Received: 26 July 2021 | Revised: 17 December 2021 | Accepted: 1 January 2022

DOI: 10.1111/jce.15383

ORIGINAL ARTICLES

WILEY

Pulmonary vein isolation using cryoballoon ablation versus RF ablation using ablation index following the CLOSE protocol: A prospective randomized trial

Cathrin Theis MD | Bastian Kaiser MD | Philipp Kaesemann MD | Felix Hui MD | Giancarlo Pirozzolo MD | Raffi Bekeredjian MD | Carola Huber MD

Department of Cardiology, Robert Bosch Hospital Stuttgart, Stuttgart, Germany

Correspondence
Cathrin Theis, MD, Department of Internal Medicine 3, Cardiology/Electrophysiology, Robert Bosch Hospital Stuttgart, Auerbachstr. 101, 70376 Stuttgart, Germany.
Email: cathrin.theis@rbk.de

Disclosures: None.

Abstract

Background: The single procedure success rates of durable pulmonary vein isolation (PVI) for paroxysmal atrial fibrillation (AF) vary between 80% and 90%. This prospective, randomized study investigated the efficacy of cryoballoon PVI (CBA) versus PVI with radio-frequency (RF)-energy following the CLOSE protocol (ablation index [AI], interlesion distance ≤6 mm, surround flow catheter) in terms of single-procedure arrhythmia-free outcome and safety.

Methods and Results: A total number of 150 patients undergoing de novo catheter ablation for paroxysmal AF were randomized to two different treatment arms. In group A patients, PVI was performed with the 23 or 28 mm cryoballoon (Artic Front™ Balloon in conjunction with an Achieve Mapping Catheter, Medtronic Inc.). The ablation procedure in group B was performed with RF-energy, using AI and following the CLOSE protocol. PVI using AI incorporates stability, contact force (CF), time, and power. The CLOSE protocol combines AI and ≤6 mm interlesion distance using a surround flow catheter (Biosense Webster Thermocool STSF). A total of 75 patients were randomized into each group without significant differences in baseline characteristics. During a mean follow-up of 12 ± 4.5 months after a single procedure, 64 (85.33%) patients of group A were free of arrhythmia recurrence versus 65 (86.67%) patients in group B (p = ns). A total of 14 patients (group A: 7 [9.33%]; group B: 7 [9.33%]; p = ns) underwent a redo-procedure. No significant difference between both groups was observed in terms of PV recovery (group A: 4 [5.33%] vs. group B: 3 [4%]; p = ns). In two patients of group A and four patients of group B, the PVs were durably isolated, whereas the patients had AF recurrence caused by extra-PV AF sources. Two patients of each group had continued paroxysmal AF but did not undergo redo-procedure. Patients of group A showed significantly more AF recurrence during the blanking period of 3 months (group A: 14 [18.67%] vs. group B: 6 [8%]; $p < .05$). With regard to the procedural data, the procedure time was significantly shorter in group A (70.53 ± 16.13 vs. 115.35 ± 15.38; $p < .01$); the

Presented in part at the Annual Meeting of the European Heart Rhythm Association, EHRA 2021 Online Congress from April 23–25, 2021, and published in abstract form (*EP Europace Journal*, supplement).

flouroscopy time and dose area product showed no significant differences (Table 2). Both procedures were performed with a low number of complications; no pericardial effusion was seen in either group; in group A two patients had a significant hematoma of the groin with the need for surgical repair.

Conclusions: Cryoballoon PVI and PVI using ablation index following the CLOSE protocol are equally efficient in achieving durable PV isolation. In this study, cryoballoon ablation led to significantly more AF recurrence during the blanking period.

KEYWORDS

atrial fibrillation, catheter ablation, CLOSE protocol, Cryoballoon ablation

1 | INTRODUCTION

Pulmonary vein isolation (PVI) has become the cornerstone of the interventional treatment of paroxysmal trial fibrillation (PAF). Durable PVI is necessary to prevent arrhythmia recurrence. Despite intensive research during the past 15 years in the field of catheter ablation for PAF, recurrence rates after PVI remain as high as 10%–25% after a single procedure even in highly experienced centers.[1–3] The main reason for recurrence of atrial fibrillation (AF) after PVI basically is a recovery of initially isolated PVs. Thus, efforts to overcome these limitations have been focused on techniques to enhance the durability of PV isolation. The recent introduction of contact force catheters, AI, and the CLOSE protocol to encircle the PVs has been established to improve the contiguity of the lesions and lesion size and therefore, an enhanced PVI.[4–6]

Cryoballoon ablation (CBA) has emerged as an alternative to radio-frequency (RF) ablation of PAF.[7] PVI performed with the second-generation cryoballoon (CB) has been successful in achieving durable PVI and is comparable with RF ablation.[8] A proper position of the cryoballoon to establish a good surface-tissue contact as well as a short time to isolation improve the outcomes after PVI.[9] Several studies have compared CBA with RF ablation with similar results. Whereas CBA shows a lower rate of pericardial effusion but, with a higher incidence of nerve palsies.[10]

The aim of the present study was to compare cryoballon ablation with the second-generation cryoballon to RF ablation using the CLOSE protocol in regard to long-term durable PVI and procedural data.

2 | METHODS

2.1 | Study population

This prospective, randomized analysis comprised a total of 150 patients with symptomatic PAF. The mean age was 61.62 ± 11.84 years in group A and 66.11 ± 8.86 in group B. All patients were referred for an interventional treatment of PAF. A detailed diagnostic work-up was performed in our outpatient department before admission. All antiarrhythmic drugs, with the exception of amiodarone, were ceased at least five half-lives before the procedure. The study was approved by the institutional review board and ethics committee and all patients provided written informed consent.

2.2 | Study protocol

Paroxysmal AF was defined according to the current guidelines. However, patients with AF episodes lasting >48 h or requiring electrical cardioversion later than 48 h after the onset of AF were excluded from the study. All patients were characterized by self-terminating episodes with at least one documentation in Holter-ECG.

2.3 | Ablation procedure

For both groups, the procedures were performed under sedation with propofol infusion. The presence of left atrial thrombi was excluded by transesophageal echocardiography in the electrophysiological laboratory directly before the procedure. Access to left atrium was achieved by a single transseptal puncture. A single bolus of 5000 IU of heparin was administered before transseptal puncture. After transseptal puncture, an additional bolus of 5000–10 000 IU of heparin was added, according to the patient´s body weight. The activated clotting time was assessed every 30 min and maintained within a range of 250–350 s. A temperature probe (S-CATH M; Circa Scientific) was positioned in the esophagus and the endoluminal temperature was monitored throughout the procedure.

2.3.1 | Group A

A steerable decapolar catheter (Biosense Webster) was introduced via the right femoral vein and positioned within the coronary sinus. CBA was performed with the second- generation Arctic Front™ Cryo Ablation System, the FlexCath steerable sheath, and the Achieve inner lumen mapping catheter (Medtronic Inc.). A 23 or 28 mm CB

was used; for every PV the occlusion was documented by contrast application and the absence of a leakage. A freeze time of 240 s was conducted for each PV; additional applications were performed to achieve PVI, if necessary. If a time-to-isolation of less than 30 s was documented, the freeze time was reduced to 180 s. Whenever possible, the PV potentials were monitored by means of the inner lumen mapping catheter and time to isolation was documented. To avoid phrenic nerve injury, the phrenic nerve was monitored continuously during ablation and the thaw period of the right veins by pacing in the superior vena cava. In case of esophageal temperature fall below 20°C, ablation was stopped immediately. PVI was confirmed by entrance- and exit-block of the PVs using a circular mapping catheter. Touch-up ablation was performed if an isolation of the PVs was not achieved after CBA.

2.3.2 | Group B

The following catheters were introduced via a right femoral vein access: (1) A steerable decapolar catheter (Biosense Webster) was positioned within the coronary sinus; (2) a circumferential decapolar diagnostic catheter (Lasso NAV 15 or 10 mm; Biosense-Webster) for mapping of the pulmonary vein ostia; and (3) a 3.5 mm externally irrigated-tip, surround flow ablation catheter with contact force measurement (Thermocool STSF; Biosense-Webster). For anatomical guidance, a three-dimensional reconstruction of the left atrium and the PVs was created using the Carto 3 system (Biosense Webster). PVI was performed following the CLOSE protocol: point-by-point RF delivery was performed with an interlesion distance of ≤6 mm to achieve a contiguous circle enclosing the ipsilateral veins. Real-time automated display of RF applications (VISITAG^{TM}, Carto 3; Biosense Webster) was used with predefined settings of catheter stability (3 mm for 8 s) and minimum CF (30% of time >4 g). RF application was continued until an ablation index (AI) of 380 at the posterior wall and 480 at the anterior wall was reached. Ablation index was determined by a tailored approach for the workflow of the operator recommended and performed by Biosense Webster.

In the absence of first pass PVI after completion of the ipsilateral circle, PVI was accomplished with additional RF applications upon the discretion of the operator.

PVI was confirmed by entrance- and exit-block of the PVs using a circular mapping catheter. RF was delivered in a power-controlled mode without ramping with 30 W (irrigation flow: 8 ml/min) with the SmartAblate generator and pump; Biosense Webster).

In case of esophageal temperature rise above 39°C, ablation at the posterior wall was stopped immediately. To achieve complete isolation the circle resp. the energy level was modified to avoid esophageal temperature rise. After PVI a waiting period of 20 min was obtained. Early reconnection was treated with touch-up ablation until PVI was reached.

Troponin levels were measured the day after the procedure in all the patients to display myocardial injury after ablation.

2.4 | Follow-up

In all patients a total follow-up of 12 months was performed; a 48 h Holter-ECG was performed every 3 months. A detailed history of the patients' symptoms suggestive of potential arrhythmia recurrences was taken. In case of undocumented symptoms suspicious for arrhythmia recurrences, documentation by additional external ECG event recordings was performed. A documented symptomatic or asymptomatic arrhythmia episode lasting >30 s was defined as recurrence.

An initial blanking period of 3 months was accepted. The antiarrhythmic drug treatment was not re-initiated after ablation. If patients experienced an early recurrence within the initial three months after the procedure, antiarrhythmic drugs were re-initiated for the remaining time of the blanking period. However, all antiarrhythmic drugs were ceased at the end of the blanking period. Patients with an arrhythmia recurrence after the blanking period were considered procedural failure.

The primary study endpoint was freedom from any atrial tachyarrhythmia occurring after the blanking period during a follow-up of at least 12 months. Secondary endpoints were procedural complications and PV recovery during redo procedures.

The study was approved by the local ethics committee and performed according to the Declaration of Helsinki.

2.5 | Statistical analysis

All continuous variables are reported as mean ± SD and/or medians with ranges, while categorical variables were summarized as proportions. Categorical variables were compared using the χ^2 test. Comparison between groups was performed with either Student's t test or the χ^2 test. Statistical significance was established at p value < .05. Time to arrhythmia recurrence was estimated using the Kaplan–Meier method and compared by the log-rank test.

To observe a difference with a power of 0.8 and an α level of .05, the inclusion of 59 patients in each group was estimated. The power calculation was performed with the G*Power 3.1 program (University of Duesseldorf). Multivariate analysis by means of a logistic regression model and stepwise backward selection was performed to identify significant and independent predictors of AF inducibility and arrhythmia persistence after completion of PVI. Independent variables were chosen when a $p < .10$ emerged on univariate analysis. Statistical analysis was performed with a statistical software package (SPSS, version 27; IBM).

3 | RESULTS

A total number of 150 consecutive patients undergoing de novo catheter ablation for paroxysmal AF were analyzed. Patient characteristics were well-balanced except for the age, the anticoagulation

with Vitamin K Antagonist, and electrical cardioversion. Those parameters were significantly lower in group A and are displayed in Table 1. The prescribed electrical cardioversions were performed before ablation within 48 h after the onset of AF. Left atrial diameter was measured in all patients and showed no significant differences (group A: 3.9 ± 0.2 vs. group B: 4.1 ± 0.3). In both groups some patients were on antiarrhythmic drug treatment before the procedure (group A [CBA]: Class Ic: 3; Dronedaron: 2; Amiodaron: 2; group B [CLOSE protocol]: Class Ic: 3; Dronedaron: 2, Amiodaron: 4) (Table 1).

TABLE 1 Baseline characteristics

	Group A (Cryoballoon)	Group B (CLOSE protocol)	*p* value
Age (years)	61.62 ± 11.84	66.11 ± 8.86	.01
Male (%)	41 (55%)	45 (60%)	.87
BMI	27.19 ± 3.78	27.17 ± 4.26	.97
AHT (*n*)	44 (59%)	55 (73%)	.45
EF (%)	55.74 ± 4.46	56.4 ± 5.38	.42
Left atrial diameter (cm)	3.9 ± 0.2	4.1 ± 0.3	.54
valv HD (*n*)	1 (1.3%)	3 (4%)	.77
CHD (*n*)	6 (8%)	10 (13.3%)	.88
Stroke (*n*)	4 (5.3%)	7 (9.3%)	.87
CHADS-Vasc-Score	1.77 ± 1.58	2.15 ± 1.74	.17
ECV prior ablation, within 48 h after onset (*n*)	6 (8%)	18 (24%)	.04
NOAK (*n*)	69 (92%)	68 (91%)	.84
Vitamin K antagonist (*n*)	1 (1.3%)	7 (9.3%)	.03
AADs (*n*)	7 (9.33%)	9 (12%)	.76
Class I agent	3 (4%)	3 (4%)	.98
Class III agent	4 (5.33%)	2 (2.67%)	.69

Note: The data are presented as mean ± SD or *n* (%).

Abbreviations: AAD, antiarrhythmic drug treatment; AHT, arterial hypertension; BMI, Body mass index; CHADS, congestive heart failure hypertension age Diabetes mellitus stroke; CHD, coronary heart disease; ECV, electrical cardioversion; EF, LV ejection fraction; valv HD, valvular heart disease; NOAK, non vitamin K antagonist oral anticoagulants.

3.1 | Procedural results

Electrical isolation of the PVs was achieved in all patients. The mean procedure duration was significantly shorter in group A: 70.53 ± 16.13 min versus 115.35 ± 15.38 min in group B ($p < .01$). Mean fluoroscopy time and dose area product showed no significant differences: group A: 8.56 ± 3.18 min/390 ± 268.57 cGy/cm^2 versus group B: 9.66 ± 3.86 min/330.84 ± 150.36 cGy/cm^2 ($p = .06/.10$) (Table 2).

In CBA in all but one patient the 28 mm CB was used. No touch-up ablation in the CBA group was performed as PVI was achieved in every patient solely with CBA. The ablation parameters are displayed in Table 3a.

In the RF ablation group first pass isolation was achieved in 69 (92%) patients for the left circles and in 69 (94.67%) for the right circles. Eleven touch-up ablations for the left circles and eight touch-up ablations for the right circles were necessary to achieve PVI (Figure 4). Ablation time and further procedural data are displayed in Table 3b.

Abbreviation: RF, radio-frequency ablation

For RFA a waiting period of 20 min was performed as recurrence during the procedure is more often in RFA as compared with CBA.

The measured troponin levels the day after ablation were significantly higher in the CBA group, indicating a more pronounced myocardial injury, most possibly due to the larger surface of abladed tissue by the cryoballoon (Figure 1).

Oral anticoagulation was performed in every patient after the ablation procedure for at least 3 months. After 3 months the OAK was either stopped or continued according to the CHA_2DS_2-VASc-Score of the individual patient.

3.2 | Primary endpoint: 12-month follow-up

All patients completed the per protocol endpoint of a 12-month follow-up. The Kaplan–Meier 1-year arrhythmia-free survival estimation revealed no significant differences concerning the arrhythmia-free survival estimation during an overall mean follow-up of 12 ± 4.5 months after a single procedure: group A: 85.33% versus group B: 86.67%, p = ns. The first endpoint was defined as off any antiarrhythmic drugs. In group A, arrhythmia recurrences were

TABLE 2 Procedural data

	Group A (Cryoballoon)	Group B (CLOSE protocol)	*p* value
Procedural time (min)	70.53 ± 16.13	115.35 ± 15.38	<.01
Fluoro time (min)	8.56 ± 3.18	9.66 ± 3.86	.06
Dose area product (cGy/cm^2)	390.34 ± 268.57	330.84 ± 150.36	.10

TABLE 3a Procedural data of CB ablation

	LSPV	LIPV	RSPV	RIPV
No. of freezes per vein (*n*)	1.3 ± 0.6	1.1 ± 0.4	1.3 ± 0.5	1.1 ± 0.4
Time to isolation (s)	46.8 ± 26.9	42.8 ± 33.9	69.5 ± 44.1	63.9 ± 51.8
TTI achieved, *n* (%)	42 (56)	42 (56)	31 (41.33)	26 (34.67)
Minimal balloon temp (°C)	49.0 ± 11.3	47.3 ± 7.5	50.3 ± 12.6	49.0 ± 13.2
Ave esophageal temp (°C)	29.0 ± 12.3	28.1 ± 12.5	32.1 ± 10.2	30.8 ± 10.4
No. of phrenic nerve palsy (*n*)	0	0	4	3
Esophageal temp <20°C (*n*)	8	11	1	4
No PV leakage (*n*)	56	53	48	47
Pull down (*n*)	0	10	15	18

Abbreviation: CB, cryoballoon; LIPV, left inferior pulmonary vein; LSPV, left superior pulmoary vein; PV, pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; TTI, time to isolation.

TABLE 3b Procedural data of RF ablation (CLOSE protocol)

	Left circles	Right circles
RF ablation time (min)	21 ± 6	18 ± 5
RF tags (mean ± SD)	48 ± 9	45 ± 7
Ablation index achieved (%)	92	96
First pass isolation, *n* (%)	69 (92)	71 (94.67)
Touch-up applications (*n*)	11	8
Ave power (W)	28.9 ± 2.4	26.6 ± 4.2
Perimeter (mm)	32 ± 6	31 ± 4

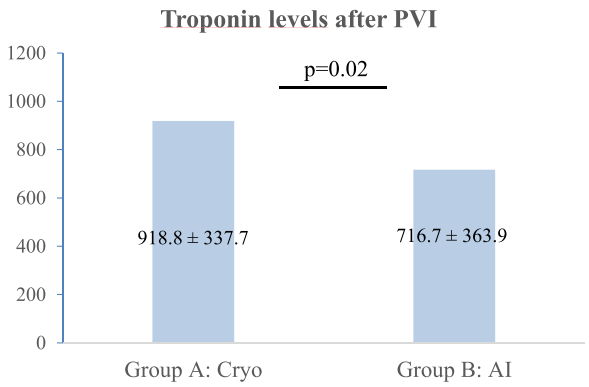

FIGURE 1 Troponin levels (pg/ml) 24 h after PVI. PVI, pulmonary vein isolation.

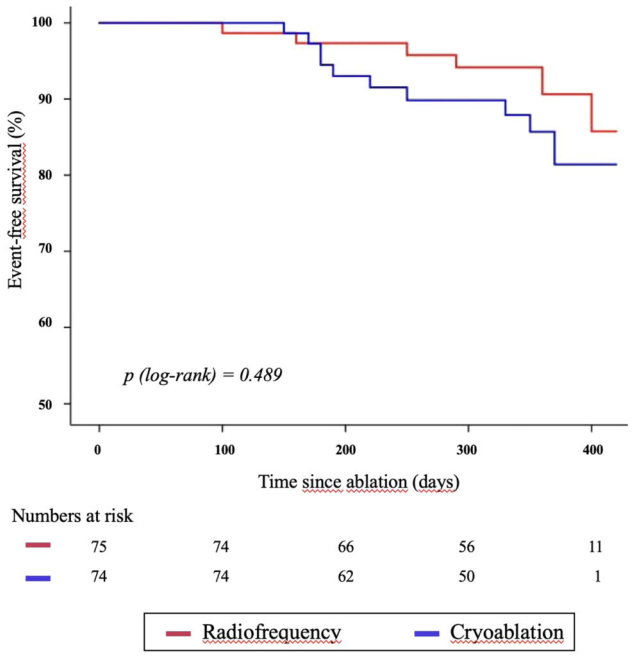

FIGURE 2 Kaplan–Meier arrhythmia-free survival estimation during an overall mean follow-up of 12 ± 4.5 months after a single procedure. No significant differences concerning the outcome based on a follow-up of 12 ± 4.5 months were seen

characterized as paroxysmal AF in eight (10.67%) and persistent AF in three (4%) patients. Recurrences occurred in group B patients as paroxysmal AF in six (8%) patients and persistent AF in four (5.33%) patients (Figure 2).

Significantly more patients of group A showed AF recurrence during the blanking period: group A: 14 (18.67%) versus group B: 6 (8%); $p < .05$ (Figure 3).

3.3 | Secondary endpoint: Electrophysiological findings during repeat procedures and complications

A total of 14 patients underwent repeat ablation (group A: 7 [9.33%] patients, group B: 7 [9.33%] patients). The rate of PV recovery, displayed as PV recovery per PV, during repeat procedures showed no significant differences in both groups (group A: 4 [5.33%] vs. group B: 3 [4%]; p = ns) (Table 4).

In both groups a re-isolation of the pulmonary veins was performed if PV recovery was seen. If the PVs were still isolated at the

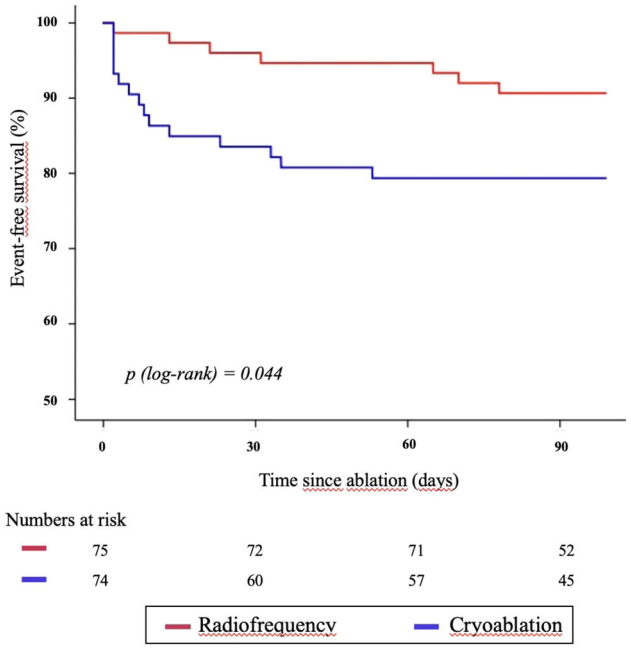

FIGURE 3 Kaplan–Meier arrhythmia-free survival estimation during the blanking period of 3 months. Patients with radiofrequency ablation (CLOSE protocol) had a significantly better outcome as compared with the patients with Cryoablation ($p = .044$ based on 3 months of follow-up)

TABLE 4 Recurrence AF types and repeat procedures

	Group A (Cryoballoon)	Group B (CLOSE protocol)	*p* value
Recurrence at 3 months	14 (18.67%)	6 (8%)	.044
Recurrence at 6 months	11 (14.67%)	10 (13.33%)	.89
PAF at 6 months	8 (10.67%)	6 (8%)	.67
PersAF at 6 months	3 (4%)	4 (5.33%)	.78
Redos	7 (9.33%)	7 (9.33%)	.99
PV recovery (*n*)	4 (5.33%)	3 (4%)	.86

Abbreviation: AF, atrial fibrillation; PAF, paroxysmal trial fibrillation; PV, pulmonary vein.

time of the repeat procedure, a substrate modification resp. electrogram-guided ablation was performed to terminate AF.

The PV recovery sites at redo procedures are displayed in Figure 4.

A univariate and multivariate analysis of the baseline parameters and procedural data was performed an showed no significant results.

No pericardial effusions, thromboembolic events, or atrio-esophageal fistula occurred. Two patients in group A suffered from significant hematoma of the groin, requiring surgical repair. The mean hospital stay was 24 ± 8 h.

4 | DISCUSSION

4.1 | Main findings

The presented study revealed the following key findings: (1) The arrhythmia-free survival is equally efficient in CBA and RF ablation using the CLOSE protocol. (2) The procedural time is significantly lower in CBA. (3) In this study, significantly more AF recurrence occurs after CBA during the blanking period.

4.2 | Strategies to achieve durable PV isolation

The PVs are the predominant source of PAF and electrical PV isolation is the cornerstone of catheter ablation for PAF.[11] Arrhythmia recurrences after ablation are mainly attributed to electrical PV reconnection with a strong correlation between the clinical magnitude of arrhythmia recurrences and the number of atrial-to-vein conduction recovery of the PVs.[12] Thus, significant efforts were made to develop techniques and tools that may help to enhance the durability of PVI after a single procedure. In this attempt, several different strategies were investigated, such as elimination of dormant conduction induced by adenosine, the implementation of a waiting period after PVI, contact force-guided ablation (TOCCATA),[13] and implementing AI following the CLOSE protocol, respectively. AI and the CLOSE protocol increased the rate of durable PVI significantly as compared with previous ablation strategies.[6] In this study we also showed a high rate (>90%) of durable PVI after one procedure.

A number of studies have demonstrated the efficacy of CBA for the treatment of PAF[14,15]; however, RF ablation has improved significantly with implementing CF, AI, and the interlesion distance. Few randomized studies comparing CBA of the second generation with RF ablation with AI and the CLOSE protocol were conducted. In the present study, we demonstrate equally efficient results in terms of the primary endpoint of freedom of any atrial arrhythmia and a durable PVI of more than 90% in both groups.

In addition to efficacy, some other factors should be taken into account, such as safety, procedural time, and fluoroscopy time. Concerning safety, both procedures were performed with very low complication rates. Two significant groin complications occurred after CBA, whereas the RF group showed no relevant complications. Procedure time was significantly shorter in CBA, as some other studies have reported as well.[16] Flouro time was slightly shorter in CBA, whereas the dose area product was higher (not significant), which is due to the need for higher resolution to prove balloon occlusion.

Early AF recurrence during the blanking period was significantly higher in the CBA group, most likely due to a more extensive myocardial injury. The troponin levels, measured the day after the PVI, were significantly higher in the CBA group (group A: 918.79 ± 337.66 pg/ml vs. group B: 716.68 ± 363.87 pg/ml; $p = .02$), which is supporting the more extensive myocardial injury. Buzianowski et al. reported that troponin levels after CBA are an independent predictor of early recurrence of AF.[17,18] In our study early recurrence did not have an impact on long-term freedom of AF.

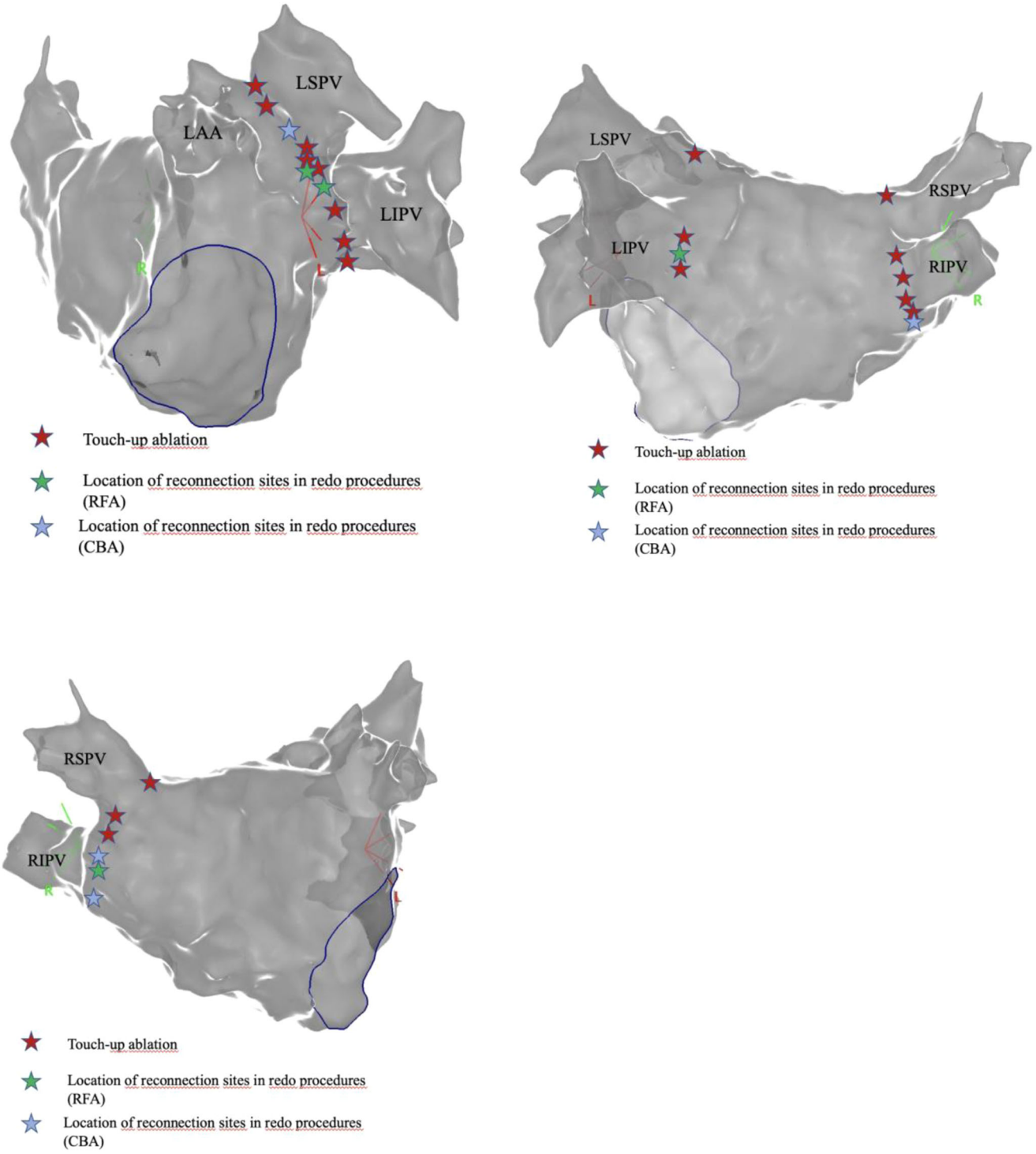

FIGURE 4 Sites of touch-up ablation in group B and location of reconnection sites in redo procedures after CBA and CLOSE protocol. CBA, cryoballoon ablation

5 | CONCLUSIONS

Cryoballoon PVI and PVI using ablation index following the CLOSE protocol are equally efficient in achieving durable PV isolation. In his study, CBA led to significantly more AF recurrence during the blanking period.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Cathrin Theis https://orcid.org/0000-0001-5442-4464

REFERENCES

1. Cappato R, Negroni S, Pecora D, et al. Prospective assessment of late conduction recurrence across radiofrequency lesion producing electrical disconnection at the pulmonary vein ostium in patients with atrial fibrillation. *Circulation*. 2003;108:1599-1604.
2. Cappato R, Calkins H, Chen SA, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2010;3:32-38.
3. Nanthakumar K, Plumb VJ, Epstein AE, Veenhuyzen GD, Link D, Kay GN. Resumption of electrical conduction in previously isolated pulmonary veins: rationale for a different strategy? *Circulation*. 2004; 109:1226-1229.
4. Kautzner J, Neuzil P, Lambert H, et al. EFFICAS II: optimization of contact force improves outcome of pulmonary vein isolation for paroxysmal atrial fibrillation. *Europace*. 2015;17:1229-1235.
5. Das M, Loveday JJ, Wynn GJ, et al. Ablation index, a novel marker of ablation lesion quality: prediction of pulmonary vein reconnection at repeat electrophysiological study and regional differences in target values. *Europace*. 2017;19:775-783.
6. Duytschaever M, de Pooter J, Demolder A, et al. Long-term impact of catheter ablation on arrhythmia burden in low-risk patients with paroxysmal atrial fibrillation: the CLOSE to CURE study. *Heart Rhythm*. 2020;17:535-543.
7. Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol*. 2013;61:11713-11723.
8. Kuck KH, Fürnkranz A, Chun KRJ, et al. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality.of.life outcomes in the FIRE AND ICE trial. *Eur Heart J*. 2016;37:2858-2865.
9. Ciconte G, Mugnai G, Sieira J, et al. On the quest for the best freeze: predictors of late pulmonary vein reconnections after second-generation cryoballoon ablation. *Circ Arrhythm Electrophysiol*. 2015; 8:1359-1365.
10. Knecht S, Sticherling C, von Felten S, et al. Long-term comparison of cryoballoon and radiofrequency ablationof paroxysmal atrial fibrillation: a propensity score matched analysis. *Int J Cardiol*. 2014; 176:645-650.
11. Cheema A, Dong J, Dalal D, et al. Incidence and time course of early recovery of pulmonary vein conduction after catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2007;18:387-391.
12. Verma A, Kilicaslan F, Pisano E, et al. Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. *Circulation*. 2005;112(5):627-35.
13. Reddy VY, Shah D, Kautzner J, et al. The relationship between contact force and clinical outcome during radiofrequency catheter ablation of atrial fibrillation in the TOCCATA study. *Heart Rhythm*. 2012;9:1789-1795.
14. Luik A, Radzewitz A, Kieser M, et al. Cryoballoon versus open irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2015;132:1311-1319.
15. Kuck KH, Fürnkranz A, Chun JKR, et al. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. *Eur Heart J*. 2016;37:2858-2865.
16. Mugnai G, Chierchia GB, de Asmundis C, et al. Comparison of pulmonary vein isolation using cryoballoon versus conventional radiofrequency for paroxysmal atrial fibrillation. *Am J Cardiol*. 2014;113: 1509-1513.
17. Budzianowski J, Hiczkiewicz J, Burchardt P, et al. Predictors of early recurrence following cryoballoon ablation of pulmonary veins using statistical assessment and amchine learning algorithms. *Heart Vessels*. 2019;34:352-359.
18. Tokuda M, Yamashita S, Matsuo S, et al. Clinical significance of early recurrence of atrial fibrillation after cryoballoon vs. radiofrequency ablation—a propensity score matched analysis. *PLoS ONE*. 2019; 14(7):e0219269.

How to cite this article: Theis C, Kaiser B, Kaesemann P, et al. Pulmonary vein isolation using cryoballoon ablation versus RF ablation using ablation index following the CLOSE protocol: a prospective randomized trial. *J Cardiovasc Electrophysiol*. 2022;33:866-873. doi:10.1111/jce.15383