be excited at the frequency of pacing, i.e. slightly more frequently than the atria. As a rule, this phenomenon is caused by low conductivity of the AV node in the retrograde direction. Nevertheless, such response variant shows that atrial rhythm does not depend on ventricular activation (VA dissociation) and allows to exclude AVRT [9-11]. When such a response is detected on VOP, it usually appears to be atrial tachycardia, but additional pacing techniques are needed to be sure that it is AT [9, 11] and not AVNRT.

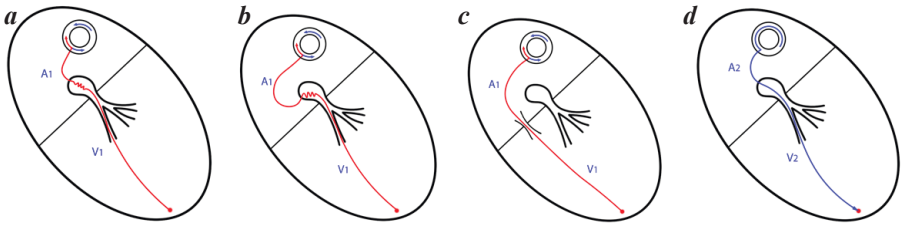

Fig. 9. Schematic of pulse propagation in atrial re-entry tachycardia entrainment during VOP. Retrograde pulse conduction (red line) from the ventricles to the atria can be through a fast AV junction pathway (a), a slow AV junction pathway (b), or an additional conduction pathway (c). Atrial and ventricular re-excitation (d) after one lap (blue line) in the re-entry loop.

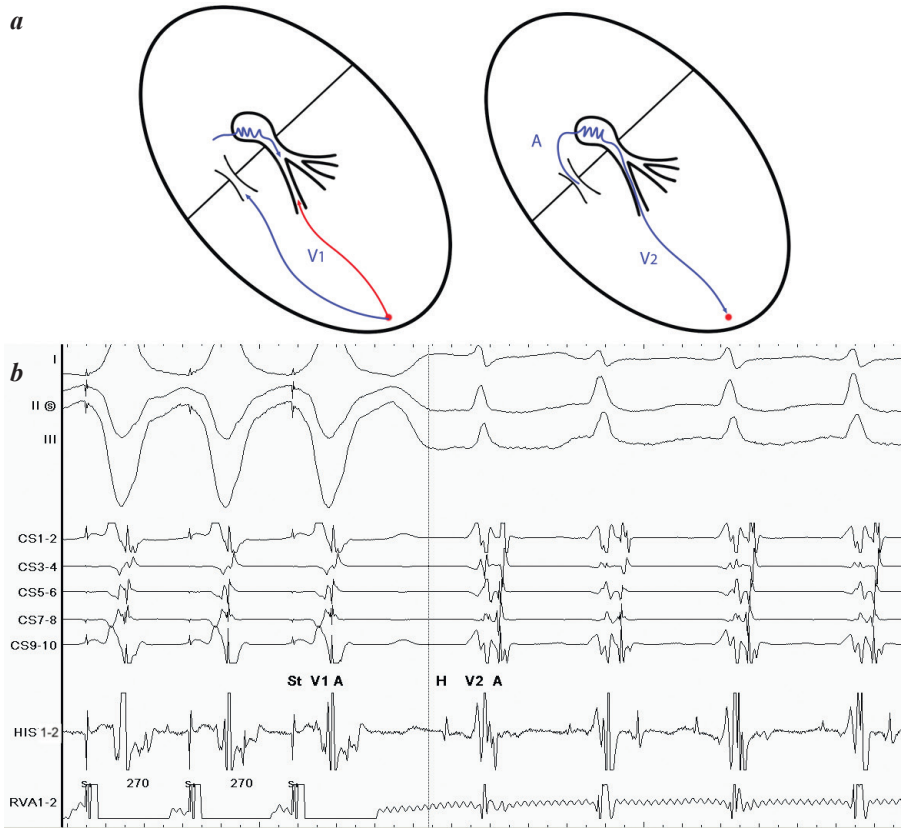

Fig. 10. Entrainment during VOP during orthodromic AVRT. a) Schemes of stimulated excitation wave propagation along the circuit of re-entry. b) ECG and electrograms during entrainment of orthodromic AVRT. During stimulation, the shape of the QRS complexes (the first 3 complexes) has a confluent character, intermediate between stimulated (not shown) and spontaneous (the last 4 complexes). After termination of stimulation, the sequence V-A-H-V is observed.

TECHNICAL DIFFICULTIES IN THE QUALITATIVE ASSESSMENT OF THE RESPONSE TO VOP

Misinterpretation of the response to VOP can be observed in the following situations.

1. During ventricular stimulation there is no 1:1 conduction from ventricles to atria and there is ventriculo-atrial dissociation

The acceleration of atrial activation to the ventricular stimulation rate is critical in VOP. If during VOP atria continue to be excited with tachycardia rather than with stimulation frequency, the test is considered uninformative, and its result cannot be interpreted. To confirm the correctness of this stimulation technique, it is necessary to measure several consecutive A-A intervals at the end of the stimulus series and immediately after its completion. If VOP is performed correctly, A-A intervals equal to the CL of stimulation are recorded during stimulation, then (after termination of stimulation) the A-A intervals increase to the CL of tachycardia. The duration of the broadened first A-A interval may exceed the CL of the tachycardia due to decremental conduction in the re-entry circuit or temporary suppression of the ectopic focus. VA dissociation in VOP may be observed when ventricular stimulation is not frequent enough or not long enough, and when the frequency of tachycardia increases just before or during stimulation. Such a problem can be solved by repeating a longer series of stimuli with the stimulation cycle shortened by 10-20 ms (Fig. 12a).

2. Errors in the assessment of the first atrial electrogram in response to VOP

A. In atypical AVNRT ('slow-slow' and 'fast-slow'), and in AVRT involving a

'slow-functioning' ACP, the V-A interval after the last stimulus may be longer than the CL of stimulation. Then the first atrial EG after the last ventricular stimulus will reflect atrial excitation by the pulse from the penultimate stimulus. The second atrial EG after the last stimulus will be caused by the last stimulus. The interval between the first and second atrial EG (A-A) after the last stimulated ventricular complex will be equal to the CL of the stimulation. If this is overlooked, such a pseudo-«V-A-A-V»-response could be mistakenly interpreted as characteristic of AT (Fig. 12b).

B. The first atrial EG, due to the resumption of AT, may occur at an interval equal to the CL of the stimulation. Since this phenomenon can only occur by chance, it is necessary to repeat VOP several times with different CLs of stimulation to make sure that the «V-A-A-V» response is repeatable.

3. The duration of the H-V interval is longer than the duration of the H-A interval

Sometimes in AVNRT the H-V interval is greater than the H-A interval. Lengthening of the H-V interval may be associated with a decrease in the conduction velocity along the bundle branch or along the «lower common pathway» within the AV node [13]. This ratio of H-V and H-A intervals leads to a shortening or even formation of a negative V-A interval. After the last stimulated atrial EG, a bundle branch EG should follow, and then a ventricular EG. If conduction from AV node to ventricles is delayed, this ventricular EG may be preceded by a second atrial EG due to continuation of AVNRT. This pseudo «V-A-A-V» response can also lead to errors, which can be easily avoided by evaluating the response to VOP not as «V-A-A-V» or «V-A-V» but as «St-V-A-A-A-H-V» or «St-V-A-H-V». [14].

4. Blockage of first-wave tachycardia to the ventricles above the level of the bundle branch

Theoretically, the first excitation return wave can be blocked above the bundle branch (at the level of the «lower common pathway» in the AV node) after stimulation has ended. In this case, the bundle branch potential will not be registered, and the «St-V-A_1-(H_1-V_1)-A_2-H_2-V_2» type response may be formed instead of the «St-V-A_1-A_2-H_2-V_2» response during AVNRT. The registration of such a response to VOP can be expected if a transient spontaneous AV conduction disturbance is observed during SVT. In this situation, the evaluation of the response to VOP may be unreliable, and other diagnostic techniques must be used.

5. The presence of two SVTs in a patient.

An «A-H» type response indicates that the patient is suffering from AVNRT or AVRT. However, this does not rule out the possibility of this patient starting AT. Therefore, after eliminating the substrate of SVT, it is necessary to repeat the diagnostic protocol with programme and pacing to rule out other types of tachycardia.

DIFFERENTIAL DIAGNOSIS OF AVNRT AND ORTHODROMIC AVRT. MORPHOLOGICAL AND QUANTITATIVE ASSESSMENT OF THE VOP RESPONSE

If AT is diagnosed in VOP, you can proceed to mapping and ablation of the tachycardia substrate. If, on the other hand, the possibility of AT is excluded as a result of VOP, the differential diagnosis between AVNRT and orthodromic AVRT can easily be made using the parameters presented in Table 1. Difficulties may arise in situations with concentric atrial activation and V-A interval duration greater than 80 ms. In such cases, in order to distinguish between AVRT involving septal ACP and atypical AVNRT, evaluation of additional quantitative parameters of the response to VOP is necessary.

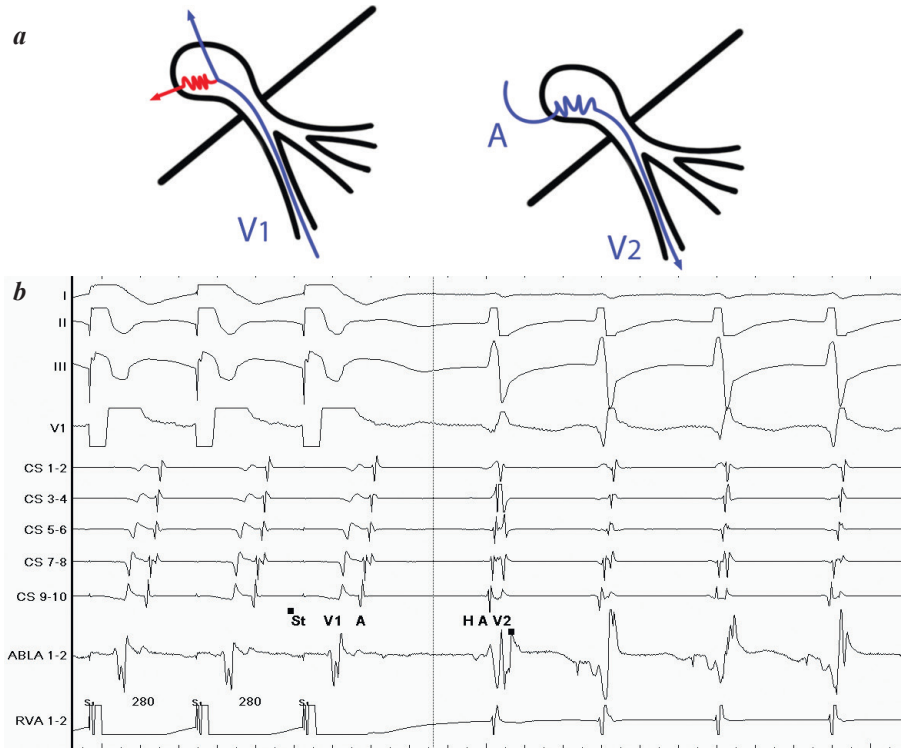

Fig. 11. Entrainment in VOP during AVNRT. a) Schematic depicting the propagation of the stimulated excitation wave along the circuit of re-entry. The retrograde wave (red arrow) travels along the slow pathway of the AV connection, collides with the tachycardia wave (not shown), and disappears. The antegrade wave is conducted into the atria through the fast AV junction pathway and becomes a tachycardia wave after the tachycardia wave and retrograde wave collide. This leads to the formation of a V-A-V type response. b) ECG and electrograms during AVNRT entrainment. During stimulation, the shape of the QRS complexes (the first 2 complexes) has a fully stimulated morphology, and after stimulation (the last 4 complexes) has a spontaneous morphology. After termination of stimulation, the sequence V-A-V or V-A-H-V is observed.

Assessment of ventricular excitation pattern during entrainment

As stated earlier, a V-A-V type response to VOP is indicative of a patient having an AVNRT or AVRT. A sign that helps to diagnose AVRT with high specificity is the formation of confluent QRS complexes during tachycardia entrainment with VOP. Since the formation of confluent QRS complexes is impossible in AVNRT, the registration of this phenomenon during entrainment allows diagnosing orthodromic AVRT (see Fig. 2). Unfortunately, the sensitivity of this sign is relatively low because in AVRT entrainment the collision of excitation fronts occurs more frequently within the conduction system and the QRS complexes on the surface ECG have a stimulated morphology, as in AVNRT (see Fig. 10b), i.e. there is entrainment with local collision of excitation fronts. The following methods can be used to detect the confluent nature of ventricular excitation.

A. Study of local conduction entrainment by antegrade stimulated wave

In order to facilitate the detection of the confluent nature of excitation during an AVRT entrainment (that is, to increase the sensitivity of this diagnostic method), not only the morphology of QRS complexes on the surface ECG, but also the shape and sequence of the intracardiac EGs can be evaluated. Sequential registration of EG the bundle branch and its right limb captured by the antegrade excitation wave shows that the previous impulse crossed the AV node and the bundle branch and collided with the stimulated retrograde wave in the more distal parts of the conduction system or in the working myocardium (see Fig. 10b). It is very important to pay attention to these nuances: the morphology of QRS complexes in these cases will be almost indistinguishable from the stimulated one.

B. Selecting the ventricular stimulation point

It is obvious that the probability of detecting confluent QRS complexes on the surface ECG depends directly on the myocardial volume that the stimulated antegrade wave can entrain before colliding with the retrograde wave. The antegrade excitation wave begins to depolarise the ventricular myocardium only after it leaves the conductive system. At the same time, the retrograde wave begins to excite the myocardium immediately after the next stimulus is applied, and the sooner it enters the conduction system, the less likely the manifest entrainment will be. Therefore, the best stimulation point is the one that is as far away as possible from the cardiac conduction system and as close as possible to the AVRT circuit. Such an area is near the ventricular end of ACP (on the ventricular side of the AV sulcus, opposite the place of the earliest atrial activation during SVT) (Fig. 13). The closer the stimulation point is to the ventricular end of ACP, the more likely it will be possible to register a fusion QRS morphology. Therefore, in AVRT involving septal or right-sided ACP, manifest entrainment (fusion QRS complexes) is easier to detect during stimulation of the apex or basal segments of the RV. Accordingly, at AVRT with participation of the left ventricular ACP, the signs of manifest entrainment are more likely to be received when VOP is conducted from the left ventricle (LV) [11]. By bringing the stimulation point as close as possible to the ACP, one can sometimes achieve a latent collision of the excitation fronts. In this case, the morphology of the imposed QRS complex will be identical to SVT due to complete entrainment of the ventricles by the antegrade wave from the previous impulse (restarted tachycardia wave). (see Fig. 3b,c).

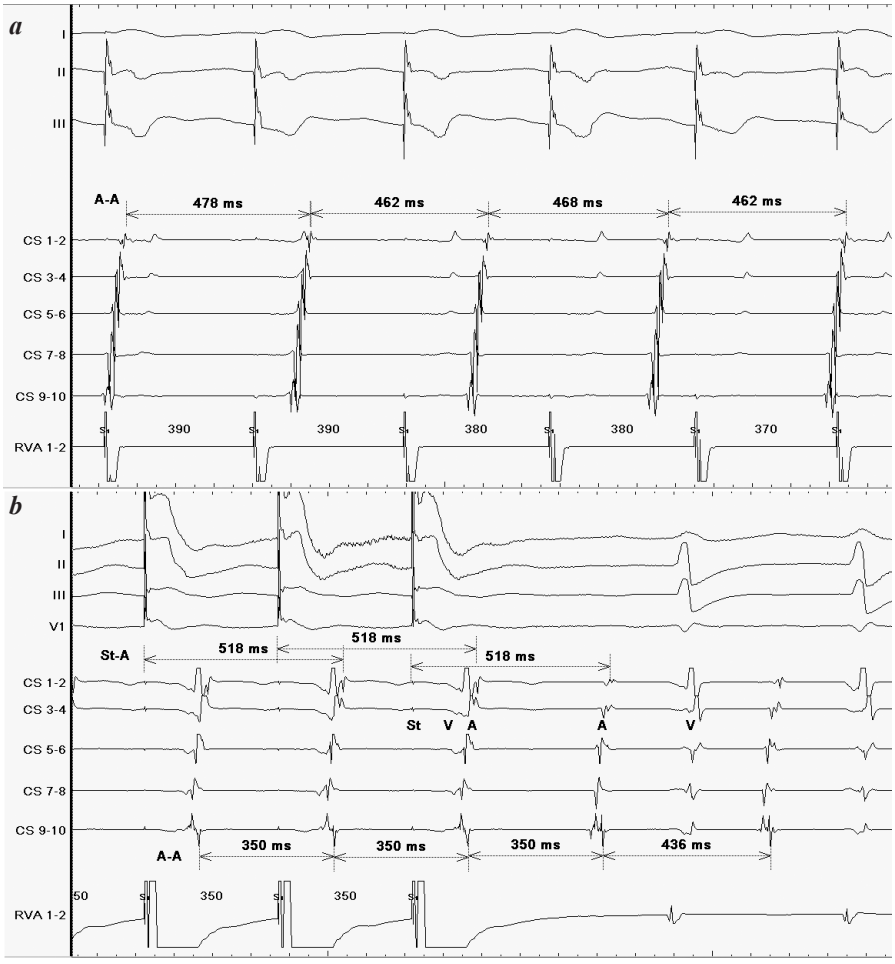

Fig. 12. a) Absence of atrial entrainment in VOP of atrial tachycardia. b) Pseudo-VAAV response in VOP of atypical AVNRT. St-A intervals are longer than St-St intervals, so that the last A-A interval accelerated to the stimulation frequency is entirely after the last stimulus. If this is not taken into account during the electrophysiological study, a false positive diagnosis of atrial tachycardia is possible.

C. Determining the moment of "shift" of atrial activation in VOP

a. The shape of the QRS complexes on the surface ECG.

After the onset of the VOP, there is usually a gradual change in the morphology of the QRS complexes from the form characteristic of SVT, through intermediate forms reflecting different degrees of collision of the excitation fronts, to the stable morphology of the QRS complex (stimulated or drained) (Fig. 14). Identification of the first QRS complex with stable morphology is central to this algorithm.

b. Momentum of acceleration of atrial activity to ventricular stimulation rate

In AVNRT (in the absence of ACP), the excitation wave from the ventricles can reach the atria only through the AV node. For this purpose, successive stimulated excitation waves from the ventricles outpace the corresponding tachycardia waves and entrain the higher parts of the conductive system. In this regard, atrial capture occurs only after complete entrainment of the ventricular myocardium by stimulation (Fig. 14a). In AVRT, the pulses from the VOP will reach the atria immediately after the wave of excitation from the ventricles reaches the ACP (Fig. 14b). In both cases, the «shift» in atrial activation may manifest itself in earlier arousal (shortening of the next A-A interval, the most common variant), slightly delayed atrial activation (prolongation of the next A-A interval, quite rare in decremental ACP), or termination of tachycardia without further atrial activation.

A «shift» in atrial activation that occurs before or simultaneously with the first QRS complex and has stable morphology has a positive predictive value of more than 90% for the diagnosis of AVRT. Similarly, if the «shift» of atrial activation occurs later than the first QRS complex, which has a stable morphology, AVNRT can be diagnosed with a positive predictive value of more than 90% [15-17]. This hallmark is attractive because it does not require the continuation of tachycardia after the termination of the VOP to be assessed. Nevertheless, it is important to keep in mind the possible difficulties in using this technique. These include:

- fluctuations in the duration of the tachycardia cycle;
- rapid atrial entrainment in AVNRT and AT, when using a stimulation CL that is shorter than TCL by more than 40 ms;
- delayed «shift» of atrial activation during AVRT involving decremental ACP;
- rapid atrial entrainment in AVNRT and AT via bystander accessory pathway,
- errors in determining the first QRS complex with stable morphology, the accuracy of which, according to different authors, is about 80% [17].

To increase the diagnostic value of this technique, you can compare stimulation from the apex and basal parts of the ventricles, as close as possible to the place of the earliest atrial activation. In doubtful cases it allows providing earlier acceleration of atrial excitation in AVRT, and later in AVNRT.

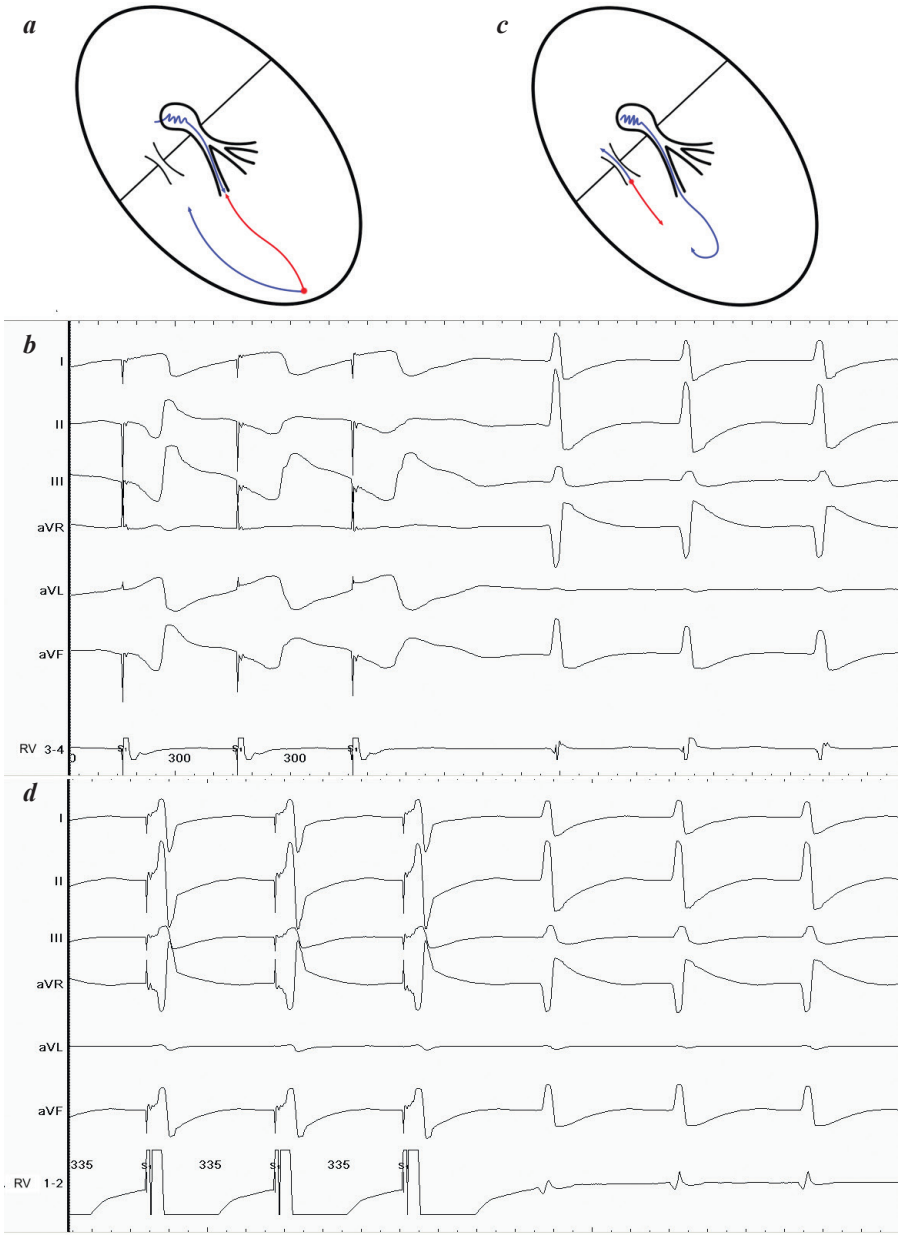

Fig. 13. Differences in the morphology of the QRS complexes during entrainment of orthodromic AVRT from different pacing points in the ventricles. a) Schematic of pacing from the apex region. b) ECG and electrograms during pacing from the apex of the RV. c) Schematic of ventricular pacing versus earliest atrial activation. d) ECG and electrograms during pacing from basal parts of the ventricular myocardium.

Technical difficulties in assessing the character of ventricular excitation in entrainment

A. Concealed bundle branch entrainment during right ventricular basal stimulation

When VOP is performed from the basal septal regions, accidental entrainment of the bundle branch (or proximal left or right leg) can result in relatively narrow QRS complexes. The pseudo-leaky nature of the excitation in this case can lead to overdiagnosis of AVRT. This can be avoided by stimulating above or below the level of the bundle branch and the right leg, checking that the stimulated QRS complexes are fully suspended or «draining» after the tachycardia has subsided.

B. AT entrainment or AVNRT, in the presence of bystander AP

The spillover character of ventricular excitation during SVT entrainment with the help of VOP allows three conclusions to be drawn:

- SVT develops by the mechanism of re-entry,
- impulses conducted along ACP can affect the mechanism of SVT,
- ventricular extrastimuli can lead to «resetting» of re-entry.

The most logical and probable conclusion from these three theses is that the patient has AVRT. Nevertheless, the same signs would theoretically be observed in the presence of a bystander AP whose atrial end is in the re-entry circuit of another tachycardia (AT or AVNRT). Such exceptional circumstances would make it necessary to develop during stimulation two tachycardias, or tachycardia with two circuits, one of which is AVRT. Therefore, such ACP could no longer be considered a «bystander» that is, passively activated, in the full sense of the word. Therefore, ACP ablation would be essential, both clinically and for the detection of a second mechanism of tachycardia in repeated EPI. Thus, the endpoint of SVT with the confluent character of ventricular excitation in VOP indicates the presence of AVRT, irrespective of whether the patient has a second tachycardia with a different mechanism or not [18].

Quantitative parameters of the VOP response

As mentioned above, the detection of the confluent nature of ventricular excitation during SVT ventricular pacing allows the diagnosis of AVRT with a high degree of reliability. The weak side of this technique is the need for additional, sometimes difficult to perform, catheter manipulations (to select the optimal stimulation point or to record local EG) and careful measurement of intracardiac intervals. At the same time, the differential diagnosis between AVRT and AVNRT can be made using simple and objective quantitative parameters: PPI and the interval between the stimulus and the atrial electrogram (St-A).

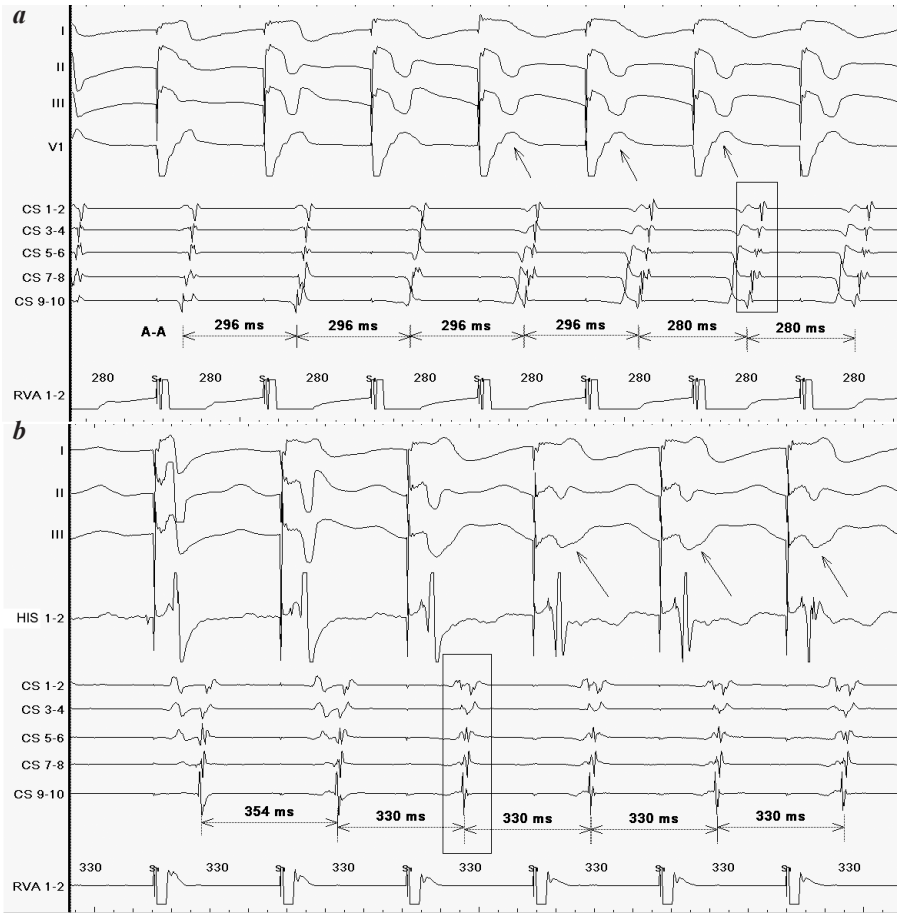

Fig. 14. Determination of the time of the «shift» of the atrial electrogram. a) In AVNRT, the atrial cycle length is accelerated to the pacing cycle length 2 cycles after the first QRS complex with stable morphology (first complex indicated by arrow). b) In AVRT, the atrial cycle length (third A-A interval) is accelerated in one cycle before the stabilisation of the QRS morphology (first complex indicated by arrow). In addition, in the case of AVNRT there is a prolongation of the VA interval, while in AVRT the duration of the VA interval remains stable.

1. PPI-TCL indicator (PPI minus TCL)

The term PPI refers to the time it takes for the last stimulated antegrade excitation wave to complete one revolution in the re-entry circuit and return to the place of stimulation. Accordingly, if the stimulation point is in the re-entry circuit, the PPI value will be almost equal to the tachycardia CL, and the difference between them will not exceed 30 ms [6, 7]. As the distance from the stimulation point to the re-entry circuit increases, the duration of the PPI increases (see Fig. 4). In AVRT, part of the ventricular myocardium is a component of the re-entry circuit (see Fig. 10a). Therefore, in AVRT entrainment, the impulse along the ventricular myocardium reaches the re-entry circuit, passes once through ACP, atrial myocardium, and conduction system, and returns along the ventricular myocardium to the stimulation point. The difference between PPI and TCL is small (usually less than 100 ms) and depends on the mutual location of the stimulation point and ACP. In AVNRT, the ventricular

myocardium is always far away from the tachycardia circuit (see Fig. 11a). Therefore, in AVTRT entrainment, before returning to the point of stimulation, the pulse must pass the conduction system in the direction from the place of stimulation to the re-entry circuit, make one turn in the tachycardia circuit, and then pass through the conduction system a second time in the opposite direction to the ventricular myocardium. Therefore, the PPI-TCL difference is much larger (usually more than 150 ms) in AVNRT entrainment with VOP than in AVNRT entrainment (Fig. 15) [19].

2. Corrected PPI-TCL indicator

The magnitude of PPI can increase not only when the distance from the place of stimulation to the tachycardia circuit increases, but also when there is a decremental slowing of conduction during VOP (the severity of the effect depends on the frequency of contractions). This phenomenon is most typical for the AV node. When performing an AVRT entrainment, the atrial contraction rate increases to the CL of the stimulation. Excitation waves also enter the AV node with higher frequency than during tachycardia, and the time of conduction through the AV node increases decrementally. After termination of stimulation, the first A-H interval (since the H-V interval is fairly constant, it is possible to measure the A-V interval) is often longer than the A-H (or A-V) interval during tachycardia, which has nothing to do with the distance from the stimulation point to the re-entry circuit that we seek to estimate. The changes described can introduce some error into the measurement, so the PPI-TCL difference can be corrected for decremental conduction. To do this, subtract the magnitude of the increase in the duration of the A-H interval (or the A-V interval) in the first return cycle compared to the duration of this interval during the AVRT (Fig. 15) from the result obtained by the PPI-TCL. When corrected for decrementation, this criterion makes it possible to reliably differentiate between AVNRT (kPSI-TCL>110 ms) and AVRT with septal ACP (kPSI-DCT <110 ms) [20].

3. Difference between St-A and V-A intervals

In patients with AVRT, both during tachycardia and during VOP, ventricles and atria are excited sequentially. Both the V-A interval and the St-A interval will be long enough, but comparable with each other. Therefore, the difference between the durations of intervals St-A and V-A will tend to zero (Fig. 16a,b).

In patients with AVNRT, atrial and ventricular activation during tachycardia occur simultaneously, while in VOP it occurs sequentially. Therefore, the duration of the V-A interval during a typical AVNRT tends to zero, and during ventricular stimulation in a patient with AVNRT the St-A interval will be quite long. The difference between the intervals St-A and V-A will be relatively large (Fig. 16c,d).

Accordingly, the difference between the V-A interval values during entrainment and during tachycardia should be greater in AVNRT patients than in AVNRT patients (Fig. 15, Fig. 16). In AVRT the (St-A)-(V-A) difference is usually < 85 ms, and in AVNRT it is (St-A)-(V-A) > 85 ms [19].

4. Differential entrainment

To exclude the possibility of delayed antegrade conduction (due to the decremental AV node or its «double physiology»), we proposed a way to distinguish the parameters cPPI-TCL and (St-A)-(V-A) described above during stimulation of basal and apex portions of the RV. If the values of these parameters during basal stimulation exceed the values of the same parameters during apex stimulation by 20-30 ms, it is more likely that AVNRT is present (if stimulation is closer to the AV node, decremental conduction along the node is more pronounced). Using a single CL for both stimulation points eliminates the decremental prolongation of the A-H interval mentioned above. The term «differential entrainment» is used to describe this phenomenon [21].

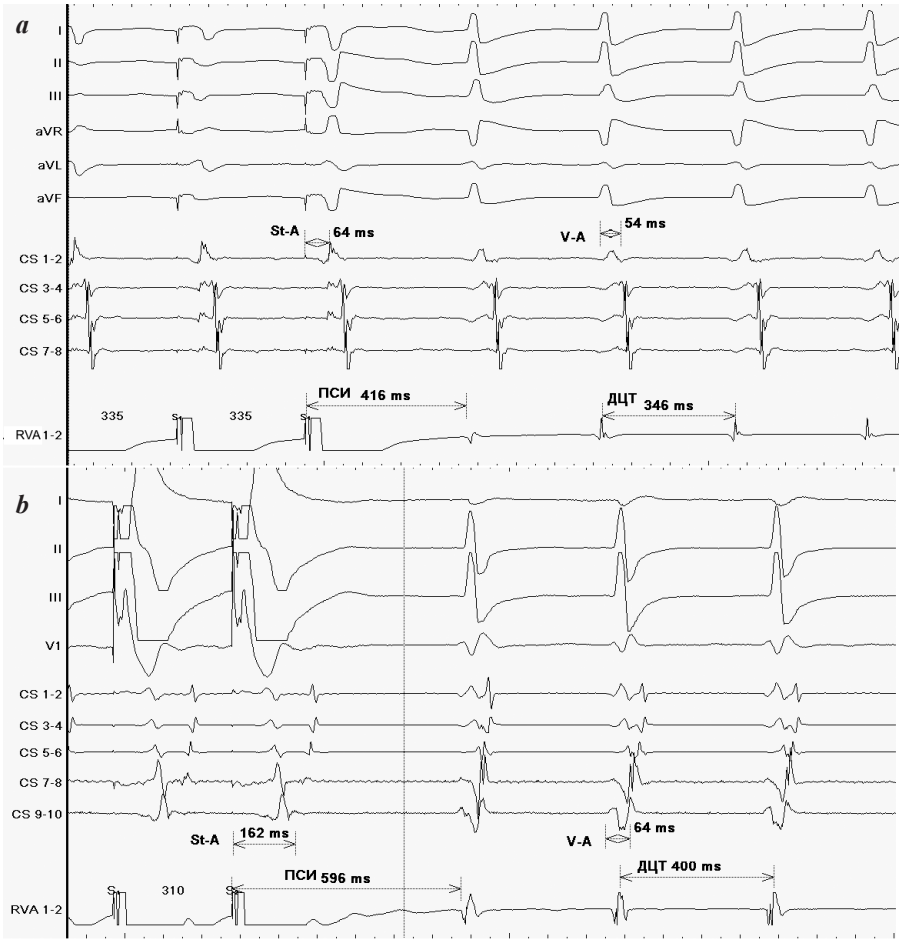

Fig. 15. PPI-TCL and (St-A)-(V-A) difference in AVRT (A) and AVNRT (B). A. PPI-TCL difference is 416-346=70 ms. Difference (St-A)-(V-A)=64-54=10ms. These values are diagnostic for AVRT. B. PPI-TCL difference is 596-400=196 ms. Difference (St-A)-(V-A)=162-64-98 ms. These values are diagnostic for AVNRT.

Accordingly, the cPPI-TCL and (St-A)-(V-A) parameters are also called differential.

Technical difficulties in determining the PPI-TCL, cPPI-TCL, and (St-A)-(V-A) differences

1. Determination of PPI-TCL, cPPI-TCL and (St-A)-(V-A) difference in patients with left lateral ACP

Recall that cPPI-TCL > can be 110 ms and (St-A)-(V-A) > 85 ms and that in AVRT the pacing point is distant from the re-entry circuit (AVRT entrainment involving left ventricular ACP is performed from the apex of the right ventricle. This can easily be avoided by following the algorithm described earlier. A patient with left-sided ACP will have an eccentric sequence of atrial activation during AVRT. It is therefore possible to proceed to mapping and ablation without additional pacing techniques immediately after the tachycardia has been triggered and AT has been excluded from the analysis of the type of response to VOP (VAV or VAAV).

2. Determination of PPI-TCL, cPPI-TCL and (St-A)-(V-A) difference in patients with decremental or slow ACP

In a patient with a slow or decremental ACP, the cPPI-TCL difference score may also be >110 ms, and (St-A)-(V-A) >85 ms. To avoid overdiagnosis of AVNRT in these patients, attention should be paid to the duration of the V-A interval. If a long V-A interval (V-A > ½ R-R) is observed during SVT, it is not appropriate to perform VOP.

3. Determination of PPI-TCL, cPPI-TCL and (St-A)-(V-A) difference in patients with AVRT and dual AV node conduction physiology

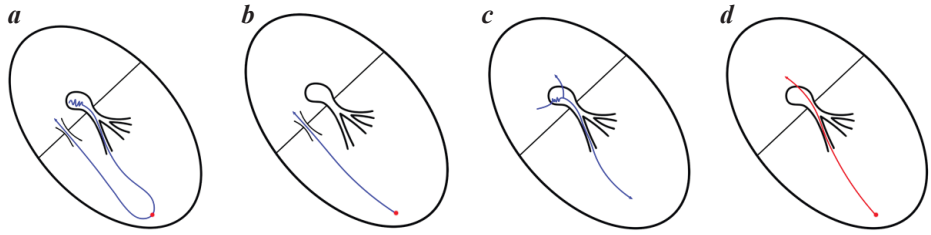

Fig. 16. Schematic representation of the differences in the formation of St-A and V-A intervals in AVRT (a and b) and AVNRT (c and d). a) The excitation wave in AVRT spreads from the apex (exit from Purkyně fibers to the working myocardium) to the base of the heart. A relatively long V-A interval is formed. b) The stimulated excitation wave propagates from the apex of the right ventricle, as in tachycardia. A relatively long St-A interval is formed. c) The excitation wave in AVNRT spreads simultaneously along the fast pathway to the atria and along the conduction system to the ventricles. V-A interval is formed, the value of which tends to zero due to almost simultaneous excitation of atria and ventricles. d) Stimulated excitation wave spreads to atria through conductive system. A relatively long St-A interval is formed.

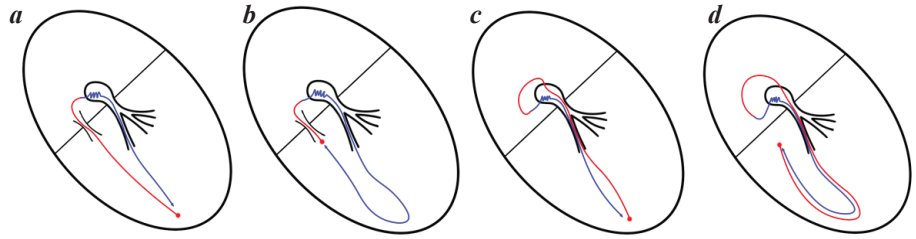

Fig. 17. Differential entrainment in AVRT (a and b) and AVNRT (c and d). a) The stimulated excitation wave in AVRT spreads from the apex (exit from Purkyně fibers into the working myocardium) to the base of the heart, and then returns to the stimulation point through the conduction system. The post-stimulation interval is similar in duration to the tachycardia cycle b) The stimulated excitation wave propagates from the ventricular base through the accessory pathway into the atria, then through the conduction system into the ventricles, and then from the Purkyně fibers in the apical ventricular region to the stimulation point. The post-stimulation interval is similar in duration to the tachycardia cycle. c) The stimulated excitation wave in AVNRT spreads simultaneously along the fast pathway to the atria and along the conduction system to the ventricles. The V-A interval is formed, the value of which tends towards zero due to the almost simultaneous excitation of the atria and ventricles. d) The stimulated excitation wave propagates from the basal region to the apex of the heart, then enters the conduction system and is conducted to the atria, makes one turn in the re-entry circuit within the node AV, returns through the conduction system to the apex of the heart and then reaches the stimulation point in the basal region of the ventricle through the working myocardium. A relatively long St-A interval is formed.

During entrainment AVRT, which uses the «fast» AV connection pathway as the antegrade pathway, the antegrade conduction may switch to the «slow» AV connection pathway during VOP. In this case, the A-H interval in the first recurrent contraction after the termination of stimulation will be significantly prolonged, which may lead to overdiagnosis of AVNRT [22]. The above correction of the PPI-TCL difference (replacing it with cPPI-TCL) helps to avoid complications in patients with a combination of «double conduction» along the AV node and AVRT with septal ACP involvement. The use of (St-A)-(V-A) parameter, in which there is no estimation of conduction along the antegrade knee at all, also allows avoiding errors associated with decremental or «double» conduction along the AV node [23].

4. Selection of the stimulation point for the determination of cPPI-TCL and (St-A)-(V-A)

Ventricular pacing near the sulcus AV means that the pacing point is closer to the ACP involved in the AVRT circuit (when performed in the area of earliest retrograde atrial activation) and further from the AVNRT circuit (due to the extra distance the excitation wave must travel through the ventricular myocardium before entering the conduction system at the apex of the heart) (Fig. 17). There-

fore, in comparison with the apical stimulation, the stimulation of the basal parts of the ventricles:

- increases the values of cPPI-TCL and (St-A)-(V-A) in AVNRT
- decreases cPPI-TCL and (St-A)-(V-A) at AVRT.

Thus, when performing entrainment from the basal segments of the ventricles, the cPPI-TCL and (St-A)-(V-A) values allow for better discrimination between AVNRT and AVRT regardless of ACP localisation. In addition, as mentioned earlier, basal stimulation of the ventricles, as close as possible to the site of earliest retrograde activation, helps to reveal the confluent nature of the excitation (see Fig. 10) and to obtain signs of manifest entrainment in AVRT.

Basal stimulation has some technical difficulties. These include the less stable position of the catheters in this area, the possibility of rhythm influence on the atria or the bundle branch, which can complicate the interpretation of the results and lead to false conclusions. Therefore, VOP from the basal compartments should be used only when the apex stimulation registers a «V-A-V» response, entrainment with full ventricular retrograde entrainment is noted, and the cPPI-TCL and (St-A)-(V-A) values demonstrate borderline values.

What if the answer to VOP is not subject to interpretation?

Thus, VOP is most effective and useful when relatively slow tachycardia continues after the termination of stimulation, and retrograde conduction along the AV node allows acceleration of atrial activation to the rate of ventricular stimulation.

At the same time, there are two types of response to VOP that are often considered inappropriate for interpretation, but can still serve as a source of important diagnostic information.

Atria are not accelerated before CL stimulation. If the atria fail to accelerate in response to stimulation from CL on several VOP attempts, the diagnosis of AVRT can be ruled out and it can be said with a high degree of probability that the mechanism of SVT is AT (see Fig. 12).

Atria are accelerated before CL stimulation, but SVT is terminated after termination of VOP. The cause of termination of SVT during stimulation is usually the blocking of the next antegrade excitation wave by the AV node and its subsequent entrainment by the retrograde wave. After termination of stimulation, the last antegrade wave of excitation cannot return to the ventricles in the form of an echo response and continue tachycardia. In such situations, artificial shortening of the refractory period of AV node by intravenous injection of atropine often helps. If it is still not possible to overcome this problem, the response to VOP may still be of diagnostic value, e.g. in assessing atrial capture time or in performing differential entrainment (although in the situation where SVT is stopped after VOP termination, we cannot speak of entrainment and the term «differential entrainment» is not applicable). If SVT is repeatedly terminated during VOP, frequent ventricular stimulation with a short series of pulses (3 to 6) with a CL of 200-250 ms may be useful. In 60% of cases ventricles will dissociate from SVT (excludes AVRT) or SVT will be stopped without conduction on atria (excludes AT) [9].

CONCLUSION

Thus, VOP is a reliable and relatively simple way of differential diagnosis of sustained SVT. This stimulation technique gives the electrophysiologist a large amount of qualitative and quantitative information without greatly increasing the duration of the EPE.

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THREE FACES OF ONE PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

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Fragments of a transesophageal electrophysiological study of a 35-year-old patient with induction of paroxysmal atrioventricular nodal re-entry tachycardia occurring with three different electrocardiographic patterns are presented.

Key words: paroxysmal atrioventricular nodal re-entry tachycardia; atrioventricular conduction; aberrant conduction; electrophysiological study

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Atrioventricular (AV) nodal re-entry tachycardia (AVNRT) is perhaps the most versatile of the supraventricular tachycardias. Depending on the direction of excitation propagation through fast and slow channels in the AV node, it can proceed in a slow-fast and a fast-slow version, and in the presence of a polyvascular structure of the AV node - in a slow-slow version. Against the background of AVNRT, an aberrant conduction of excitation may develop which does not lead to a change in tachycardia frequency because the legs of the branch bundle are not involved in the re-entry circuit. In the presence of obstruction above or below the re-entry loop, AVNRT may be recorded with AV or ventriculoatrial lead in a ratio other than 1:1. In addition, in this tachycardia, atrial or ventricular ectopias may not interrupt its course. Finally, it should be borne in mind that AVNRT may take on additional features after radiofrequency catheter ablation, related to the procedure performed, if it recurs.

Patient C., 35 years old, was referred for a transoesophageal electrophysiological examination because she had been suffering from palpitations for several years, but these had become more frequent in recent months. The patient stopped it herself using vagus techniques, it was not possible to record an ECG during the seizure. The electrophysiological examination showed the signs of AV conduction duality on the background of the initial rhythm, but it was not possible to induce AVNRT. After administration of 1 ml of 0.1% atropine sulphate solution on a background of sinus tachycardia with a heart rate of over 130 bpm, AVNRT was induced (fig. 1). Initially,

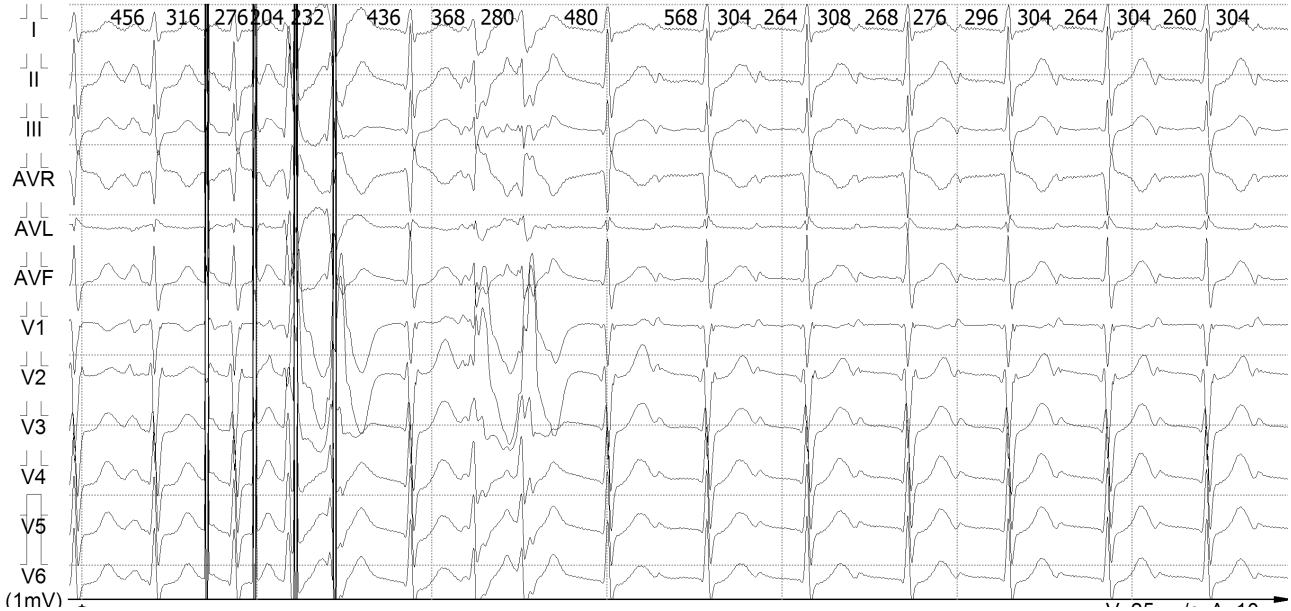

Fig. 1. Induction of tachycardia after atropinization. Explanations in the text.

AVNRT flowed with a 2:1 AV conduct. In the middle between the QRS complexes, you can see P' waves, negative in the lower leads. They are narrower than the sinus waves P caused by the concentric covering of the atria by the excitation of the AV node. An interesting feature of this AVNRT is that the P' waves that are in the QRS complexes do not form pseudo-beats s (as is quite common), but pseudo q. They are particularly striking in the right thoracic leads, where the r-waves registered against the background of sinus rhythm have been replaced by q-waves during tachycardia induction.

Against the background of the vagus manoeuvre, the 2:1 AVNRT changed into a 1:1 tachycardia accompanied by a twofold increase in heart rate (fig. 2). The increased frequency of the ventricular complexes led to the appearance of a tachycardia-dependent complete blockade of the right bundle branch and within a few seconds a tachycardia with «wide» QRS complexes could be observed. Then conduction was restored along the right limb of the bundle branch, which was accompanied by constriction of the QRS complexes. Changes in the width of QRS complexes had no significant effect on the frequency of tachycardia. The electrocardiographic changes shown, in combination with the signs of conduction duality found AV, allowed the tachycardia to be considered AVNRT. The paroxysm was terminated by transesophageal electrocardiostimulation. The patient was referred for modification of the slow pathway in the AV node.

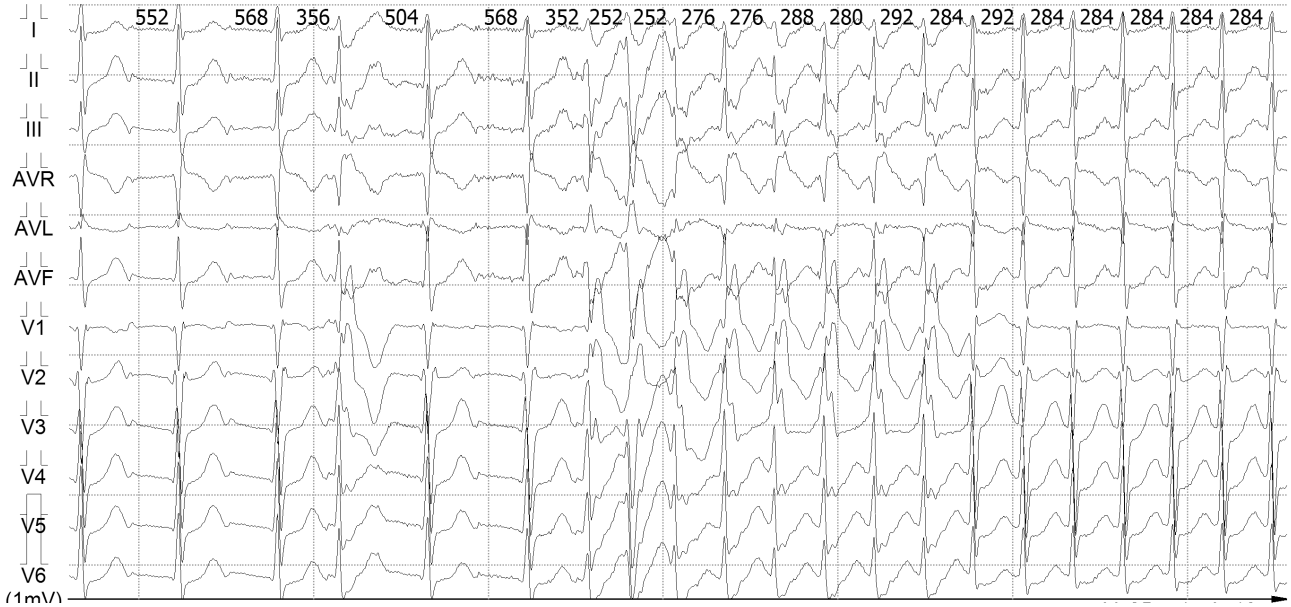

Figure 2. Tachycardia response to the vagus maneuver. Explanations in the text.

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ROSTISLAV S KARPOV - 85 YEARS

8 September 2022 marks the 85th anniversary of the birth of Rostislav Sergeyevich Karpov, Doctor of Medical Sciences, Professor and Full Member of the Russian Academy of Sciences.

Karpov Rostislav Sergeyevich was born in Tomsk on 08 September 1937 and successfully graduated from the Tomsk Medical Institute in 1960, specialising in General Medicine. He worked his way up from clinician at the Tomsk Medical Institute (1962) to Head of the Department of Departmental Therapy with a course in clinical pharmacology at the State Budgetary Educational Institution of Higher Professional Education Siberian State Medical University of the Russian Ministry of Health (from 1979 to 2018) and Director of the Research Institute of Cardiology, Tomsk (1985-2015). Since 30 June 2015, he has been working as the Scientific Director of the Research Institute of Cardiology at the Tomsk Scientific Research Centre, and since 2016, he has been the Head of the Scientific Management of the Tomsk Scientific Research Centre.

Rostislav Sergeyevich Karpov is a prominent Russian scientist and therapeutic cardiologist who has received well-deserved recognition both in Russia and abroad. Behind his shoulders lies a worthy school of life, rich experience in medical and scientific-pedagogical activity - more than 60 years in the service of good, his patients, students and colleagues. The foundation and development of the cardiology service in Siberia is associated with his name. With the direct involvement of R.S. Karpov, the Siberian branch of the All-Union Cardiology Scientific Centre of the USSR Academy of Medical Sciences (now the Cardiology Research Institute) was opened in Tomsk in 1980 and developed into a major research, clinical and educational complex in the east of the country, with the Tyumen branch (1985-2016) being the leading cardiology institution in Siberia and the Far East for 36 years.

The main priorities of Rostislav Sergeyevich's scientific and organisational activities were the introduction of the most modern technologies for the prevention, diagnosis and treatment of diseases of the cardiovascular system in the region and the improvement of specialised cardiological care for the scattered population. On the initiative of R.S. Karpov, the first cardiology outpatient clinic in the Urals with a capacity of 40 thousand visits per year was opened in Tomsk. Under his leadership, for the first time in Russia, a mobile automated system for cardiological care of the scattered population was developed and introduced into practical health care in the Tomsk region. In order to develop innovative technologies, the Siberian Federal Arrhythmological Centre was established in 1998 on the basis of the Department of Surgical Treatment of Complex Cardiac Arrhythmias. Over the years of its operation, it has been rightly recognised as a leading regional centre for arrhythmology, significantly determining progress in the treatment of complex cardiac arrhythmias in the population of Siberia and the Far East. In 2010, with the active support of R.S. Karpov, an innovative structure «Children's Heart Centre» was established on the basis of the Department of Paediatric Cardiology to provide access to modern high-tech medicine for children and adolescents with cardiovascular diseases. The Paediatric Heart Centre is recognised as one of the leading clinics in Russia in terms of the range of procedures and treatment outcomes. The Institute's clinic, headed by Academician R.S. Karpov for 30 years, is a unique cardiovascular cluster that enables solving urgent public health problems in the fields of «cardiology» and «cardiovascular surgery». The clinic is among the «top five» federal medical institutions involved in providing high-tech medicine to the citizens of the Russian Federation.

In 2016. R.S. Karpov was one of the initiators of the unification of six Tomsk medical research institutes (cardiology, oncology, medical genetics, psychiatry, pharmacology and regenerative medicine, obstetrics, gynaecology and perinatology) into a single Tomsk National Medical Research Centre of the Russian Academy of Sciences, which within 5 years became the largest scientific medical organisation in the country and ranked 1st in the scientific rating among the organisations of the Ministry of Education and Science in the field of «Clinical Medicine».

Rostislav Sergeyevich made a significant contribution to the development of medical science, including cardio-rheumatology. He proposed a new comprehensive clinical-immunological and morphological approach to diagnosing the activity of rheumatic processes using computer data processing. This allowed optimising the diagnosis of rheumatic process activity from fundamentally new positions, which was of great practical importance for the early diagnosis of rheumatism and its recurrence. The results of his research have contributed to the development of modern ideas about the pathogenesis of rheumatism as an immunologically mediated disease. He studied and described the features of the clinical manifestations of rheumatic process activity at different stages of the disease, which was also of great scientific and practical importance. Together with the Academician of the Russian Academy of Medical Sciences V.V. Pekarsky, he organised one of the first systems in Russia for the continuous therapeutic care and surgical treatment of patients with rheumatic heart disease.

Professor R.S. Karpov was the organiser and first dean of the Faculty of Advanced Training at the Tomsk Medical Institute (1979), which was of fundamental importance for the professional training of doctors in the region. A brilliant lecturer, he was actively involved in the pedagogical process. On his initiative and with his direct participation, functional and immunological diagnostics laboratories were created, which later became interclinical and facilitated the implementation of new diagnostic technologies in practical health care. The result of R.S. Karpov's scientific, educational and practical activities during his active supervision of the rheumatology service of Tomsk Region was the reduction of morbidity, disability and mortality of rheumatological patients.

Well-known works by Academician R.S. Karpov in co-authorship with Professor V.M. Yakovlev and other colleagues, devoted to manifestations of hereditary imperfections of connective tissue development, cardiac dysplasia - approaches to diagnosis and prognosis assessment. Special attention was paid to connective tissue abnormalities of the valves and subclavian structures, as well as the entire fibrous framework of the heart, which determine the severity of structural-functional and electrophysiological remodelling of the left ventricle of the heart.

For more than 30 years of his scientific and clinical activity, Rostislav Sergeyevich has devoted his research to such pressing problems of modern medicine as atherosclerosis and chronic coronary heart disease, which form the basis of the modern «epidemic» of cardiovascular disease. Under his leadership, a professional team of scientists and doctors, whose work is recognised in Russia and abroad, has been formed within the framework of this theme. They successfully solve the priority tasks of diagnosis, treatment and prevention of chronic ischaemic heart disease, dyslipoproteidaemia, arterial hypertension, type 2 diabetes mellitus and cardiomyopathies on the basis of modern achievements of medical science and practise.

The basic scientific researches of R.S.Karpov and his students are devoted to the pathogenetic, pathophysiological, diagnostic and therapeutic aspects of combined atherosclerosis, including simultaneous lesions of the coronary and extracerebral arteries. Special attention has been given to the study of blood supply to the heart and brain, mechanisms of regulation of systemic, coronary and cerebral circulation, imaging of lesions of the coronary and carotid arteries, methods of functional assessment of coronary, myocardial and cerebrovascular reserves, and treatment of combined coronary and cerebrovascular insufficiency.

The work on the physiology of the heart and respiratory organs, dealing with the functional relationships in the unified cardiorespiratory system, is of primary character. The study of the clinical and physiological features and the diagnosis of pathological shifts in the oxygen transport system in cardiac and pulmonary dysfunction have been of great importance. The variants of adaptation of the organism's functional systems and the development of ischaemic heart disease and chronic obstructive pulmonary disease in northern conditions were considered; approaches to the treatment of combined forms of ischaemic heart disease, arterial hypertension and chronic obstructive pulmonary disease in the high latitude population were proposed.

R.S. Karpov created a famous therapeutic and cardiological school of science. His scientific works adequately reflect the main stages in solving the most important problems of modern medicine and health care. His main research areas are rheumatology, cardiology, clinical pharmacology, clinical and population epidemiology, prevention of cardiovascular diseases, and public health and health care. He is the author of more than 1,000 scientific papers, including 38 monographs and 43 patents for inventions. Under his guidance, 42 doctoral theses and 81 Ph.D. dissertations were written and defended. Students of Rostislav Sergeyevich successfully work in the fields of therapy, cardiology, rheumatology and clinical cardiology in more than 40 leading organisations in the country and the world.

Rostislav Sergeyevich has received numerous state and public awards for his outstanding services.

Rostislav Sergeyevich's entire life has been dedicated to the true service of his patients, students and colleagues. A clever and creative person, he exemplified an active approach to life, dedication, commitment, high responsibility, devotion to the chosen cause and love for people in all his offices. Today he still stands in the ranks and generously shares his mature wisdom and invaluable human and professional experience with the people around him.

The administration and staff of the Research Institute of Cardiology of the Tomsk Research Centre warmly congratulate Rostislav Sergeyevich Karpov, teacher, friend and colleague, on his anniversary and wish him good health, inexhaustible energy and optimism, implementation of plans, creative inspiration and all the best! May happiness and success accompany you in everything! We wish you joy, kindness and prosperity, warmth of heart and support from students, colleagues, relatives and friends!