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Bonus vs No Bonus Cryoballoon Isolation for Paroxysmal Atrial Fibrillation Ablation

Aysenur Ekizler, Dursun Aras, Serkan Cay, Ozcan Ozeke, Firat Ozcan, Serkan Topaloglu

Division of Cardiology, Heart Rhythm Service, Kingston General Hospital, Queen's University, Kingston, Ontario, Canada.
Department of Mathematics and Statistics , Queen's University, Kingston, Ontario, Canada.

Abstract

Aim

To evaluate the benefit of Bonus freeze using second generation cryoballoon after pulmonary vein isolation (PVI) for paroxysmal atrial fibrillation (PAF)

Methods

A bonus freeze is performed after proven pulmonary vein isolation (PVI) for cryoballoon ablation of paroxysmal atrial fibrillation (PAF) as standard. In the current study, no additional freeze (No Bonus) after PVI was compared with additional freeze (Bonus) after PVI using second generation cryoballoon.

Results

A total of 136 patients (mean age 58 ± 13 years, 76 male) were included. No Bonus and Bonus groups had 56 and 80 patients, respectively. Follow-up electrocardiography and Holter monitoring were performed at 1, 3, 6, 12 months, and biannually thereafter. The PVI rate was similar after the initial ablation (82% in No Bonus group, 80% in Bonus group, p>0.05) and, at the end of the procedure (99% in No Bonus group and 99% in Bonus group, p>0.05). The median procedure and fluoroscopy times in No Bonus group were 67 (60-74) minutes and 13 (10-15) minutes, which were significantly shorter than the median durations, 85 (76-90) minutes and 17 (15-21) minutes in Bonus group, respectively (all p<0.001). Phrenic nerve palsy was observed less frequently in No Bonus group compared to Bonus group (1 patient (2%) vs. 5 patients (6%), respectively) without statistically significant difference. During a median follow-up of 13 (11-15) months, the rates of patients free from AF were 82% in No Bonus group and 84% in Bonus group, respectively (p>0.05).

Conclusions

The rate of sinus rhythm at 18 months was similar in patients with PAF who received bonus cryoablation vs patients who did not receive bonus cryoablation.

Introduction

Cryoablation is an effective and reliable therapy in achieving pulmonary vein isolation (PVI) in the treatment of paroxysmal atrial fibrillation (PAF).[1]-[4] Conventionally, 240 seconds freeze duration and then a bonus freeze is applied for successful electrical isolation of the pulmonary veins (PVs). The novel second-generation cryoballoon (CB-Adv) (CB, Arctic Front Advance, Medtronic, Inc., Minneapolis, USA) facilitates PVI by technical improvements compared to its predecessor.[5], [6] Therefore, a strategy that limits the number of freezing cycles might still achieve durable PVI with CB-Adv. There is limited data on the early and late outcomes of cryoablation without bonus freeze applications. The current study sought to assess the acute procedural success, early and 18 months clinical outcomes after PVI, as well as procedural parameters using the novel CB-Adv in patients undergoing a single 240 seconds application per vein compared to the standard bonus freeze application.

Key Words

Atrial Fibrillation,Bonus,Cryoablation,Recurrence

Corresponding Author
Serkan Cay,
Department of Cardiology,
Division of Arrhythmia and Electrophysiology,
Yuksek Ihtisas Heart-Education and Research Hospital,
Sihhiye, Ankara, Turkey,
E-mail - cayserkan@yahoo.com

Methods

Study design

This study was a non-randomized single center trial. All data including clinical, laboratory and procedural were retrospectively examined and prospectively analyzed. The study protocol was approved by the institutional review board. All participants enrolled provided written informed consent.

Study population

The study population consisted of 136 consecutive patients with drug-resistant symptomatic PAF who underwent PVI using the CB-Adv. All inclusion and exclusion criteria for eligible patients were detailed in Supplement 1. Informed consent to the ablation procedure was also obtained from all patients. A transesophageal echocardiogram was performed to exclude the presence of thrombi in the LA and LA appendage before the procedure. Patients were assigned to No Bonus and Bonus groups if they underwent PVI with no additional cryoballoon ablation or additional ablation after PVI, respectively. After ablation, patients entered a standard 3-month blanking period in which recurrent atrial tachyarrhythmia were recorded and also

included in the analyses after the 3-month blanking period.

Ablation procedure

Continuation of oral anticoagulants was permitted until the day of procedure. The procedure was performed under conscious sedation using midazolam, fentanyl and propofol. Femoral venous and arterial accesses were gained from the right and left femoral veins and left femoral artery. A 6F quadripolar or decapolar catheter was introduced via the left femoral vein and positioned in the coronary sinus (CS) for atrial pacing and intracardiac rhythm monitorization. During right-sided PVI, this diagnostic catheter was positioned within the superior vena cava (VCS) for phrenic nerve stimulation. Transseptal access to the left atrium was gained with brockenbrough transseptal needle and 8F transseptal sheath under fluoroscopic guidance. This was exchanged over a guidewire for a 15F steerable sheath (Flex Cath, Medtronic, Inc., Minneapolis, USA). A full dose heparin was administered just before or after transseptal puncture according to operator preference and, additional boluses were given to maintain an activated clotting time between 300-350 seconds during the procedure. Also transseptal sheath was continuously flushed with heparinized saline. Selective PV angiographies were performed via multipurpose catheter using standard views. Real-time PV recordings were obtained with a circular mapping catheter (Achieve, Medtronic, Inc., Minneapolis, USA) during cryoablation. A 28 mm CB advanced to the PV ostium and occlusion assessed by distal contrast media injection through the central lumen of the inflated CB. If optimal vein occlusion was achieved, single cryotherapy was applied for 240 seconds with confirmation of entrance and exit block for each vein 20 minutes after the last application. For the first group, all procedures were performed with a single 240 seconds application for each vein. If PVI was not achieved with a single freeze cycle, an additional freeze application was delivered until electrical isolation was demonstrated. If electrical isolation could be verified after the first freeze, no additional bonus freeze was applied. In the second group, after successful PVI, an additional freeze cycle was applied. In the presence of a common ostium, the ablation was applied as separate branches. Various maneuvers including pull down, hockey stick, C or reverse C were used to improve the occlusion and temperature drop. No additional ablation lesion except cavo-tricuspid isthmus linear ablation for typical atrial flutter during the procedure was permitted. During ablation of the right-sided PVs, pacing catheter in the CS was advanced in the VCS for continuous phrenic nerve pacing at 1500 ms cycle length and 20 mA output in order to avoid phrenic nerve palsy (PNP). Freezing was immediately discontinued if weakening or loss of diaphragmatic movement was noted during tactile sense. Transthoracic echocardiography was performed after the procedure to exclude pericardial effusion. Oral anticoagulation with warfarin or novel oral anticoagulants were started in the same evening of ablation and continued for at least 3 months or longer according to the CHA_2DS_2-VASc score. Antiarrhythmic drugs at the discretion of the investigator were allowed during the 3-month blanking period but were discontinued at the end of the blanking period. In the case of recurrence, antiarrhythmic treatment was reordered and a redo procedure was suggested if symptoms persisted.

Table 1: Baseline demographic, clinical and laboratory characteristics

	No Bonus Group (n=56)	Bonus Group (n=80)	P value
Age (years)	58 (48-67)	62 (49-68)	0.299
Male, n (%)	32 (57)	44 (55)	0.862
Male, n (%)	32 (57)	44 (55)	0.862
Hypertension, n (%)	25 (45)	35 (44)	1.000
Diabetes mellitus, n (%)	7 (13)	8 (10)	0.782
Hyperlipidemia, n (%)	14 (25)	19 (24)	1.000
Smoking, n (%)	21 (27)	20 (21)	0.539
Coronary artery disease, n (%)	7 (13)	9 (11)	1.000
CHA_2DS_2-VASc score	1.1 ± 1.3 / 1.0 (0-2.0)	1.1 ± 1.2 / 1.0 (0-2.0)	1.000
AF duration (months)	36 (24-48)	42 (24-60)	0.167
Hemoglobin (gr/dl)	14 (12-15)	14 (13-16)	0.090
Creatinine (mg/dl)	0.9 (0.7-1.0)	0.9 (0.7-1.0)	0.837
Left ventricular EF (%)	57 (54-66)	56 (54-66)	0.599
Left atrial diameter (mm)	38 (36-42)	39 (36-42)	0.312
Antiarrhythmic drug			
Propafenone, n (%)	44 (79)	65 (81)	0.828
Amiodarone, n (%)	9 (16)	12 (15)	1.000
Sotalol, n (%)	3 (5)	3 (4)	0.690

AF, atrial fibrillation; EF, ejection fraction
For continuous variables, the data were presented as median (25th and 75th interquartile ranges).
CHA2DS2-VASc score was also presented as mean ± SD.

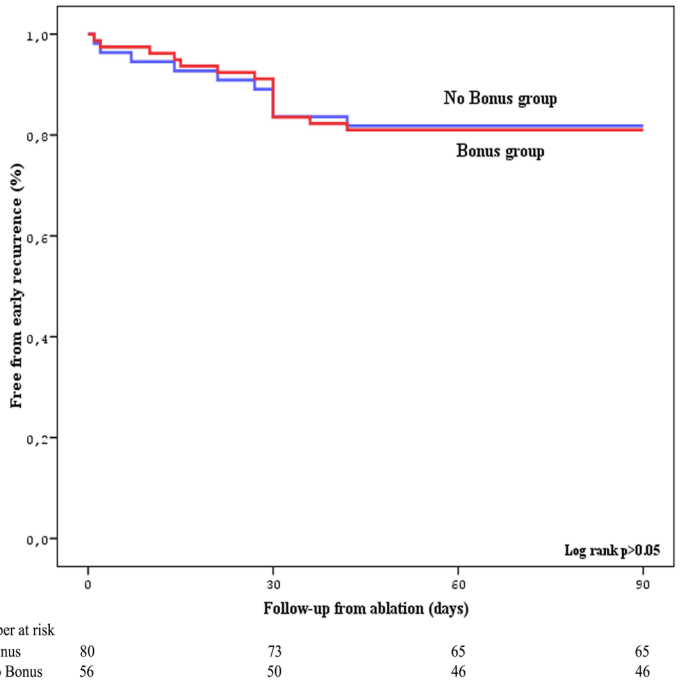

Figure 1: Kaplan-Meier curves of the freedom from any ATs recurrence in the blanking period.

Follow-up

All patients underwent continuous ECG monitoring during hospital stay. After discharge from the hospital, all patients were scheduled for follow-up visits at 1, 3, 6, 12 months, and biannually thereafter. Baseline ECG and 24-hour Holter recordings were obtained at each follow-up visit, and also during symptom driven admission. All documented atrial tachyarrhythmia (ATs) episodes of >30 seconds beyond the blanking period by ECG or Holter monitoring were considered as a recurrence. All recordings were blindly analyzed

and reviewed by experienced electrophysiologists. Time to first recurrence of symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia lasting >30 seconds documented by ECG or Holter monitoring was the primary efficacy outcome. Serious adverse events related to the procedure were also recorded.

Statistical analysis

The primary objective of this study was to demonstrate the efficacy of no bonus application during cryoballoon PVI compared to bonus application. Continuous variables were compared using the T test or Mann-Whitney test for independent samples and categorical variables were compared using the X2 or Fisher's tests as appropriate. Continuous variables were expressed as mean ± SD and median values with interquartile ranges. Data were presented as frequencies and percentages for categorical variables. Cox regression analysis was performed and presented as hazard ratios (HRs) with 95% confidence intervals. Event rates were plotted over time using Kaplan-Meier method. In addition to primary analysis, patients who suffered from a recurrence within the 3-month blanking period were recorded as having had the primary event at the beginning of the follow-up period. All analyses were performed using SPSS 17.0. A P value of ≤0.05 was considered significant.

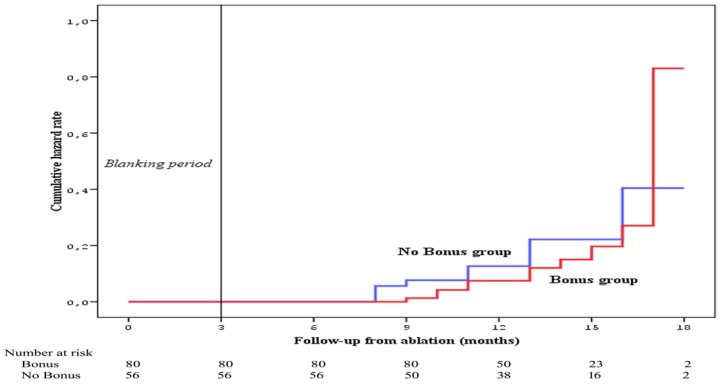

Figure 2: Kaplan-Meier curves of time to first recurrence of any ATs after the blinking period.

Results

Baseline characteristics

In total, 136 consecutive patients (mean age 58 ± 13 years, 76 male [56%]) were included in the study. No Bonus group consisted of 56 patients who did not have additional cryoablation whereas Bonus group was comprised of 80 patients who did have additional ablation. [Table 1] gives baseline demographic and clinical characteristics of the study population. No differences were found in regard to demographic, laboratory and echocardiographic findings.

Procedural characteristics

In 136 patients, a total of 529 PVs including 17 left common PVs, 1 right common PV and 3 right accessory PVs were detected. In total, 523 of 529 (99%) PVs were successfully isolated. After initial freeze application, PVI was observed in 104 of 119 (87%) left superior PVs, 100 of 119 (84%) left inferior PVs, 115 of 135 (85%) right superior PVs, 97 of 135 (72%) right inferior PVs, 8 of 17 (47%) left common PVs, 3 of 3 (100%) right accessory PVs, with no isolation of 1 right common PV.

In No Bonus group, 290 cryoablations were performed on 217 PVs (1.34 ablation per PV). The PVI rate after the initial ablation was 82%. In Bonus group, 722 cryoablations were performed on 312 PVs

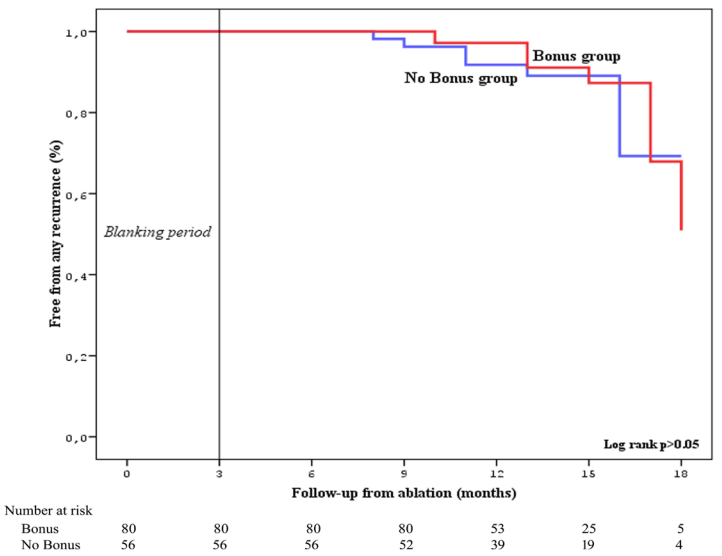

Figure 3: Kaplan-Meier curves of the freedom from any ATs recurrence after a redo procedure.

(2.31 ablation per PV). After the first application, PVI was achieved in 80% of PVs. No differences could be observed regarding first application isolation rate (p>0.05). Study population in the current study underwent cryoballoon isolation performed by senior operators and also arrhythmia fellows. Therefore, the PVI rate after the first application was rather low. The procedure and fluoroscopy times in No Bonus group were significantly shorter compared to procedure and fluoroscopy times in Bonus group. Cavo-tricuspid isthmus ablation was performed in 7% of the population ([Table 2]).

Complications

The most frequent complication observed was PNP during PVI. The occurrence of PNP was observed less frequently in No Bonus group compared to Bonus group, without statistically significant difference. All PNPs were resolved during follow-up. Four patients, all in Bonus group, showed resolution before discharge. One patient in Bonus group and 1 patient in No Bonus group showed PNP recovery at 1 and 6 months after ablation respectively. One patient developed femoral pseudoaneurysm without surgical intervention and one patient had pericardial tamponade requiring pericardiocentesis in Bonus group during the catheter manipulation. No other procedure-related complications were noted ([Table 2]).

Efficacy outcomes

The median time to the first early recurrence was 27 (12-30) days. There was no significant difference between Bonus and No Bonus groups, 30 (14-30) days vs 24 (6-30) days, p>0.05, respectively. The freedom from early recurrence was 82% in No Bonus group compared to 81% in Bonus group ([Figure 1]).

The mean follow-up duration after the 3-month blanking period in No Bonus group was 12 ± 3 months and 13 ± 3 months in Bonus group (p>0.05). During follow-up, recurrence of any ATs occurred in 10 patients (18%) in No Bonus group compared with 13 patients (16%) in Bonus group (HR, 0.72; 95%CI, 0.31-1.67; p = 0.440; [Figure 2]).

With including recurrences in the blanking period, recurrence of any ATs occurred in 15 patients (27%) in No Bonus group compared with 25 patients (31%) in Bonus group (HR, 0.96; 95%CI, 0.50-1.84; p = 0.898).

Table 2: Procedural parameters and adverse events

	No Bonus Group (n=56)	Bonus Group (n=80)	P value
Anatomic characteristics			
Voltage Points (N)	1479	145	146
Percentages of voltage points (%)	100	9.8	9.9
Number of Critical points ≥ (n, %)	526	0	146, (27.8 %)
PV number per patient*	4 (3-5) / 4 (4-4)	4 (3-5) / 4 (4-4)	0.709
Anomalous PV, n (%)	9 (16)	12 (15)	1.000
Total number of PVs	217	312	
Procedural characteristics			
Total number of cryoballoon	290	722	
The number of cryoballoon per PV	1.3 (1-1.5)	2 (2-2.5)	<0.001
Acute procedural success, n (%)	215/217 (99)	308/312 (99)	1.000
Nadir temperature (°C)			
LSPV	48 (46-51)	49 (45-52)	0.573
LIPV	46 (44-49)	46 (44-49)	0.301
RSPV	48 (46-50)	47 (45-49)	0.224
RIPV	44 (43-47)	45 (43-48)	0.105
LCPV	50 (49-52)	48 (47-52)	0.225
RCPV¶	47	-	-
RAPV¶	46	46 and 44	-
Time to isolation (seconds)			
LSPV	38 (32-49)	38 (32-52)	0.931
LIPV	40 (33-51)	40 (33-53)	0.903
RSPV	37 (30-48)	36 (29-49)	0.914
RIPV	41 (34-56)	41 (34-54)	0.964
LCPV	64 (50-73)	44 (38-54)	0.107
RCPV	No recording	-	-
RAPV☐	28	No recordings	-
Real-time PVI, n (%)			
LSPV	35 (71)	49 (70)	0.866
LIPV	34 (69)	48 (69)	0.925
RSPV	38 (69)	56 (70)	0.910
RIPV	36 (66)	54 (68)	0.804
LCPV	4 (57)	7 (70)	0.644
RCPV	No recording	-	-
RAPV	1(2)	No recordings	-
Procedure duration (minutes)	67 (60-74)	85 (76-90)	<0.001
Fluoroscopy duration (minutes)	13 (10-15)	17 (15-21)	<0.001
CTI ablation, n (%)	5 (9)	5 (6)	0.740
Complications			
Phrenic nerve palsy, n (%)	1 (2)	5 (6)	0.400
Pericardial effusion requiring			
pericardiocentesis, n (%)	0	1 (1)	1.000
Access site complication, n (%)	0	1 (1)	1.000
Death, n	0	0	-
Systemic embolism, n	0	0	-

CTI, cavo-tricuspid isthmus; LCPV, left common PV; LIPV, left inferior PV; LSPV, left superior PV; PV, pulmonary vein; RAPV, right accessory PV; RCPV, right common PV; RIPV, right inferior PV; RSPV, right superior PV
For continuous variables, the data were presented as median (25th and 75th interquartile ranges).
*First numbers are single mean value with lower and upper values.
¶Exact temperatures for each patient.

Exact time to isolation.

A redo procedure was performed in 5 patients in No Bonus group, and 6 patients in Bonus group. A cavo-tricuspid isthmus dependent atrial flutter was present in one patient in No Bonus group. Radiofrequency ablation of the isthmus with demonstration of bidirectional block was performed. All remaining redo procedures were also cryoballoon isolation using the CB-Adv with previously described no bonus technique. The median reconnected vein number was 1 (1-2) in No Bonus group compared to 1 (1-1) in Bonus group (p>0.05). In No Bonus group, 3 of 6 (50%) reconnected PVs were right inferior PV, 1 was right superior PV, 1 was left inferior PV, and 1 was left common PV. In Bonus group, 4 of 7 (57%) reconnected PVs were right inferior PV, 1 was right superior PV, 1 was left superior PV, and 1 was left common PV. The mean time to redo procedure was 8 ± 3 months with no difference between the two groups (p>0.05). After the second procedure, the mean follow-up time was 4 ± 1 months with no difference between the two groups (p>0.05). After the redo procedure, 88% of patients in No Bonus group and 89% of patients in Bonus group were free from any recurrent ATs ([Figure 3]).

Discussion

The main findings of our study were as follows:
(1) The rate of sinus rhythm during 18-month follow-up period in patients who received no additional cryoablation was high and similar to patients who received a bonus freeze after proven isolation.
(2) The most common complication was PNP and, it occurred more frequently with routine use of a bonus freeze application.
(3) Mean fluoroscopy and procedural times were significantly lower with no bonus freeze application.

Previous single-center studies applying different numbers of freezing cycles on the use of the second generation CB demonstrated different results.[7]-[9] In earlier studies on applying one or two additional freeze applications following proven PVI, PNP was observed more frequently during the second bonus freeze.[10], [11] Accordingly, the reduction of the freeze cycle times may contribute to the avoidance of potential serious complications.

The novel second-generation CB redesigned to improve procedural outcomes significantly. The number of injection ports has been doubled, from 4 to 8 and these have been positioned more distally. These changes result in a large cooling area lying between the equator and the tip with a consequent more homogeneous zone of freezing on the balloon surface compared to the previous version.[8], [9], [11], [12] In a conventional ablation procedure using a second generation CB, repeat freeze cycle is deployed on the PV once successful isolation has been demonstrated. However, in the current study, the rate of sinus rhythm at 18 months was similar in patients who received additional cryoablation vs those who did not. Considering the findings from the present study, the routine use of an insurance freeze application may not be essential.

Our results are consistent with a recent study by Wisner at al.[13] The authors have concluded that with implementing a 'no bonus' freeze protocol, 82% of patients treated with the second generation CB remained free from ATs during a follow-up period of 1 year, similar to our results. The mean procedure duration was 113 minutes and the average fluoroscopy time was 19 minutes. It was, however, a study

conducted without a comparison group. Therefore, they underlined that the procedure duration and fluoroscopy time were lower than previously reported from their laboratory utilizing a single-bonus freeze cycle per PV by 16 minutes and 5 minutes, respectively while procedural success rates were similar in both groups. In Wisner's observation, PNP developed 2% of patients during the second freeze-cycle, which was lower than earlier studies.[9], [11], [13] In the current study, PNP was observed less frequently with no bonus freeze protocol. However, there was no statistically significant difference. Presumably, the sample size was relatively small and larger studies may demonstrate a statistical significance.

The rationale to utilize no additional freeze cycle after proven PVI is based on recent observations reporting a single application success rate ranging from 84% to 90%.[14], [15] Similarly in our study, we demonstrated an overall 81% isolation rate during the initial 240 seconds freeze cycle.

Recently, Ciconte at al. have demonstrated encouraging 1-year follow-up results applying single 3-minute freeze cycle. In their observation, a single 3-minute strategy showed equal efficacy compared to the conventional 4-minute plus bonus freeze approach at 1-year follow-up, providing shorter procedure and fluoroscopy times.[16] Our results extending beyond 1 year have also demonstrated that PVI without bonus freeze was highly effective with and without redo procedure as 88% and 82% in sinus rhythm, respectively.

Study limitations

This study also has limitations. First, this was a single center retrospective trial enrolling a relatively limited number of patients. Follow-up was limited to ECG and 24-hour Holter recordings without using extended methods such as longer Holter recordings, external loop recorders and implantable devices, might have resulted in underestimation of asymptomatic cases and potentially affecting the primary outcome. In addition, we had no data regarding PV stenosis and esophageal temperature during the procedure. Future multicenter and randomized studies with long-term follow-up are necessary to confirm our findings.

Conclusion

A single 240 seconds application per vein using the second generation CB strategy seems to show equal efficacy compared to the conventional 240 seconds plus bonus freeze approach in 18-month follow-up. Furthermore, this shortened CB ablation protocol significantly reduced procedure time with lower fluoroscopy exposure. Whilst the optimal ablation duration has to be defined, it becomes more evident that further cryoenergy applications if isolation is already proven during the first freeze, may not be necessary. Further randomized studies are needed to confirm these promising results.

Conflict Of Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Disclosures

None.

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