

# Efficacy and Safety Results of Different Ablation Technologies for Persistent Atrial Fibrillation Treatment

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## ABSTRACT

**Introduction:** Pulmonary vein isolation is the primary goal in treating patients with paroxysmal atrial fibrillation using catheter ablation. This study's purpose is a comparative assessment of the efficacy and safety of two strategies for catheter treatment in patients with persistent atrial fibrillation.

**Patients and methods:** The study included 127 patients with persistent atrial fibrillation during the last six months before inclusion in the study. The average follow-up period was 24 months.

**Results:** The primary efficacy endpoint (death, cerebrovascular event, or serious complications associated with treatment) occurred in 15 patients in the cryoballoon ablation group and 14 patients in the radiofrequency ablation group. The Kaplan-Meier survival estimates were 30% and 28%, and the risk ratio 0.96 and 95% of the confidence interval.

**Conclusions:** The treatment in patients with persistent atria fibrillation, using catheter ablation with contact force control catheter treatment with the pulmonary vein isolation, was more efficient.

## INTRODUCTION

Pulmonary vein isolation (PVI) is the cornerstone for the catheter treatment of atrial fibrillation (AF) [Haissaguerre 2000; Revishvili 2012]. Nowadays all catheter technologies have focused on the PVI, like the standard catheter ablation treatment, based on the following point by point applications, and later developed (single-shot technique) cryoballoon ablation (CBA) [Verma 2015; Su 2018; Kuck 2016; Baimbetov

2018; Kuck 2016]. Large observational studies reported acceptable success rates with a low level of adverse events with AF paroxysmal forms [Baimbetov 2018; Ouyang 2010; Pokushalov 2013].

This study presents a comparative assessment of the efficacy and safety of catheter treatments: catheter ablation treatment versus CBA in patients with persistent AF (PerAF) based on long-term follow up using implantable electrocardiogram (ECG) monitors (for 24 months). In this case, a routine analysis of each automatically-detected episode of arrhythmia was performed to differentiate the "false" detections. The local ethics committee of the Syzganov National Scientific Center of Surgery approved the research.

## METHODOLOGY

**Study design:** The study is a prospective, randomized, controlled research designed to compare the results of modern catheter technologies (radiofrequency and cryoballoon ablation) in patients with persistent AF. The ethics committee of our center approved the study design. The study included patients with persistent AF during the last six months before inclusion in the study. Exclusion criteria were the following: sizes of the left atrium >5.0 cm, left ventricular ejection fraction was <40%, heart failure with the New York Heart Association (New York Heart Association) class III or IV, chronic heart failure requiring intervention, stroke, or transient ischemic attack within six months. Also excluded were patients who had ablation performed in the left atrium or surgery for AF, those with prosthetics of the heart valve, and who had more than one cardioversion for two years or implanted cardiac devices. Figure 1 shows the distribution of patients in the studied groups after screening and randomization. (Figure 1)

**Cryoballoon ablation:** During cryoablation, all four pulmonary veins were isolated (left superior (LSPV), left inferior (LIPV), right superior (RSPV) and right inferior (RIPV)), with confirmation of the entrance and/or exit block the left atrium out of PVs. Left common PVs also were isolated to achieve similar block from the PVs. Transseptal puncture was performed under the control of fluoroscopy or transseptal echocardiography (ICE), using a standard transeptal introducer. A controlled 15-Fr FlexCath delivery system then replaced the introducer. After that, a 28 mm Arctic Front

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cryoablation balloon catheter was placed on a guide to the LSPV. Cryoablation usually was performed for 240 seconds, with an assessment of the entry and/or exit block using circular mapping catheter pacing after a 30-minute waiting period. Additional “bonus” effects were made at the discretion of the operator if isolation was not achieved.

**Catheter ablation treatment:** In the catheter ablation

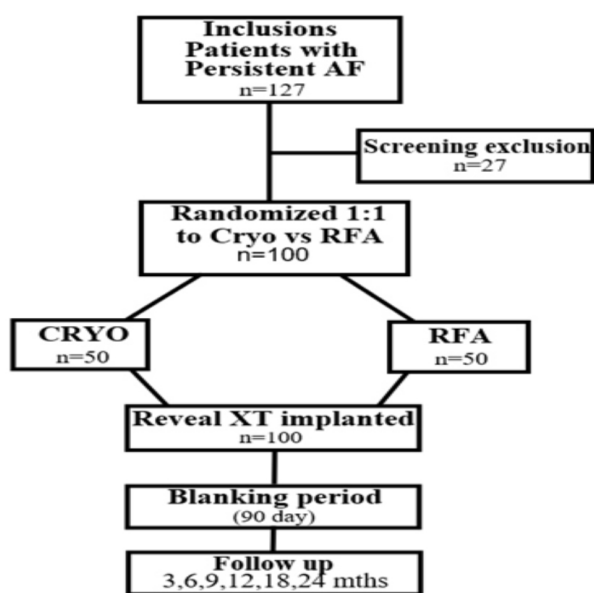


Figure 1. Distribution of patients in the study

treatment of the RFA group, radiofrequency energy was used to ablate, which was delivered using an irrigated Thermo Cool Smart Touch catheter (Biosense Webster Inc., CA, US). This catheter has the contact force-sensing function on the irrigated tip. After transseptal puncture with the same catheter, a three-dimensional electroanatomical map of the left atrium with pulmonary veins was constructed using the Carto 3 navigation system (Biosense Webster Inc.), with the VisiTag module. RFA was performed in the antrum of the ipsilateral pulmonary veins, with a wide capture of nearby endocardium tissue. RFA also was performed between the superior and inferior veins, if necessary. The power indicator was at 30 W, a limited range of 25–30 W to the posterior wall and 30–35 W to other left atrium areas. A contact force was 5–40 g, and the application duration of radiofrequency was 20–40 s to target each spot for local attenuation of the signal by 0.80%. The automatic lesion's marking (VisiTag, Biosense Webster, Inc.) was used to mark the location of each injury. No additional ablation was performed. The isolation was confirmed by demonstrating the entry and exit block by pacing, from the Lasso diagnostic electrode sequentially placed in each of the PV. The final PVI was confirmed after a 30-minute waiting period at the end of the procedure after re-demonstration of the entry and exit block of the PV.

Cavotricuspid isthmus was ablated using an irrigated radiofrequency catheter in patients with previous clinical or

induced atrial flutter, depending on the cavotricuspid isthmus, with the need for bidirectional block. After the procedure, the pacing was used to demonstrate the entry and/or exit block; isoproterenol and adenosine were not used to verify the block.

During the ablation procedure, the patient took heparin (100 units per kg), simultaneously until the value of the activated coagulation time (ACT) >300s was reached, then fractionally, to maintain the ACT level. Sedation and/or anesthesia and withdrawal of anticoagulation were performed, according to the standards. Before discharge, patients after ablation underwent control X-ray studies on inhalation and exhalation to detect the phrenic nerve palsy. Anticoagulation prevention therapy was carried out during the first six months after ablation. Subsequently, the anticoagulant was replaced with aspirin, if there was no indication of risk stratification by CHA2DS2-VASc [Camm 2012]. During the 90-day blanking period, patients also took 1 or 2 antiarrhythmic drugs for preventive purposes, after which the drug was cancelled. One cardioversion and one ablation were allowed during this blanking period, with the recommendation that all repeated ablations use the same catheter ablation technique.

**Implantation of ECG loop recorders:** The next day after the ablation procedure, a loop recorder Reveal XT, (Medtronic, USA) was implanted subcutaneously in the left front part of the chest. After implantable cardiac monitors (ICM) were inserted, patients were given manual activators and instructed in using a manual activator to activate ICM, in case of acute symptoms. ICM can detect AF episodes longer than 2 minutes, and other arrhythmias with such criteria: asystole (R-R pause of more than 4.5 s); and tachycardia (R-R intervals shorter than 400 ms, rhythm more than 150 beats per minute).

**Follow up:** All patients were monitored for 24 months, from the date of catheter ablation. Each patient underwent repeated examinations after 3, 6, 9, 12, 18, and 24 months. Cases of AF during the blanking period were not considered a primary goal and were not considered chronic treatment failures.

Repeated research of echocardiography and CT of left atrium and PVs were carried out at the beginning of the study, and after 12 and 24 months. All clinical adverse events and study endpoints were reviewed by an independent clinical event expert. At each visit, all reports of ECG loop recorders manually were evaluated, i.e. they automatically transmitted episodes and provided full coverage of the episode transmission with additional manual transmissions, if necessary. Episodes manually were classified from recorded electrograms as AF, atrium tachycardia, sinus rhythm, asystole, tachycardia, or lack of electrograms. Figure 2A through Figure 2E shows the examples of reports from ICMs. (Figure 2)

**Endpoints:** The main endpoint of study effectiveness was freedom from chronic treatment failure, which was determined by the absence of any detectable arrhythmias after the blanking period; use of an unidentified, antiarrhythmic drug; and any out-of-protocol intervention for AF (i.e. cardioversion and ablation).

Unregistered AF after ablation at treatment time with a previously ineffective antiarrhythmic drug at the same or

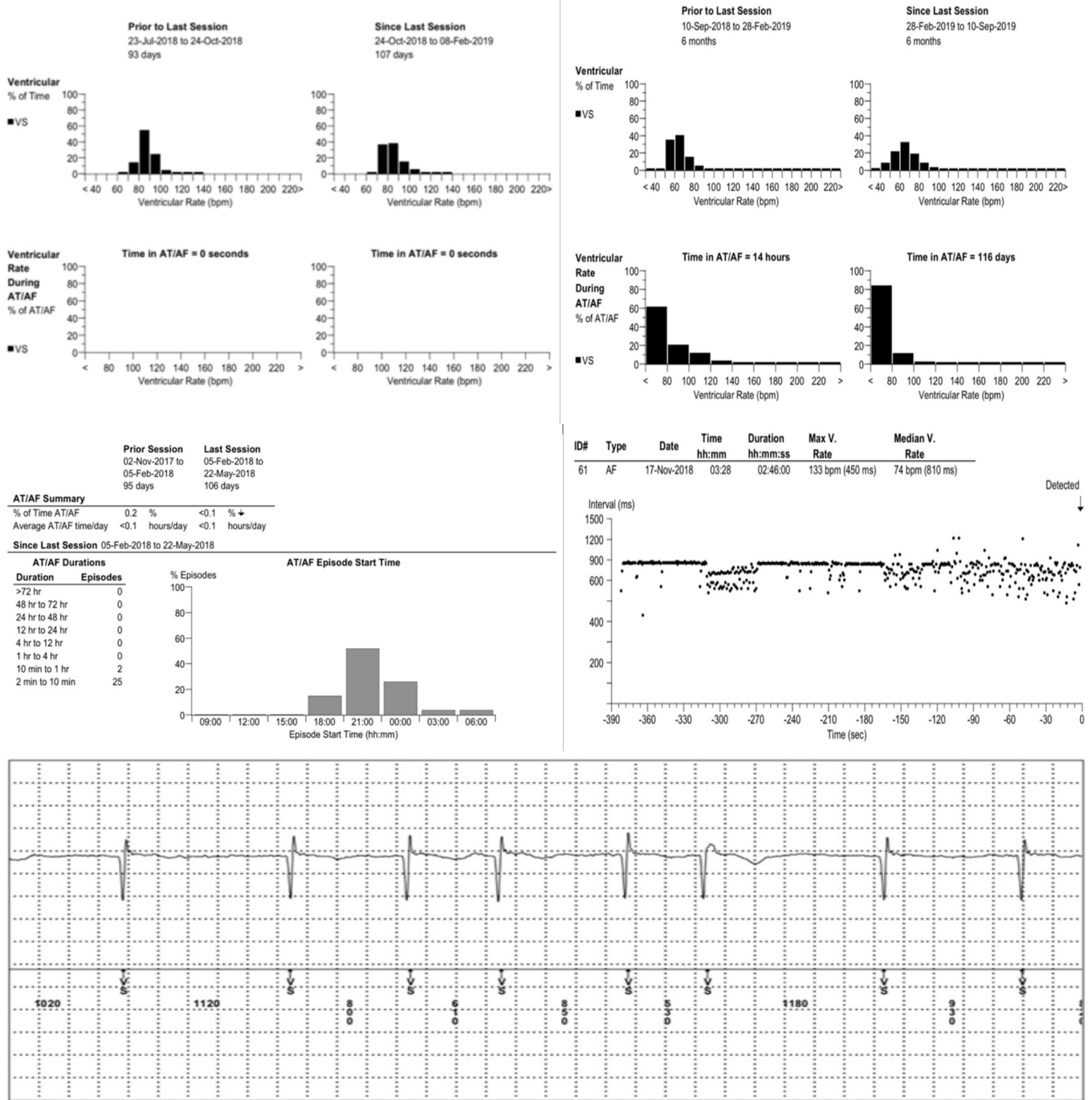


Figure 2. Examples of reports from ICMs

lower dose was considered successful, if the patient maintained sinus rhythm.

**Statistical analysis:** The results of continuous variables are given as arithmetic mean ± standard deviation. Comparisons of mean values were carried out using the Mann-Whitney U-test, depending on the distribution of values. Categorical variables were compared using exact binomial or chi-square analysis. Long-term results were shown using the Kaplan-Meier curve,

with the significance of differences in values indicated using a log-rank test. Differences between groups also were identified using proportional risk models. The primary efficacy endpoint was assessed using Fisher's double-sided exact test of binomial proportions. Statistical analysis was performed using the IBM SPSS Statistics-19 program.

**Patient characteristics:** Each group (RFA and CBA) consisted of 50 patients. Table 1 shows the general characteristics

of patients. (Table 1) All patients had severe symptoms with persistent AF and episodes of heart palpitations two months before they were included in the study. Previous cardioversion and a history of atrial flutter were similar in both groups. The median number of patients in whom antiarrhythmic drugs were ineffective before registration was 2.1 in the CBA group and 2.2 in the RFA group ( $P = NS$ ). All patients in both groups also had a low risk of stroke, according to the CHA2DS2VASc scale, and had no differences between the groups.

## RESULTS

**Short-term results of ablation in the CBA group:** A number of 198 PVs were isolated in one procedure in 50 patients randomized to ablation. In 48 (96%) patients, three or more PVs were isolated, which was confirmed by the entrance and/or exit block. All four PVs were isolated in 46 (92%) patients, as well as seven of seven left common PVs (LCPV). All patients underwent cryoballoon ablation and were sufficient for complete isolation, and for all PVs, only  $6 \pm 2$  applications were required. The average cryoballoon application time was  $225 \pm 15$  s. The average cryoablation temperature was  $-49.6 \pm 4.2^\circ\text{C}$ . Four patients required additional ablation at the PVs of one or more, at the 19 PVs; an average of two cryoablations was taken where isolation couldn't be achieved in one application. All patients used a 28 mm balloon.

The average duration of the procedure, including all repeated PV's evaluations, was  $141.1 \pm 13.9$  minutes, the fluoroscopy time averaged  $27.2 \pm 9.6$  minutes, and the total cryoablation time averaged  $42.3 \pm 9.9$  minutes. In the cavotricuspid isthmus, ablation was performed in 19 (38%) patients, and the bidirectional block was achieved in 17 (90%).

**Short-term results in the RFA group:** In all patients, PVs were completely isolated in the antrum until the

potentials disappeared on the circular diagnostic electrode, which was installed separately for each PV. It also was used to confirm the complete circular isolation of the PV with the input and/or output unit. The RFA value was 30 W, with a limited range of 25–30 W for the posterior wall and 30–35 W for other areas of the left atrium. The contact force is from 5 to 40 g with a duration of application of a radiofrequency of 20–40 s. Ablation index also was used here. The ablation index values for each lesion are automatically calculated by the CARTO 3 system (Biosense Webster, Inc.). The formula used to calculate the IA is a complex weighted exponential formula that assigns different weights of power, contact force and time. The average number of IA used for the posterior wall was 400, for the anterior wall and other areas it was 450 of the PV.

The average duration of the RFA procedure was  $178.1 \pm 22.6$  minutes, the reconstruction time for left atrium and PVs took  $16.2 \pm 2.9$  minutes on average, and the total ablation time was on average  $62.2 \pm 11.6$  minutes. Fluoroscopy time averaged  $15.1 \pm 4.2$  minutes, taking into account the fact that less X-ray control was used throughout the procedure since ablation was performed based on a three-dimensional reconstruction of the left atrium and the PVs. In the cavotricuspid isthmus, ablation was performed in 17 (34%) patients, while bidirectional block was performed in 16 (94%).

Differences in the duration of procedures, the ablation itself and fluoroscopy are shown in Figure 3. (Figure 3)

**Long-term results:** The primary efficiency endpoint was evaluated by analyzing the time before the first event, after a 90-day blanking period. In the blanking period, recurrence of arrhythmias was not accounted for by the primary endpoint. The following failure events were documented episodes of AF for more than 30 seconds, atria tachycardia, or atria flutter; taking antiarrhythmic drugs to restore sinus rhythm; and repeated catheter ablation treatment.

Table 1. Patient baseline characteristics

Analyzed parameters	Group 1 CRYO (N = 50)	Group 2 RFA (N = 50)	P
Age (years)	61.3±10.2	61.6±6.5	0.893
Male, n (%)	31 (62%)	29 (58%)	0.572
Left atrium size (mm)	41±5	39±7	0.621
Arrhythmia duration, months	19±17	22±15	0.075
EHRA, (I-IV)	II-III	II-III	-
LV ejection fraction, %	59±5	54±6	0.956
CHA2DS2VASc	1±0.5	0.9±0.6	0.787
Warfarin, %	57	61	0.862
Xarelto, %	43	39	0.575
Amiodarone, n (%)	37 (74%)	41 (82%)	0.391
Beta blocker, n (%)	33 (66%)	27 (54%)	0.175
Atrial flutter, n (%)	6 (12%)	8 (16%)	0.664
Previous cardioversion, n (%)	18 (36%)	22 (44%)	0.452



Assessment of primary efficiency 24 months after the procedure, as an indicator of freedom from arrhythmia, was 70% in the CBA cohort and 72% in the RFA cohort, confirming a statistically insignificant difference between ablation methods ( $P < 0.672$ ). Neither were there differences found in this study at the primary safety endpoint between treatment cohorts ( $P = 0.77$ ). Although there was no statistical difference in the absolute number of patients who reached the primary safety endpoint, there were differences in the type of safety and events that occurred in patients with CBA vs RFA. In particular, the phrenic nerve injury during discharge was greater in the CBA group (2.7%) than in the RFA group (0%;  $P < 0.001$ ), and in the RFA group there were more groin complications associated with vascular access site (inguinal area) than in the CBA group (5.1% versus 2.7%;  $P < 0.01$ ). The presence of atrial flutter or atrial tachycardia after catheter ablation of AF was recorded, and although it is assumed that it is created (partially) by incomplete lesions or gaps in the ablation lines AF, which transform into a new substrate for the re-entry mechanism.

Occurrences of atrial flutter and atrial tachycardia also have been included as severe adverse events. It was reported that atrial flutter and atrial tachycardia tended to be more common in the RFA cohort (6 (12%) compared with the CBA cohort versus (2 (4%);  $P < 0.09$ ). This observation may

indicate that new arrhythmogenic tissue, potentially due to an incomplete line between ablation points or tissue heterogeneity, tends to occur more often after RFA than cryoablation.

Secondary endpoints in this research were designed to compare the procedure and fluoroscopy time between the subjects of study and to assess the quality of life, cardiovascular events, hospitalization, and repeated ablation. The average overall procedure time and left atrium dwell time were significantly shorter in the CBA group, while the average fluoroscopy time was significantly shorter in the RFA group. Table 2 shows indicators of time characteristics of procedural data of ablation technology. (Table 2)

According to the SF-36 quality of life questionnaire, patients experienced similar results, characterized by the improvement of mental and physical indicators of quality of life for six months. Secondary analysis also showed that in the cohort of patients with the CBA group, there were significantly fewer repeated admissions for all reasons (29.6%) compared with the RFA group 39.7%;  $P < 0.01$ ). The rehospitalization for heart disease (23.8% versus 16.2%;  $P < 0.01$ ), and repeated ablation, on the contrary, were higher in the CBA group compared with the RFA group (21.1% versus 14.6%;  $P < 0.03$ ).

By the end of 12 months, only 26% of patients in this group took antiarrhythmic drugs; 56% of patients took

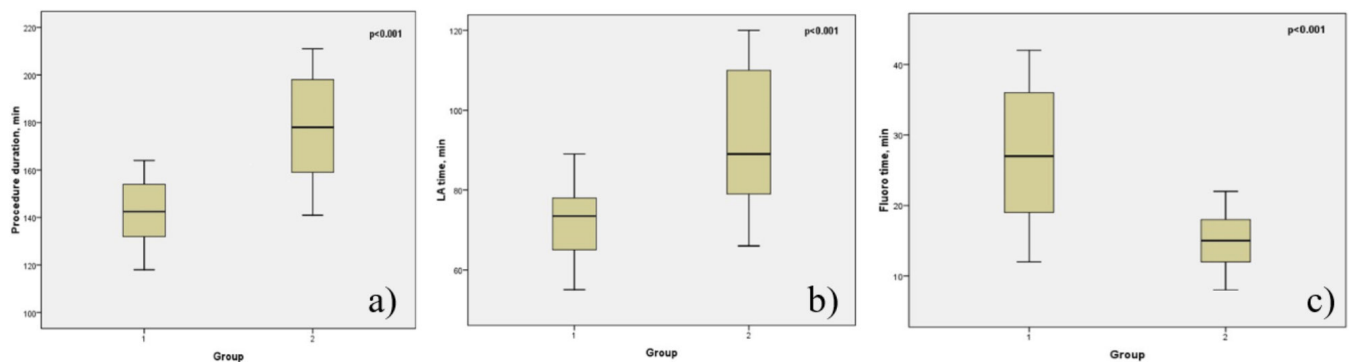


Figure 3. Differences in the duration of procedures

Table 2. Indicators of time characteristics in ablation technology

	N	Mean	SD	Median	Min	Max
Group 1						
Procedure duration, min	50	141.14	13.952	142.50	118	164
LA time, min	50	72.30	9.910	73.50	55	89
Fluoro time, min	50	27.20	9.570	27.00	12	42
Group 2						
Procedure duration, min	50	178.10	22.615	178.00	141	211
LA time, min	50	93.66	16.507	89.00	66	120
Fluoro time, min	50	15.08	4.189	15.00	8	22

warfarin, and 54% took xarelto 20 mg at admission, and only 24% of patients continued this treatment after 12 months of the follow-up period. The CHA2DS2-VASc score did not differ between those who stopped and those who continued to take anticoagulants. The incidence of clinical symptoms of AF decreased from 100% at the start of the study to 19.0% within 24 months. Symptoms associated with arrhythmia dramatically were reduced by 24 months of observation: AF symptoms (100% to 20%), dizziness (48% to 9%), palpitations (86% to 25%), and fatigue (76% to 13%). This clinical improvement has been confirmed by an improvement in the quality of life of SF-36.

**Phrenic nerve palsy:** Phrenic nerve palsy (PNP) was assessed by chest X-ray during inspiration/expiration after all cryoablation procedures. PNP was recorded in four (8%) patients, and all of them were asymptomatic. In two patients, PNP was cured by the end of the operation; in one patient, paresis lasted for one week. Full radiographic resolution of PNP in the fourth patient occurred after four months of observation. All cases of PNP were recorded during ablation of RSPV.

**Other adverse events:** No one patient had atrial-esophageal fistula. Femoral arteriovenous fistula occurred in 2 patients, while pseudoaneurysm developed in 3 other patients. Post-procedural cough developed after 11 of 100 (11%) procedures that completely disappeared in 96% of patients by the end of the research. Pericardiac chest pain after ablation was a rare incidence. Serious adverse events occurred in 17 of 100 (17%) patients.

## DISCUSSION

**Main findings:** The primary efficacy of treatment between the groups was the same, yet in the long-term period, the superiority of RFA with the use of the contact-force catheters was noted. However, the difference in results was statistically insignificant ( $P < 0.672$ ). There also was no significant difference in the primary safety endpoint between the RFA group and CBA group.

Previous research (which mainly were conducted in patients with a paroxysmal form of AF) comparing efficacy and safety of these two methods showed statistical equivalence between the two technologies [Evonich 2007; Aryana 2016; Ang 2018]. Some studies showed higher cryoablation efficacy, possibly for the paroxysmal form of AF and the preserved anatomy of the left atrium of the patients under investigation [Packer 2013]. The FreezeAF study showed the best safety profile in the RFA group, and there were more episodes of phrenic nerve injury in the CBA group. However, the FreezeAF analysis included incidents of the phrenic nerve injury that resolved before discharge, and in most cases, a first-generation balloon was used [Luik 2015]. In studies like “Fire & Ice,” the efficacy of cryoballoon and radiofrequency catheter isolation of PVs was compared, where no statistically significant differences were demonstrated by the results of ablation (absence of arrhythmia in 88 and 92% after 1.2 procedures with an observation period of 33 months) [Kuck 2019].

The primary endpoint was reached, according to the effectiveness criterion. It was proved that Arctic Front cryoballoon ablation catheters are not inferior to Thermo Cool radiofrequency ablation catheters with three-dimensional mapping technology ( $P = 0.0004$ ). Recurrences of arrhythmia, antiarrhythmic drug therapy, and/or re-ablation were less in this group. The primary endpoint also was reached, according to the safety criterion, namely, the time until the first death for any reason, to a stroke or TIA (transient ischemic attack) for any reason or too severe adverse events due to treatment ( $P = 0.24$ ). Both technologies showed comparable low complication rates. The technique of cryoballoon ablation provides a shorter duration of procedures (average value = 124 minutes) in comparison with the radiofrequency ablation group (average value = 141 minutes;  $P < 0.0001$ ). This patient cohort also consisted of paroxysmal forms of atrial fibrillation in this study.

**Comparative effectiveness of ablation techniques:** The success rate of radiofrequency ablation using a new generation of catheters with the contact force control at the tip of the catheter is most likely due to the improvement of the ablation process, using optimal parameters as the “ablation index.” However, the ablation process itself requires lengthy catheter manipulations like point-by-point, which may increase the number of adverse events associated with the ablation procedure. The efficacy and safety results of cryoballoon ablation were higher than predicted by a recent meta-analysis of randomized and observational studies [Heeger 2017]. The overall outcomes are similar to that proposed in our recent cryoballoon ablation studies [Baimbetov 2018]. Randomized studies of cryoablation compared with RF ablation will be required to more accurately establish the comparative effects of type of energy, researcher's experience, underlying disease, AF type, and requirement of additional lesions in the left atria or RA besides PV isolation [Chun 2017].

The procedure and ablation time was longer than in some previous studies of RF or cryoablation [De Lavallaz 2019; Calkins 2012; Chen 2017], but they were similar to the average times observed in previous observational studies of catheter ablation [Wechselberger 2018]. The study protocol components, in particular the 30-minute evaluation period at the end, also contributed to an increase of the procedure duration [Tuleutayev 2017]. With experience accumulation, the total time for the ablation procedure itself decreased, and the success rates of individual ablation processes increased, reflecting the expected learning experience curve.

**Application for clinical practice:** This study demonstrates that catheter treatment with pulmonary vein isolation in patients with a persistent form of AF, with the use of contact force catheters, has a higher success rate in the long-term period compared with cryoisolation of PV using a second-generation balloon, with similar complication rates. Furthermore, the time of the procedure and the ablation itself in the cryoablation group were significantly shorter. The success rate of radiofrequency ablation using a new generation of catheters with the ability to control the pressure force at the tip of the catheter is rather due to the improvement of the ablation process, with the use of optimal parameters such as the “ablation index.” However, the ablation process itself

requires prolonged catheter manipulations as a "point-by-point," which can increase the number of adverse events associated with the ablation procedure.

**Translational outlook:** Cryoballoon ablation is a more effortless and shorter procedure, but it is preferable to use with the preserved anatomy of the left atrium and pulmonary veins. In the case dilated anatomy of the left atrium and persistent forms of AF relatively effective traditional RFA with VisiTag technology. However, it takes longer than ablation time. The use of Ablation Index modules reduces the duration of ablation by 25-35%. Better visualization due to the represented method can help medicals make their actions more clearly and exact, and to make surgery ablation safe and resultative.

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