Rzaev F. G.[1], Rachkova Yu I.[1], Nikolaeva O. A.[1], Gorev M. V.[1],
Nardaia Sh. G.[1], Makarycheva O. V.[2], Vasilieva E. Yu.[2], Shpektor A. V.[2]

[1] Clinical City Hospital named after I.V. Davydovsky,
Moscow Department of Healthcare, Moscow, Russia

[2] Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, Moscow, Russia

Duration of applications affects the long-term efficacy of cryoballoon ablation pulmonary veins

Aim	To evaluate the effect of cryo-exposure duration and the use of the Achieve circular mapping catheter on efficacy of cryoballoon ablation (CBA).
Material and methods	CBA of pulmonary vein ostia (PVO) is a major method for heart rhythm control in patients with atrial fibrillation (AF). Since the inception, the PVO CBA method has evolved; the recommended application time was changed, and the Achieve circular catheter appeared. We performed a retrospective analysis of PVO CBA administered to patients with AF in the I. V. Davydovsky Municipal Clinical Hospital from 2017 through 2019. The study included 100 patients with available clinical and demographic characteristics and remote results of the intervention. Three patient groups were analyzed based on differences in surgical techniques: group 1, Guidewire/240 (n=31) with the cryoballoon placing on a guidewire and PVO exposure duration of 240 s; group 2, Guidewire/180 (n=26) with the cryoballoon placing on a guidewire and PVO exposure duration of 180 s; and group 3, Achieve/180 (n=43) with the cryoballoon placing on the mapping catheter Achieve and PVO exposure duration of 180 c. The follow-up period was 33.2±4.5, 15.2±6.1, and 12.2±4.1 months in the Guidewire/240, Guidewire/180, and Achieve/180 groups, respectively. The intervention was considered effective when there was no relapse at the time of interview. A relapse of AF was determined as one or more paroxysms recorded on electrocardiogram (ECG) or during 24-h ECG monitoring; the «blind period» (first 3 months after the procedure) was excluded from the follow-up. Safety evaluation included clinically significant complications, such as phrenic nerve damage, hemopericardium, gastroparesis, hemoptysis, acute cerebrovascular disease, and formation of atrio-esophageal fistula. Effects of independent factors were determined with binary logistic regression.
Results	In the Guidewire/240 group, efficacy of PVO CBA for the maximum follow-up period was 74.4%, which was significantly different from the value for the Guidewire/180 group (57.7%, p=0.015). At the same time, the difference between the Guidewire/240 and Achieve/180 groups was statistically non-significant for a comparable follow-up period (p=0.144). Clinically significant complications were absent in all 3 groups. The independent factors that significantly increased the PVO CBA efficacy were the cryo-exposure duration of 240 s compared to 180 s (p= 0.018) and the use of the Achieve catheter (p=0.014).
Conclusion	Decreasing the cryo-exposure duration to less than 240 s is impractical (in absence of Achieve mapping catheter) since it impairs the long-term efficacy of PVO CBA and does not influence the risk of complications.

Keywords	Atrial fibrillation; catheter ablation; cryoballoon ablation
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Corresponding author Rachkova Yu.I. E-mail: yulia.dar@yandex.ru

Introduction

Pulmonary vein (PV) catheter ablation is a major way of controlling heart rhythm in patients with atrial fibrillation (AF). This procedure is now understood to improve the quality of life of patients with symptomatic AF [1]. PV cryoballoon ablation (CBA) of the pulmonary vein ostia is not inferior to radiofrequency ablation (RFA) [2] and is a procedure of choice in first-time patients with paroxysmal and persistent AF [3].

Electrical isolation of all PVs is a mandatory endpoint of catheter treatment of AF [1]. The PV CBA technique has been improved recently [4–7]. Initially, a guidewire was used to position a cryoballoon in PVs (Figure 1, adapted from [9]).

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It was only possible to assess the quality of the intervention during a guidewire procedure by the PV occlusion indirectly, and the lowest temperature was reached. LV isolation could only be verified after using a Lasso circular diagnostic catheter. This was challenging and bore a potential risk of air embolism due to the need to change the cryoballoon to the circular catheter. In the absence of isolation, the cryoballoon was re-inserted into the LV, and bonus manipulations were carried out. Later, a 15–20 mm Achieve circular multipolar diagnostic catheter was adopted in clinical practice, allowing cryoballoon positioning and recording of LV electrical activity during the procedure (Figure 2, adapted from [9]). Continuous monitoring of the LV electrical activity allows for ineffective manipulation to be stopped in a timely manner and for the position of the cryoballoon to be changed [8].

According to the manufacturer's instruction, the recommended exposure time for the second-generation cryoballoon ArcticFront advance 28 mm is 240 s. Given the risk of potential damage to surrounding extracardiac structures (phrenic nerve, esophagus, bronchi), certain authors suggest reducing the duration of exposure to 150–180 seconds under the time to isolation (TTI) control at an Achieve catheter [4, 10, 11].

Objective

To evaluate the effect of cryoexposure and the use of the Achieve circular diagnostic catheter on the CBA effectiveness.

Material and methods

We conducted a retrospective cohort study to investigate the effects of the above-mentioned factors on the effectiveness and safety of PV CBA. The study was performed in accordance with the Declaration of Helsinki.

In 2017–2019, 288 primary PV CBA procedures were carried out in I. V. Davydovsky City Clinical Hospital.

The study included 100 patients. Their clinical and demographic characteristics, features of surgical intervention, and long-term intervention outcomes were investigated.

Inclusion criteria: age 18 years and older; symptomatic paroxysmal or persistent AF (for not more than 12 months); primary CBA.

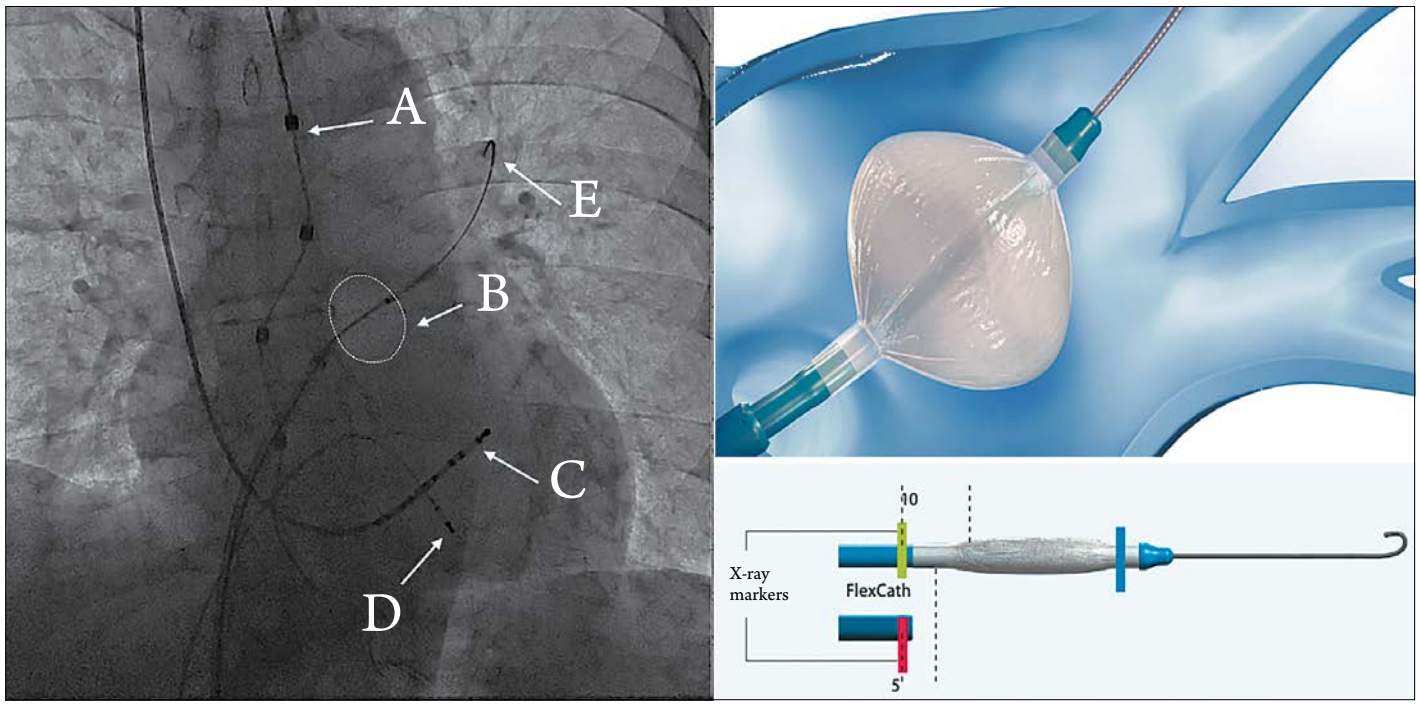
Exclusion criteria: significant renal dysfunction (creatinine clearance <25 mL/min; blood creatinine ≥220 μmol/L) and liver dysfunction (elevated levels of ALT, AST, bilirubin more than 3-fold of the upper normal limit); malignancies; extra RF exposure in the left atrium during CBA.

Patients who withdrew their consent dropped out. Figure 3 shows the study design.

Preparation for PV CBA

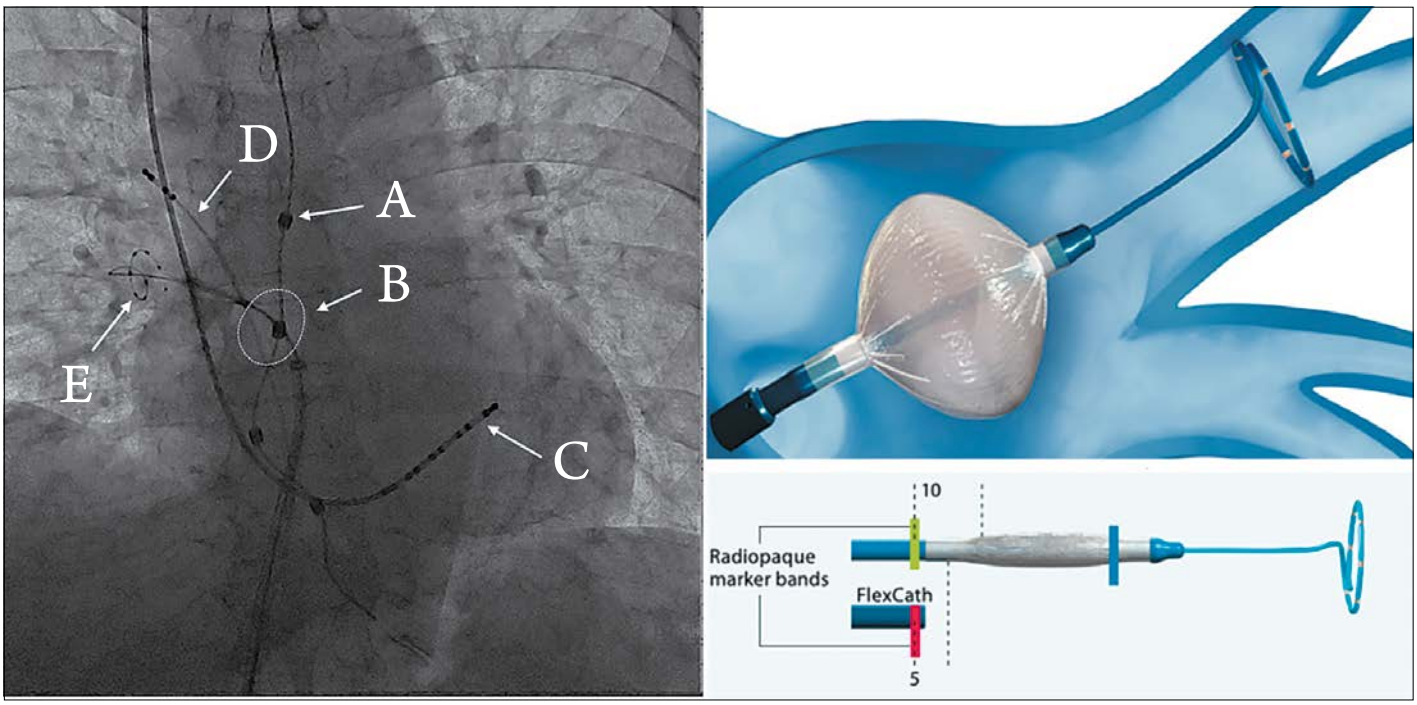
All patients received anticoagulant therapy for 1 month before and 3 months after the surgery. Left atrial (LA) appendage thrombosis was ruled out in all patients before surgery. Contrast-enhanced CT of LA has been routinely used for this purpose in our clinic since 2017 [9]. In

Figure 1. Cryoballoon ablation of pulmonary veins with cryoballoon positioning on the guidewire



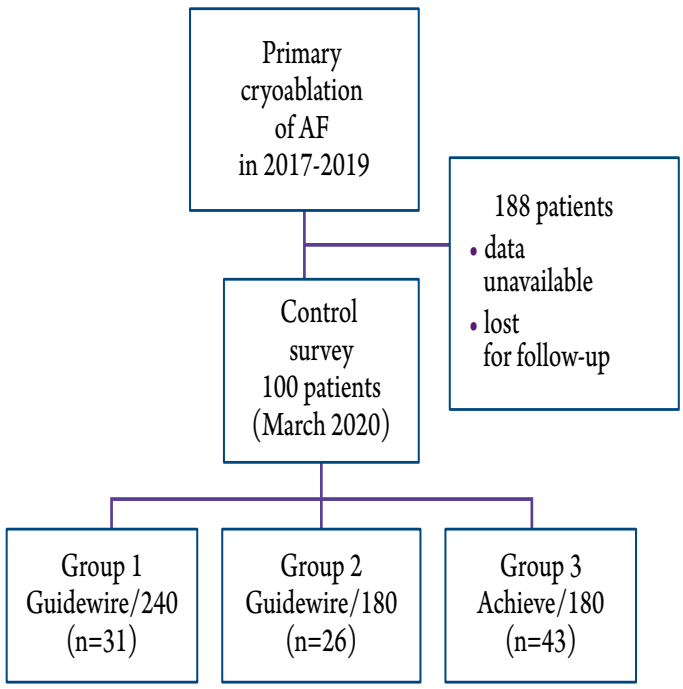
A – esophageal temperature sensor; B – positioning of the cryoballon on the guidewire in the left superior pulmonary vein;
C – multipolar diagnostic electrode in the coronary sinus; D – multi-pole diagnostic electrode in the right ventricle;
E – Guidewire in the left superior pulmonary vein.

Figure 2. Cryoballoon ablation of pulmonary veins with cryoballoon positioning on the Achieve circular diagnostic catheter



A – esophageal temperature sensor; B – cryoballoon positioning on the achieve circular diagnostic electrode in the right superior pulmonary vein; C – multipolar diagnostic electrode in the coronary sinus; D – multipolar diagnostic electrode in the phrenic nerve stimulation point; E – Achieve circular diagnostic electrode in the right superior pulmonary vein [9].

Figure 3. Study design



addition, a 3D reconstruction of the LA was performed in an ImageIntegration CARTO-3 system to study the peculiarities of the LA anatomy and the PV return. Transesophageal echocardiography was conducted LA appendage thrombosis was suspected [9, 12, 13].

Procedural technique

The right femoral vein and the right internal jugular vein were punctured separately under intravenous sedation and local anesthesia. Multipolar diagnostic electrodes were inserted into the coronary sinus and the right ventricle, and electrophysiological studies (EPS) were performed. The interatrial septum was punctured under X-ray control. This was followed by the installation of a transseptal introducer in the LA cavity. LA angiography was performed with frequent ventricular stimulation, in order to assess the topographic anatomy. A cryoballoon catheter was inserted into the LA cavity following the guidewire (Emerald 0.035 in, 180 cm, Cordis) or the circular diagnostic catheter (Achieve).

Ultravist 370 was administered to confirm PV occlusion prior to the beginning of each cryoexposure. The contrast medium was delivered to the vein through a distal opening in the balloon catheter at 1–3 mL and no more than 10–15 mL for the entire CBA procedure.

The PV CBA technique has evolved from 2017 to 2019. In 2017, a guidewire was used to position the cryoballoon in PVs. The inflated cryoballoon was installed in the pulmonary vein ostium, after which contrast medium was administered to control the PV occlusion. The lowest temperature reached was estimated during exposure. The cryoexposure time was 240 seconds. After the procedure was completed, a PV isolation test was performed using a Lasso circular diagnostic electrode.

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In 2018, after the publication of several papers on the potential risk of damaging the surrounding extracardiac structures (phrenic nerve, esophagus, bronchi), the duration of exposure was reduced from 240 to 180 seconds [6, 14–16].

In 2018–2019, an Achieve circular diagnostic catheter was introduced instead of the guidewire technique. It thus became possible to record the LV electrical activity during the exposure, estimate the time from the beginning of exposure to LV isolation (TTI), cancel ineffective exposure in a timely manner, and change the position of the cryoballoon. The exposure time was 180 seconds. If TTI was more than 90 seconds, the exposure was canceled, and the cryoballoon was repositioned.

When evaluating the safety of the intervention safety, such complications as the phrenic nerve injury, hemopericardium, gastroparesis, hemoptysis, cerebrovascular accident, atrioesophageal fistula were considered. The right phrenic nerve was stimulated at a frequency of 60 ppm during cryoexposure to avoid injury during the isolation of the right PVs. In 2018 we began to monitor esophagus temperature. Cryoexposure is canceled when it falls to +20°C. If AF continued after the isolation of all PVs, sinus rhythm was recovered using electroversion.

Thus, patients were divided into three groups for subsequent analysis and interpretation of the results:

- Group 1 – Guidewire/240 (n = 31). A guidewire was used to position the cryoballoon in PVs. Each vein was successively exposed for 240 seconds. After the procedure was completed, PV isolation was tested using a circular diagnostic electrode.
- Group 2 – Guidewire/180 (n = 26). A guidewire was used to position the cryoballoon in PVs. Each vein was successively exposed for 180 seconds. After the procedure was completed, PV isolation was tested using a circular diagnostic electrode.
- Group 3 – Achieve/180 (n = 43). Crioballon was positioned in PVs using an Achieve circular diagnostic catheter. The time to isolation (TTI) was evaluated directly during exposure, and the exposure time was 180 seconds. If TTI was more than 90 seconds, the exposure was canceled, and the cryoballoon was repositioned. If PV activity recovered, bonus applications were performed until their complete isolation.

It should be noted that the groups did not differ statistically significantly in the main clinical and demographic characteristics (Table 1).

Patient follow-up

From November 2019 to July 2020, a control survey of 100 patients with a PV CBA history was conducted. AF recurrence was regarded as one or more paroxysms recorded by electrocardiogram (ECG) or 24-hour ECG monitoring; blind period (the first 3 months after the procedure) was excluded from the follow-up.

The absence of AF paroxysms at the control survey was the primary efficacy endpoint.

The intervention was regarded as effective in the absence of recurrences at the time of the survey. Patients were invited to visit in person or answer the questionnaire by telephone. All patients were asked to answer the following questions: whether there were AF recurrences registered; the time of

Table 1. Comparative clinical and demographic characteristics by groups depending on the intervention technique

Indicator	Group 1, guidewire/240 (n = 31)	Group 2, guidewire/180 (n = 26)	Group 3, achieve/180 (n = 43)	p
Male	19 (61.3)	13 (50)	20 (46.5)	0. 286
Age, years	62 [49; 68]	66 [59; 69.25]	64 [53; 69]	0.335
Body mass index, kg/m^2	31.8 [28.3; 35.6]	27.7 [24.4; 33]	27 [24.2; 30.4]	0.153
Paroxysmal AF	27 (88.9)	22 (84.2)	39 (92)	0.346
Duration of AF history, months	6 [3; 10]	7 [3; 13]	5 [1.75; 7]	0.343
CHA_2DS_2-VASc, score	4 [1; 4]	3 [1; 4]	2 [1; 3]	0.667
HAS-BLED, score	0	1 [0; 2]	1 [0; 1]	0.271
History of concomitant diseases:				
• AH	27 (88.9)	20 (78.9)	33 (78.6)	0.465
• DM	6 (33.3)	1 (5.3)	3 (7.1)	0.204
• CHD	7 (22.2)	1 (5.3)	3 (7.1)	0.196
• CVA	6 (20)	7 (26.3)	3 (7.1)	0.371
Pacemaker/ICD	7 (22.2)	2 (10)	0	0.108
Echocardiogram findings:				
• LA dimension, mm	44.5 [34; 48.1]	44 [41; 52]	43 [39; 46]	0.424
• LVEF,%	62 [60; 64]	60 [57; 65]	60 [60; 60]	0.071

The data is expressed as the median and interquartile range (Me [25%; 75%]) or the absolute and relative values (n (%)).
AF, atrial fibrillation; AH, arterial hypertension; DM, diabetes mellitus; CHD, coronary heart disease; CVA, cerebrovascular accident; ICD, implanted cardioverter defibrillator; LA, left atrium; LVEF, left ventricular ejection fraction.

the AF recurrence onset; the frequency and duration of paroxysms; the antiarrhythmic therapy (AAT) administered; and the anticoagulant therapy used.

Perioperative and follow-up AAT

No planned withdrawal of antiarrhythmic drugs before CBA was performed. All patients received AAT during the first 3 months after the procedure, which was later corrected outside of hospital. AAT did not differ statistically significantly in all groups ($p > 0.05$). The detailed structure of AAT by groups is shown in Figure 4.

As shown in Figure 3, 50% of patients did not receive AAT at the time of the control survey.

The statistical analysis of the findings was performed using the SPSS Statistics 26.0 software suite. Normal distribution was tested using the Shapiro – Wilk test. Distribution deviating from the zero hypothesis with the level of statistical significance $p < 0.05$ was considered non-normal (zero hypothesis – normally distributed data). The values of normally distributed variables were expressed as mean and standard deviation (M±SD). The statistical significance of differences between the groups was determined using the Student's T-test. The values of non-normally distributed variables were expressed as the median and the 25th and 75th percentiles (Me [Q1; Q3]). The statistical significance of differences between the groups was determined using the Kruskal-Wallis test. The statistical differences between nominal variables were evaluated using Fisher's exact test.

The efficacy of intervention depending on the follow-up time was calculated using the Kaplan–Meier survival analysis. The significance of long-term results was compared using a log-rank test. We constructed a prognostic model of AF recurrence probability based on the factors of interest. The factors were chosen for the model by means of the elimination method (Wald) using binary logistic regression. The following equation was used to calculate the probability of AF recurrence:

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

Differences were statistically significant at $p < 0.05$.

Results

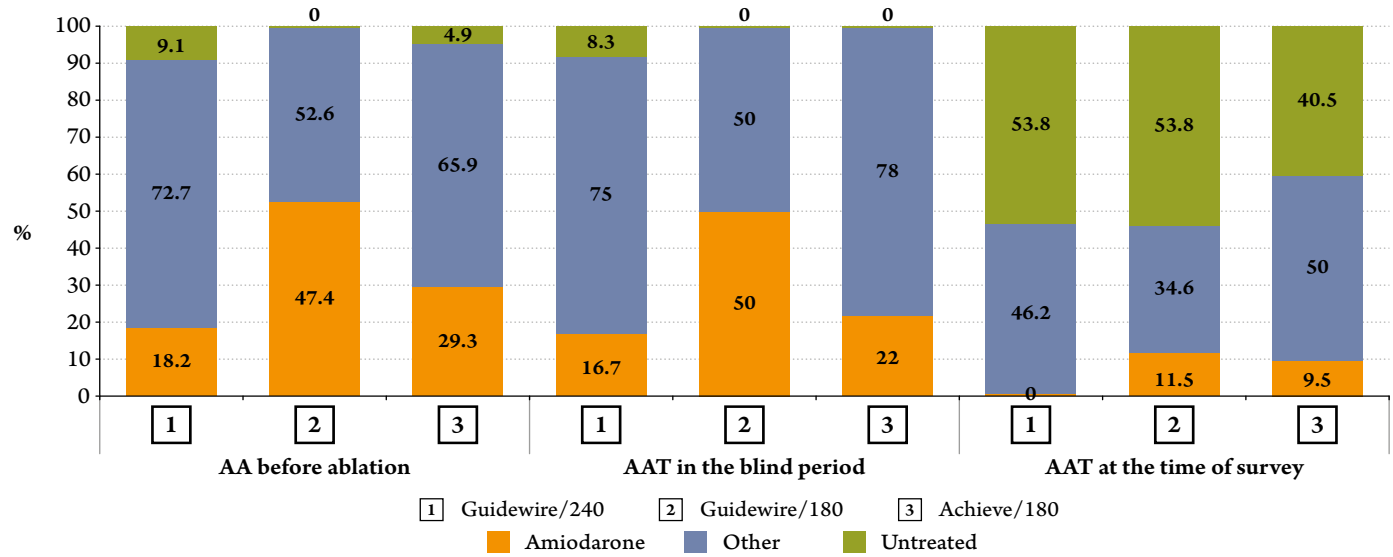
The main intraoperative characteristics of groups are presented in Table 2.

Mean TTI in the Achieve/180 group did not exceed 40 seconds. It should be noted that cryoballoon was repositioned due to the preserved potentials in PMs in 13 (30.2%) cases. In the mean one [1–3] cryoballoon reposition was required for successful PV isolation.

The different CBA tactics had no significant effects on the duration of the surgery, the duration of radioscopy, and radiation exposure, which were comparable in all three groups (Table 3). There were no clinically significant perioperative or long-term complications (hemopericardium, atrioesophageal fistula, phrenic nerve injury, gastroparesis, hemoptysis) in any group. Almost 25% of patients had stable typical atrial flutter registered anamnestically or by EPS. These patients additionally underwent cavotricuspid isthmus RFA.

The mean patient follow-up period was 33.2±4.5, 15.2±6.1, and 12.2±4.1 months in the Guidewire/240, Guidewire/180 and, Achieve/180 groups, respectively. Thus, the follow-up period was statistically longer in the Guidewire/240 group than in patients subjected to cryoexposure for 180 seconds ($p < 0.001$).

Figure 4. Antiarrhythmic therapy (AAT) before the ablation, in the blind period, and at the time of control survey



«Other» – drugs Ic (propafenone, allapinin) and III (sotalol) classes.

* there are no statistically significant differences between the groups.

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The long-term efficacy of the surgery in the groups is shown in Figure 5.

The efficacy in the Guidewire/240 group was 74.4% in the longest follow-up period, which was statistically significantly different from the Guidewire/180 group with 57.7% (p=0.015). The differences between the Guidewire/240 and Achieve/180 groups with comparable follow-up periods were statistically insignificant (p = 0.144).

In order to assess the independent effects of various factors (such as the use of the Achieve diagnostic catheter, duration of exposure, the lowest PV temperature) on the probability of AF recurrence, we performed a logistic regression analysis of the above variables and derived the following regression equation:

$$P=1/(1+e^{-z})$$
$$Z = 0{,}241 - 1{,}78 \cdot X_{\text{exp. time}} - 1{,}31 \cdot X_{\text{guidewire}},$$

Where P is the probability of AF recurrence and X is the factor of interest.

Given the regression factors, the independent factors which to a statistically significant degree reduced the probability of AF recurrence were: the duration of exposure of 240 s (odds ratio (OR) 0.17; 95% confidence interval (CI) 0.038–0.737; p = 0.018); and the use of the Achieve diagnostic catheter (OR 0.27, 95% CI 0.095–0.768; p=0.014). The lowest temperature did not have an independent effect on the efficacy of the procedures. The model's total prognostic value was 70.6%.

Discussion

Several factors may determine the success of cryo-exposure: the best possible exposure temperature; the duration of exposure; the degree of PV occlusion with the cryoballoon; and the registration of PV potentials on the Achieve circular diagnostic catheter.

Given the potential risk of damaging the surrounding extracardiac structures (phrenic nerve, esophagus, bronchi), a reduction in the duration of exposure has become relatively common [17, 18]. The routine use of an esophageal temperature sensor minimizes the risk of damaging the surrounding extracardiac structures [19].

Several cryoapplication dosing protocols have been described using the Achieve circular diagnostic catheter, in order to evaluate treatment efficacy. For example, according to the CRYO-AF DOSING protocol by Aryana et al. [6], time to PV isolation (TTI) was evaluated during the first cryoapplication. When TTI was less than 60 sec, the duration of exposure was TTI + 120 sec. Additional bonus cryoapplication was made within 120 sec with TTI from 60 to 90 sec. If TTI was more than 90 seconds, the exposure was canceled, and the cryoballoon was repositioned. If TTI could not be evaluated, two cryoapplications 180+120 sec were performed [6].

Analysis of the data obtained showed statistically significant technique-related differences in the efficacy of the procedure. Thus, the absence of AF was 74.4% in the Guidewire/240 group in the largest observation period

Table 2. Main intraoperative parameters during PV CBA

Indicator	Group 1, guidewire/240 (n = 31)	Group 2, guidewire/180 (n = 26)	Group 3, achieve/180 (n = 43)	p
Lowest temperature in LSPV, °C	–45 [–44.5; –49.5]	–44.5 [–38.5; –47]	–47 [–43.5; – 52]	p_{2-3}=0.04
Lowest temperature in LIPV, °C	–44 [–38.5; –48]	–41 [–38.5; –42.75]	–43 [–42; –46]	p_{2-3}=0.027
Lowest temperature in RIPV, °C	–48 [42.75; –51.5]	–42 [39.5; –45]	–47 [41; –50]	p_{2-3}=0.041
Lowest temperature in RSPV, °C	–50 [–46; –54]	–45 [–42; –53.5]	–48 [–42; –53]	p=0.434
TTI LSPV, sec	–	–	35.5 [24.5; 48.75]	–
TTI LIPV, sec	–	–	37 [25; 60]	–
TTI RIPV, sec	–	–	40 [28; 70]	–
TTI RSPV, sec	–	–	32.5 [20.25; 39.75]	–

CBA, cryoballoon ablation; PV, pulmonary vein; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RIPV, inferior pulmonary vein; RSPV, right superior pulmonary vein; TTI, time to isolation; PV, pulmonary vein.

Table 3. Comparative characteristics of the groups by the main intraoperative parameters

Indicator	Group 1, guidewire/240 (n = 31)	Group 2, guidewire/180 (n = 26)	Group 3, achieve/180 (n = 43)	p
CTI RFA	8 (25,8%)	8 (30,8%)	10 (23,3%)	–
Duration of radioscopy, min	14,3 [10,8; 20]	16,2 [14,5; 20,4]	15 [13,5; 20]	0,351
Radiation exposure, mGy	177 [102; 281]	194 [98; 502,5]	232 [120; 648]	0,238
Duration of procedure, min	90 [70; 115]	92,5 [80; 108,75]	90 [70; 120]	0,655
Complications	0	0	0	–

RFA, radio frequency ablation; CTI, cavo-tricuspid isthmus.

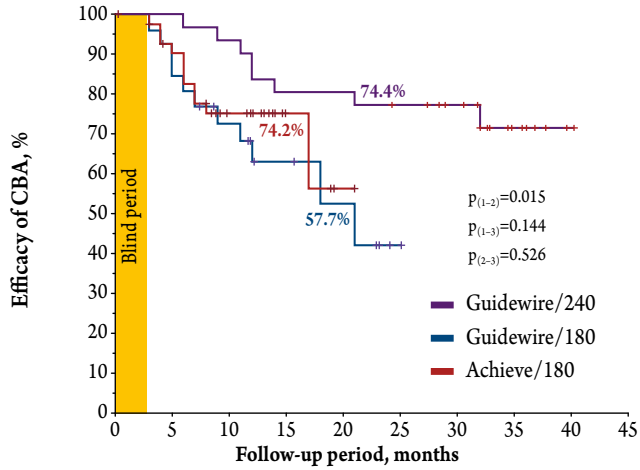
compared to 57.7% in the Guidewire/180 group (p = 0.015). At the same time, there were no statistically significant differences between the Guidewire/240 and Achieve/180 groups (p = 0.144). However, using logistic regression it was found that the exposure of 240 sec, unlike 180 sec, was an independent factor which increased CBA efficacy.

Longer cryoexposure may be associated with increased exposure depth and, consequently, a lower PV conduction recovery rate. Chen et al. [5] received similar results. They studied the effects of cryoexposure duration on the PV reconnection frequency. The authors analyzed the efficacy of CBA using second-generation cryoballoons in 788 patients. The duration of cryoexposure in each vein was 240 and 180 sec in 604 and 184 patients, respectively. The groups did not differ statistically by the degree of PV occlusion and TTI. During the 12-month follow-up period, 106 (13%) patients with AF recurrence were referred for repeat surgery (80 patients in the CBA group with 240-second exposure and 26 patients with 180-second exposure). During the repeat intervention, all patients were subjected to a three-dimensional electroanatomical reconstruction of the LA. Complete PV isolation was 61% was found in patients subjected to 240-second exposure when compared with 35% in patients exposed for 180 sec (p = 0.02). Univariate analysis showed that the duration of cryoexposure was the only significant predictor for PV reconnection (p = 0.018) [5]. Subsequently, the authors demonstrated in a more significant number of patients that 240-second applications were superior to 180-second exposures in patients with a persistent AF. The advantage of 4-minute applications was also independent of AAT [7].

Based on the results obtained, we have modified the PV CBA algorithm: the Achieve circular diagnostic catheter was used to position the cryoballoon and evaluate the isolation of PVs.

- If TTI was less than 90 sec, the duration of exposure was 240 sec,
- with TTI of more than 90 sec, cryoballoon was repositioned.

Figure 5. Comparative effectiveness of cryoballoon ablation (CBA) in the Guidewire/240 (n=31), Guidewire/180 (n=26), and Achieve/180 (n=43) groups



Guidewire/240	31	31	31	31	31	30	23	11	2
Guidewire/180	26	25	22	12	7	1	–	–	–
Achieve/180	43	41	29	6	2	–	–	–	–

Conclusion

Reducing cryoexposure duration to less than 240 sec is not reasonable, since the long-term efficacy of cryoballoon ablation of the pulmonary veins decreases in the absence of the Achieve diagnostic catheter. Control of pulmonary vein isolation, esophageal temperature, and phrenic nerve stimulation reduces the risk of complications. Further study and clarification are required to improve the cryoballoon ablation algorithm.

No conflict of interest is reported.

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