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ADDITIONAL LEFT ATRIAL LESIONS IMPROVE THE EFFECT OF CRYOBALLOON PULMONARY VEIN ISOLATION IN PAROXYSMAL ATRIAL FIBRILLATION PATIENTS

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Aim. Cryoballoon ablation (CBA) is one of the methods for catheter pulmonary vein isolation (PVI) for paroxysmal atrial fibrillation (AF). Left atrial additional lesion (LAAL) to PVI were proposed to eliminate extrapulmonary AF triggers. Nonetheless whether the additional lesions improve CBA effectiveness is not clear.

Methods. Primary CBA procedures performed for paroxysmal AF during 2017-2021 were analyzed. The study group (Algorithm group, n=82) was recruited prospectively in 2019-2021. As the first step CBA PVI were performed in all pts. In those who were on sinus rhythm (SR) after the PVI, AF induction attempts with burst atrial pacing were performed. Pts with induced AF and those who stayed on AF after PVI underwent LAAL at the left ganglionated plexus area. In case of stable SR (non-inducible AF) the procedure finished. If AF was inducible or did not terminate during CBA, the second LAAL set were performed - LA posterior wall lesions. If AF was still inducible or did not terminate, the SR was restored by electrical cardioversion. The control group (Control group, n=94) was formed retrospectively from patients with routinely performed only CBA PVI with achievement of isolation criteria in 2017-2019. If AF continued, sinus rhythm was restored by cardioversion. There were no attempts of induction AF during the procedure.

Results. The Algorithm and Control groups were comparable in terms of clinical, demographic and electrophysiological characteristics. At 12 months postoperatively, the effectiveness was higher in the Algorithm group than in the Control group (78.0% vs. 62.8%, p = 0.044). No adverse effects were found.

Conclusion. Thus, the stepwise approach with LAAL increases the effectiveness of CBA in the long-term period and does not affect the risk of complications.

Key words: atrial fibrillation; cryoballoon ablation; additional lesion; isolation of the posterior wall of the left atrium

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Pulmonary vein isolation (PVI) by cryoballoon ablation (CBA) is one of the main methods of rhythm control in patients with paroxysmal atrial fibrillation (AF) [1, 2]. The effectiveness of PVI is due to the elimination of triggers, which to the greatest extent cause the occurrence of AF [3]. According to M.Haïssaguerre et al. the detection of pulmonary vein (PV) trigger activity reaches 94% during the primary catheter ablation procedure [4]. AF relapse can be connected not only with restoration of conduction in PV, but also with activation of extrapulmonary arrhythmogenic foci (triggers or circles of re-entry), that most often is caused by development of atrial fibrosis [3, 5]. The most

frequent localizations of such AF triggers are superior vena cava, coronary sinus, left atrial (LA) appendage, Marshall ligament, border ridge, areas of fragmented activity at ganglionic plexus (GP) and posterior wall (PW) of LA [3]. It is known that PV and PW LA have a common embryological origin from the ectoderm and a similar histological structure [6, 7].

At the same time, the effectiveness of catheter ablation is also affected by comorbidity. Many studies have shown that such risk factors as arterial hypertension, obesity, chronic heart failure aggravate the processes of electrical and structural atrial remodeling [8, 9].

According to the recommendations of the European Society of Cardiology for the diagnosis and treatment of AF (2020), the necessity, localization, and volume of additional lesion (AdL) during catheter ablation procedure are at the discretion of the operating surgeon [8]. Recent studies that have investigated the issue of AdL application with CBA show ambiguous results and require careful analysis [10-13]. It is known that induction of sustained AF by increasing atrial pacing after PVI can be a predictor of AF recurrence [14]. The issue of staged application of AdL based on the possibility of AF induction after performing CBA PVI has not been previously studied.

Thus, it seems relevant to compare the efficacy of standard CBA PVI and CBA PVI procedure with staged application of AdL in the LA based on inducibility of AF. The aim of the present study is to evaluate the effect of AdL in the LA after the completion of PVI on the efficacy of CBA in patients with paroxysmal form of AF.

METHODS

The study included 176 patients in whom clinical and demographic and electrophysiological characteristics, as well as long-term results of the intervention were studied. Inclusion criteria: age of patients from 18 to 75 years old, paroxysmal form of AF, primary CBA. Exclusion criteria: malignant neoplasms, pregnancy, severe renal dysfunction (creatinine clearance <25 ml/min; blood creatinine ≥ 220 $\mu\text{mol/L}$) and liver (increased alanine aminotransferase, aspartate aminotransferase, bilirubin levels over 3 standards), patient refusal to participate in the study, loss of communication with the patient after CBA. The study was conducted in accordance with the principles of the Declaration of Helsinki.

We analyzed the primary CBA procedures performed in patients with paroxysmal AF between 2017 and 2021. The study group (Algorithm Group, $n=82$) recruited prospectively in 2019-2021 underwent CBA with staged AdL. The control group (Control Group, $n=94$) retrospectively included patients who routinely underwent only CBA PVI in 2017-2019.

Methodology of the CBA procedure

All patients underwent computed tomography of the LA or transesophageal echocardiography before catheter ablation to rule out thrombus in the LA. Under intravenous sedation and local anesthesia, venous access was performed, diagnostic multipolar electrodes were positioned in the coronary sinus and right ventricle. Electrophysiological examination (Bard, Lab system Pro, USA) was performed before and after CBA PVI to diagnose concomitant cardiac rhythm disturbances, the dynamics of effective refractory period of atrioventricular node and antegrade

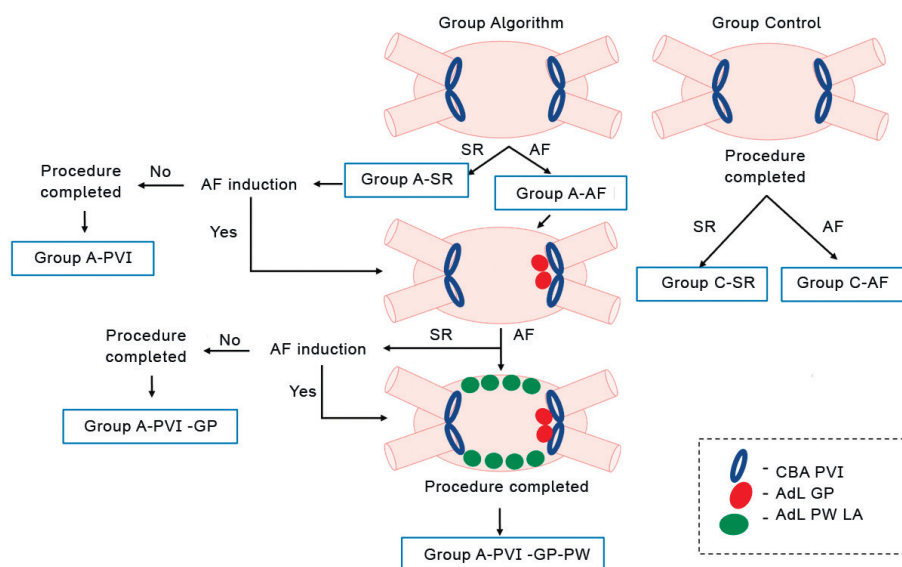


Fig. 1. Scheme of performing cryoballoon ablation (CBA) in both groups. Note: hereinafter, PVI - pulmonary vein isolation; AdL - additional influences; GP - ganglionic plexus; PW - posterior wall; LA - left atrium; SR - sinus rhythm; AF - atrial fibrillation; A - Algorithm (study group); C - Control (control group).

Table 1. Comparative characteristics of the main clinical and demographic indicators

Indicator	Group Algorithm (n=82)	Group Control (n=94)	p
Female gender, %	50	55.3	>0.05
Age, years	62 [53; 67]	65 [58; 68]	>0.05
Body mass index, kg/m ²	28.0 [26.3; 31.8]	28.8 [25.2; 33.5]	>0.05
HAF, years	4.0 [2.0; 10.0]	4.0 [1.6; 8.0]	>0.05
CHA ₂ DS ₂ -VASc, points	2 [1; 3]	2 [1; 4]	>0.05
HAS-BLED, points	0 [0; 1]	0 [0; 1]	>0.05
AH, %	74.4	85.2	>0.05
DM, %	6.2	8.6	>0.05
CHD, %	7.3	18.5	>0.05
BMR, %	7.3	12.3	>0.05
ECS/ICD	2.4	7.4	>0.05
LA size, mm	44 [39; 46]	41.0 [38; 46]	>0.05
LV EF, %	60 [58; 65]	60 [60; 65]	>0.05

Note: Data are presented as median and interquartile range - Me [Q1; Q3] or absolute and relative frequencies - n (%). HAF, history of atrial fibrillation; AH, arterial hypertension; DM, diabetes mellitus; CHD, coronary heart disease; ACS, acute cerebral circulation disorder; ECS, implanted pacemaker; ICD, implanted cardioverter-defibrillator; LA, left atrium; EF ejection fraction.

Wenckebach point were assessed, including for evaluation of response of cardiac autonomic nervous system to interference (cardioneuroablation). The interatrial septum was punctured under radiological control, transseptal SR0 8Fr (Abbott, USA) or Preface 8Fr (Biosense Webster, USA) introducer, its change to a FlexCath Advance 12Fr guided introducer (Medtronic, USA) in the LA cavity and subsequent positioning of a cryoballoon catheter (ArcticFront Advance 28 mm, Medtronic, USA) in each PV via a circular diagnostic catheter (Achieve, Medtronic, USA). PV occlusion was confirmed by the injection of iopromide X-ray contrast agent (Ultravist 370, Polysan NTFF LLC, Russia). The PVI time, minimum temperature, and total duration of exposure were evaluated. The validity of the effects was confirmed by the presence of a bidirectional conduction block. All AdL was performed under temperature control in the esophagus, where exposure was stopped

when the temperature decreased to +20°C. When the right PV was isolated, the right diaphragmatic nerve was stimulated at a frequency of 60/min to detect a disturbance in its conduction and to stop the action. It is also worth noting that in patients with a history of typical atrial flutter (AFL) or in case of induction of persistent typical AFL by increasing atrial stimulation, radiofrequency ablation of cavotricuspidal isthmus was additionally performed.

Features of the procedure in the study group (Algorithm)

Algorithm group (n=82) recruited prospectively in 2019-2021. The group consisted of patients who underwent an initial CBA PVI procedure followed by staged AdL "on demand". The first stage was the CBA PVI with achievement of the isolation criteria. Patients with sinus rhythm after the end of PVI constituted group A-sinus rhythm (SR), patients with AF after the end of PVI constituted group

Table 2.

Comparative characteristics of the main intraoperative parameters between the groups

Indicator	Group Algorithm (n=82)	Group Control (n=94)	p
HR before CBA	60 [53; 68]	64 [55; 71]	>0.05
HR after CBA	70 [62; 78]	70 [64; 80]	>0.05
EPR AVN before CBA	300 [265; 320]	300 [273; 355]	>0.05
EPR AVN after CBA	260 [240; 280]	270 [245; 335]	>0.05
Wenckebach's antegrade point before the CBA	415 [370; 485]	430 [375; 495]	>0.05
Wenckebach's antegrade point after the CBA	400 [330; 432]	410 [340; 470]	>0.05
Minimum temperature in LSPV, °C	47 [44; 51]	45 [44; 48]	>0.05
Minimum temperature in LPVI, °C	44 [42; 47]	43 [40; 46]	>0.05
Minimum temperature in RPVI, °C	46 [44; 50]	46 [42; 50]	>0.05
Minimum temperature in RSPV, °C	51 [47; 55]	48 [44; 53]	>0.05
TTI LSPV, s	55 [35; 74]	38 [30; 50]	>0.05
TTI LIPV, s	35 [26; 51]	45 [24; 60]	>0.05
TTI RSPV, s	57 [36; 77]	34 [20; 55]	>0.05
TTI RIPV, s	30 [21; 50]	36 [26; 56]	>0.05
Duration of LSPV exposure, s	240 [240; 240]	240 [180; 240]	>0.05
LPVI, exposure time, s	240 [180; 240]	240 [180; 240]	>0.05
Duration of RPVI exposure, s	240 [180; 240]	240 [180; 240]	>0.05
Duration of exposure to RSPV, s	240 [240; 240]	240 [180; 240]	>0.05
RFA CTI, %	15.9	28.7	>0.05
Radiation load, mGy	151 [88; 263]	159 [80; 329]	>0.05
Duration of operation, min	85 [73; 100]	80.0 [70; 103]	>0.05
Intraoperative complications, %	0	0	>0.05

Note: Hereafter, HR - heart rate; CBA - cryoballoon ablation; LSPV - left superior pulmonary vein; LIPV - left inferior pulmonary vein; RIPV - right inferior pulmonary vein; RSPV - right superior pulmonary vein; EPR AVN - effective refractory period of atrioventricular node; RFA - radiofrequency ablation; CTI - cavo-tricuspidal isthmus, TTI (time to isolation) - time from the beginning of exposure to LA isolation by circular diagnostic catheter Achieve. Considered intraoperative complications: persistent paresis of diaphragmatic nerve, hemopericardium, acute impairment of cerebral circulation.

A-AF. Further, in the A-SR group, induction of AF was performed using programmed and pacing atrial stimulation. In all cases, programmed and pacing atrial stimulation was performed from a diagnostic multipole electrode positioned in the coronary sinus. Programmed stimulation was performed with a baseline stimulation cycle length of 400 ms and one extrastimulus of 380 ms with further shortening of the extrastimulus until an effective atrial refractory period was achieved. The increasing stimulation was performed sequentially until the stimulation cycle length reached 300 ms, 250 ms, 220 ms, and 200 ms, respectively. When AF was not inducible, the operation was completed (subgroup A-PVI). In case of induction of stable AF (duration of the episode more than 30 s), as well as in patients from the A-AF group, the next step was to apply AdL in the left GP. GP localization was determined based on the anatomical features of the LA according to computed tomography and intraoperative contrast imaging. AdL in the right GP region were not routinely performed, since GP isolation in the right LA is achieved by routine isolation of the right LA using a cryoballoon. When a stable sinus rhythm was achieved, the procedure was terminated (subgroup A-PVI +GP). In case of continuation of AF or its induction by repeated pacing stimulation, AdL was applied on

PW LA (subgroup A-PVI +GP+PW); if AF continued after completion of AddI, sinus rhythm was restored by cardioversion (Fig. 1).

Features of the procedure in the control group (Control)

The Control group (n=94) was recruited retrospectively from patients who routinely underwent the traditional CBA PVI procedure in 2017-2018 with the achievement of isolation criteria. If the patient had AF after the operation, electrical cardioversion was performed. No attempts at induction of A were made. No additional impacts were applied. Patients with sinus rhythm after the procedure constituted the C-SR group, patients with AF constituted the C-AF group (Fig. 1).

Surveillance after CBA. After discharge, all patients received antiarrhythmic and anticoagulant therapy for 3 months. Further therapy correction was performed on an outpatient basis at the patient's place of residence. The efficacy of CBA was evaluated 12 months after the procedure. The intervention was considered effective if there was no recurrence at the time of the visit. The occurrence of one or more sustained atrial tachyarrhythmia paroxysms (atrial tachycardia/AFL/AF) recorded on an electrocardiogram or in a daily electrocardiogram monitoring was considered as relapse; "blind period" (first 3 months after the procedure) was excluded from follow-up. To assess the safety of the intervention, the following clinically significant complications were considered: diaphragmatic nerve paresis, hemopericardium, gastroparesis, acute cerebral circulation disorder, atrial-esophageal fistula formation.

Statistical analysis

Statistical analysis of the results was performed using SPSS Statistics 26.0 (IBM, USA). Analysis for normality of the distribution was carried out using the Kolmogorov-Smirnov method. A distribution deviating from the null hypothesis with the level of statistical significance $p < 0.05$ (null hypothesis - data are distributed normally) was considered different from normal. Quantitative indices in a distribution other than normal are presented as median and interquartile range [Q1-Q3]. Nominal indicators are presented as fractions (and absolute values). Quantitative variables were compared using the Kruskal-Wallis and Mann-Whitney methods. Nominal variables were compared using Fisher's exact test and Chi-square. CBA efficiency was calculated by the Kaplan-Meier method, and the LogRank test was used to evaluate the statistical significance of the obtained result. The results were considered statistically significant when the p value was less than 0.05.

RESULTS

In terms of the main clinical and demographic parameters, the studied groups were comparable (Table 1). When comparing the main intraoperative parameters, including electrophysiological ones, no significant difference between the groups was revealed (Table 2). After 12 months, the effectiveness of the CBA procedure was evaluated in both groups (Fig. 2). The overall proportion of patients without recurrence of AF in the Algorithm group was 78.0%, while in the Control group it was 62.8% ($p=0.044$). The first 3 months after the procedure ("blind"

period) was not taken into account in the efficiency evaluation. There were no clinically significant complications in either group.

A statistical analysis of the distant effectiveness of subgroups according to the stages of catheter ablation was also performed (Table 3). When comparing the subgroups among themselves, the differences were not statistically significant, except for the A-SR and C-SR subgroups, $p=0.036$ (Fig. 3). Amiodarone, sotalolol, or propafenone were administered for antiarrhythmic purposes after the CBA procedure. When analyzing antiarrhythmic therapy 12 months after the procedure, no statistically significant differences between the groups were found (Fig. 4).

DISCUSSION

Nowadays, it is of great interest to perform AdL with the help of CBA technology. The possibility of performing this type of AdL in patients with persistent AF has been most studied [13]. For example, A. Aryana et al. in a multicenter study on 390 patients with persistent form of AF revealed significantly higher both early and long-term efficacy in CBA PVI with isolation of PW LA compared to isolated CBA PVI [11].

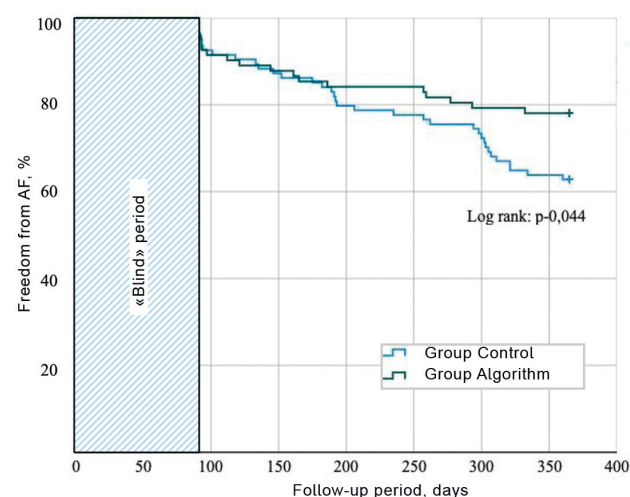


Fig. 2. Comparative assessment of the effectiveness of the CBA procedure over 12 months of follow-up in the Algorithm and Control groups.

Table 3.

Annual efficiency (AE) of the BCA in a subgroup analysis

Study groups	N	GP (%)
Algorithm Group	82	78
Algorithm-SR subgroup	58	81.0
Algorithm-AF subgroup	24	70.8
Algorithm-PVI subgroup	33	81.8
Algorithm-PVI +GP subgroup	12	83.3
Algorithm-PVI +GP+PW	37	73.0
Group Control	94	62.8
Control-SR subgroup	77	63.6
Control-AF subgroup	17	58.8

Nevertheless, the application of AdL in patients with paroxysmal form of AF also has its advantages. Thus, in patients with anatomical features of the LA and PV, the efficacy of the standard CBA PVI procedure is lower than in patients with standard anatomy due to incomplete PV occlusion [15]. In addition, patients with paroxysmal AF have extrapulmonary triggers, which may cause recurrence of atrial tachyarrhythmias after CBA PVI procedure.

It is also worth mentioning the important role of pericardial GP and the autonomic nervous system in the occurrence and maintenance of AF. An increase in its activity can lead to atrial extrasystole, and later to the manifestation of AF [16]. There are four main endocardial GP located in the myocardium around the PV. Several studies have shown that performing AdL in the GP significantly reduces the probability of recurrence of AF [17, 18].

A. Bisignani et al. in 2020 conducted a study including 80 patients with paroxysmal form of AF, the authors did not demonstrate any significant advantage of performing additional isolation of PW LA compared to standard CBA PVI. In contrast to our work, we did not study the principle of stepwise application of AdL [10].

Possible negative consequences of the procedure can be iatrogenic creation of new fibrosis zones with arrhythmogenic potential and thermal damage of the structures surrounding the heart (diaphragmatic nerve, esophagus, bronchi) [19, 20]. To prevent such life-threatening com-

plications as atrial-esophageal fistula and gastroparesis, we routinely performed temperature control in the esophagus.

When assessing the cumulative efficacy of the staged approach with the standard CBA PVI procedure, we obtained that the efficacy in the group with staged AdL was significantly higher than in the group with the standard CBA PVI procedure (78.0% vs. 62.8%, $p=0.044$). The effectiveness in each of the subgroups was also higher than in the control group, but the differences did not reach statistical significance.

Thus, the efficacy in the A-PVI subgroup, where a persistent sinus rhythm was maintained after provocation of the arrhythmia, was 81.8%. The persistence or induction of AF after this stage could indicate the presence of additional triggers and a supporting factor outside the PV. In this case, at the second stage, AdL was applied in the GP area of the left PV, and the procedure was completed when a stable sinus rhythm was achieved (subgroup A-PVI +GP). According to the data of electrophysiological study of the heart, performed before and after the intervention, we noticed a decrease in antegrade Wenckebach point, effective refractory period, rhythm acceleration, which confirms the consistency of additional effects in the pericardial autonomic ganglia. The annual effectiveness of catheter ablation in this subgroup was 83.3%. Those patients in whom AF remained or was induced in the left PV after CBA PVI and GP were treated by PW LA (subgroup A-PVI +GP+PW), annual efficacy 73.0%. In the control group, where patients routinely underwent CBA PVI procedure, patients with sinus rhythm at the end of the procedure constituted the C-SR subgroup, the annual efficiency of the procedure in this case was 63.6%. If AF continued after PVI, sinus rhythm was restored by cardioversion (C-AF subgroup), with an annual efficacy of 58.8%, respectively.

Of note is the significantly higher efficacy of CBA in the A-SR subgroup compared with the C-SR subgroup, 81.0% versus 63.6%, respectively, $p=0.036$. In both subgroups, only PVI was performed, no AdL was applied, and there was a sinus rhythm at the end of the operation. However, in the A-SP subgroup, sinus rhythm persisted even after attempts to induce AF by rapid atrial stimulation, whereas in the C-SR subgroup no stimulation trials were performed for induction of AF and no AdL was applied either.

Thus, according to the data obtained, adherence to the stepwise principle of CBA based on noninducibility of AF in patients with paroxysmal form of AF al-

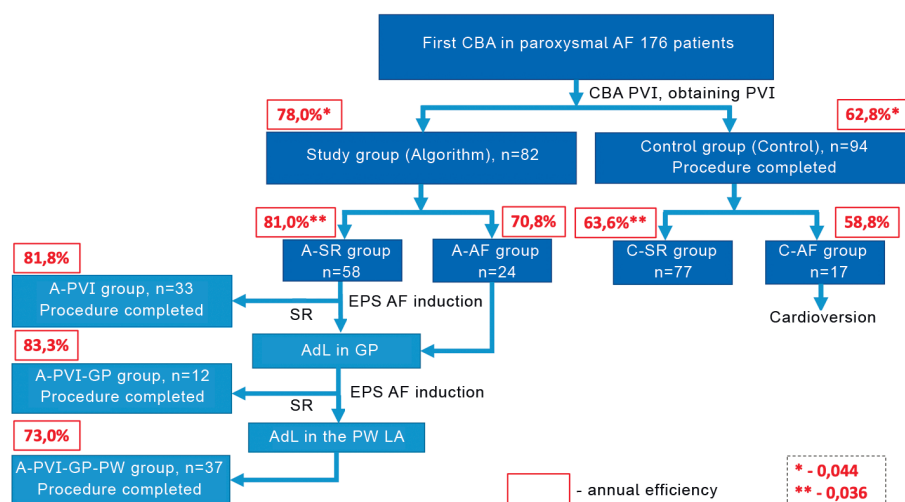


Fig. 3. A comparative evaluation of the effectiveness of the CBA in subanalysis of subgroups. Note: A - Algorithm (study group); C - Control (control group); * - significant difference between groups 1 and 2 ($p=0.044$); ** - significant difference between subgroups A-SR and C-SR ($p=0.036$).

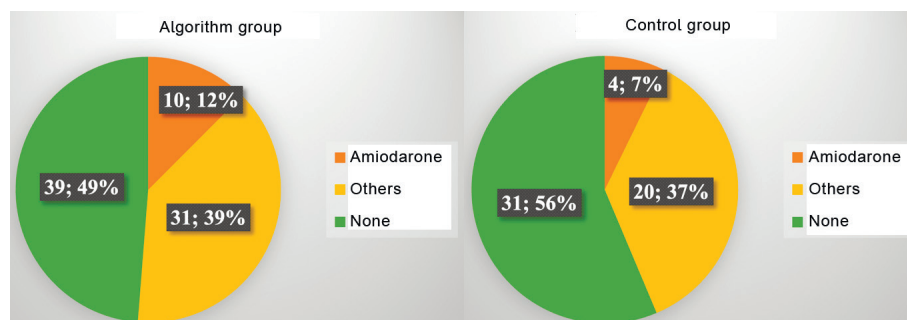


Fig. 4. Structure of antiarrhythmic therapy in the Algorithm and Control groups at the time of the visit 12 months after the CBA procedure.

lows to increase the efficiency of the procedure in comparison with CPA PVI and to optimize the number of AdL, which contributes to increased safety of the procedure.

Limitations of the study

AdL application to the LA was performed under radiological control, without confirmation of the consistency of the performed interventions using the 3D navigation mapping system. After 12 months of follow-up, all patients were not routinely subjected to a repeat procedure with 3D navigation mapping; accordingly, it was not possible to determine the cause of recurrent AF (restoration of conduc-

tion in the PV or failure of the AdL). In addition, patients were not implanted with loop recorders and some asymptomatic recurrences of AF may not have been accounted for. The absence of a significant difference between subgroups can be explained by the small size of the subgroups.

CONCLUSION

Staged execution of AdL in the LA after the completion of PVI in patients with paroxysmal AF increases the effectiveness of CBA in the long-term period and does not affect the risk of complications.

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