Cool enough? Lessons learned from cryoballoon-guided catheter ablation for atrial fibrillation in young adults

Leonard Bergau MD1 | Mustapha El Hamriti MD1 | Kerstin Rubarth MSc2,3 | Lilas Dagher MD4 | Stephan Molatta MD1 | Martin Braun MD1 | Moneeb Khalaph MD1 | Guram Imnadze MD1 | Georg Nölker MD5 | Claus P. Nowak MSc2,3 | Henrik Fox MD6 | Philipp Sommer MD1 | Christian Sohns MD1

1Clinic for Electrophysiology, Herz- und Diabeteszentrum Nordrhein-Westfalen, Ruhr-Universität Bochum, Bad Oeynhausen, Germany
2Institute of Biometry and Clinical Epidemiology, Charité-Universitätsmedizin Berlin, Berlin, Germany
3Berlin Institute of Health (BIH), Berlin, Germany
4Department of Cardiology, Tulane University School of Medicine, New Orleans, Louisiana, USA
5Clinic for Cardiology, Katharinen-Hospital Unna, Unna, Germany
6Clinic for Thoracic and Cardiovascular Surgery and Heart Failure Department, Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Bad Oeynhausen, Germany

Correspondence
Christian Sohns, MD, Clinic for Electrophysiology, Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Georgstr.11, 32545 Bad Oeynhausen, Germany.
Email: csohns@hdz-nrw.de

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WOA Institution: Ruhr-Universität Bochum

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Abstract

Introduction: Cryoballoon (CB)-guided ablation of atrial fibrillation (AF) is established in symptomatic AF patients. This study sought to determine the safety and efficacy of CB pulmonary vein isolation (PVI) in young adults.

Methods and Results: A total of 93 consecutive patients aged <45 years referred to our center for AF ablation were included in this observational study. All patients received CB-guided PVI according to a standardized institutional protocol. Follow-up was performed in our outpatient clinic using 72-h Holter monitoring and periodic telephone interview. Recurrence was defined as any AF/atrial tachycardia (AT) episode >30 s following a 3-month blanking period. A propensity matched control group consisting of patients older than 45 years were used for further evaluation. Mean age was 35 ± 7 years, 22% suffered from persistent AF, 85% were male. Mean follow-up was 2.6 ± 2 years. At the end of the observational period, 83% of patients were free of any AF/AT episodes. There was an excellent overall 12-month success rate of 92%. In comparison to a matched group the overall recurrence rate was noticeably lower in the young group (15% vs. 27%). Increasing age was associated with a hazard ratio of 1.16 for recurrence. In a multivariate analysis model, left atrial diameter remained as significant predictor of AF/AT recurrence. The complication rate was low, no permanent phrenic nerve palsy was observed.

Conclusion: CB-guided PVI in young adults is safe and effective with favorable long-term results. It may be considered as first-line therapy in this relatively healthy population.

KEYWORDS
complications, cryoballoon ablation, intracardiac ultrasound, lone atrial fibrillation, long-term success, pulmonary vein isolation, young adults

[Correction added on 17 February 2021, after first online publication: Projekt Deal funding statement has been added.]

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1 | INTRODUCTION

Pulmonary vein isolation (PVI) is considered as a first-line treatment in patients suffering from paroxysmal atrial fibrillation (AF) and is regularly performed in patients with drug-refractory AF. Besides the conventional approach using radiofrequency (RF) energy, cryoballoon (CB) has emerged as a promising technique for successful and durable PVI. In this context, the second generation CB (Arctic Front Advance™; Medtronic Inc., Minneapolis, MN, USA) was designed to further improve the acute efficacy of this single-shot device for PVI. While the general AF population tends to be old, a substantial part of AF patients reports symptoms suggesting AF or documented tachycardia episodes at earlier ages. Furthermore, the pathogenesis of AF might differ between young and older AF patients. In the latter, the underlying pathophysiology can be related to comorbidities, such as left ventricular dysfunction or coronary artery disease, resulting in left atrial (LA) fibrosis and remodeling. In young patients, diverse mechanisms including trigger foci in or in close relationship to the pulmonary veins (PVs), foci in the right and left atrium, as well as additional underlying arrhythmias may be responsible for the presence and maintenance of AF. The long-term effect of PVI in young adults on arrhythmia progression remains unclear. However, ablation strategies in younger AF patients in general consist of performing a PVI after ruling out supraventricular tachycardia (SVT)-triggered AF. Despite its limitation regarding ablation strategies beyond PVI, a single-shot device is a very useful tool to reliably create continuous lesions around the PVs. Based on these assumptions, personalized paths in AF management, especially in young patients, are warranted and deserve further investigation. Therefore, this study sought to determine the acute and long-term effect of CB-guided PVI in young adults and to identify predictors of AF/atrial tachycardia (AT) recurrence following catheter ablation in this specific patient cohort.

2 | METHODS

This observational single-center analysis consists of symptomatic AF patients aged <45 years and scheduled for CB-guided PVI at our institution between 2012 and 2018. Written informed consent was obtained from each patient before the procedure. The study was reviewed and approved by our local institutional review board and conducted in accordance with the Declaration of Helsinki. In all patients, documented AF by 12-lead ECG, Holter ECG or during continuous monitoring via an implanted device was a prerequisite for catheter ablation. All patients were routinely scheduled in our outpatient clinic 3, 6, and 12 months following the intervention. Thereafter, structured telephone interviews were scheduled. If any history of AT/SVT was suspected, an electrophysiologic (EP) study was conducted before AF ablation and AT or SVT ablation was performed, if necessary. The CB ablation was then indicated in case of a persistence of AF following a successful SVT- ablation or in case of failure to induce another tachycardia during the EP study.

Transesophageal echocardiography was routinely performed before ablation to rule out LA thrombus formation. Furthermore, ECG-guided contrast enhanced computer tomography or MR imaging of the LA was utilized to identify variants in PV or LA anatomy and to determine the ostial PV diameter. If already present, oral anticoagulation with phenprocoumon was continued with a target international normalized ratio of 2.0–2.5. Direct oral anticoagulants (DOACs) were discontinued on the day of the procedure and resumed the same day after ruling out pericardial effusion. Oral anticoagulation was continued or stopped 3 months after the ablation procedure according to the patients’ CHA2DS2-Vasc score. Antiarrhythmic drugs following the intervention were prescribed, if indicated.

As reported previously, all procedures were performed under conscious sedation using propofol, fentanyl, and/or midazolam. Intravenous heparin was administered to maintain an activated clotting time of 300 s throughout the whole procedure. A programmed atrial stimulation according to our local protocol was performed in the majority of cases. After positioning a decapolar catheter in the coronary sinus (CS), transseptal puncture was performed under fluoroscopic guidance or by using intracardiac echocardiography (ICE; AcuNav Acuson™; Siemens AG, Erlangen, Germany). Afterwards, a steerable sheath (Flexcath®; Medtronic Inc.) was advanced into the LA. A 28 mm (Arctic Front Advance; Medtronic Inc.) was used in most cases. The PV-occlusion was verified by contrast injection, freezing time was chosen between 240 and 360 s. A second freeze cycle was administered, if indicated. A multipolar mapping catheter (Achieve™; Medtronic Inc.) was introduced via the steerable sheath into each PV for verification of entrance and exit block. During freezing of the right-sided PVs, the phrenic nerve function was monitored by continuous pacing maneuvers. All patients were followed in our outpatient’s clinic 3, 6, and 12 months after the index procedure. All cardiac devices were interrogated and screened for AF episodes if such a device was implanted. At each visit, they were asked about arrhythmia-related symptoms or discomfort during respiration. Moreover, a 72-h Holter ECG was regularly performed in all patients. Following a 3-month blanking period, recurrence was defined as any symptomatic episode of AT/AF lasting >30 s.

2.1 | Statistical analysis

Continuous data are presented as a mean ± SE. Categorical variables are reported as frequencies (percentages). We performed a Cox proportional hazards regression with gender, age, body mass index (BMI), type of AF, LA diameter and CHA2DS2-Vasc score included as covariates. Kaplan–Meier curves were used to estimate event-free survival. In addition, as part of our exploratory analysis, we conducted a variable selection technique (Elastic Net) to identify relevant risk factors. Moreover, univariable Cox models for every explanatory variable were fit. All calculations were performed with the statistical analysis software R (R version 3.5.1). The factors of the
CHA2DS2-Vasc score were not included separately into the analysis model, except for the confounding variables of gender and age. Note that only a small number of recurrences occurred during the study and a relatively high number of factors was examined. Due to the relatively small sample size and the exploratory character of this study, we decided to counteract the problem of conducting multiple tests by using the Benjamini–Hochberg procedure, which controls the false discovery rate, not the family-wise error rate. Inspection of the Schoenfeld residual plots did not indicate a violation of the proportional hazard assumption.

For further exploration of the effect of age on event-free survival, we compared the results with a matched control group consisting of AF-patients older than 45 years.

3 | RESULTS

3.1 | Patients’ characteristics

A total of 93 consecutive patients were included. The mean age was 35 ± 7 years, 78% of them had paroxysmal AF, while the remaining had persistent AF. Congestive heart failure was present in 10% of the participants, and 9% had structural heart disease. The mean LA diameter in echocardiography was 36 ± 7 mm. Routine use of vitamin K antagonists or DOACs was recommended in 20 patients (19%). A total of 61% of patients were overweight (BMI ≥ 26) and 17% were obese (BMI ≥ 30). All patients’ characteristics are listed in Table 1.

3.2 | Findings from previous EP study

An EP study was regularly performed before AF ablation. Atrioventricular (AV)-nodal reentrant tachycardia, a concealed AV reentrant tachycardia, and an ectopic AT were found in three, one, and three patients, respectively. Two of the ATs originated from the right atrium (crista terminalis and posterior CS ostium). Ablation of these arrhythmias was performed using a three-dimensional (3D) mapping system. The remainder was a left-sided tachycardia, which was initially treated with antiarrhythmic drugs. EP study failed to induce sustained tachycardia other than AF in remaining patients. Participants in our study had AF recurrences despite a successful treatment of their AT/SVT and were therefore scheduled to undergo an AF ablation procedure.

3.3 | Procedural data

The mean procedure duration was 111 ± 38 min, the mean fluoroscopy time was 10 ± 7, with a mean fluoroscopy dose of 1190 ± 1470 (cGy) × cm². The mean diameters of the PVs were measured as follows: left superior PV 17 ± 3 mm, left inferior PV 16 ± 4 mm, right superior PV 18 ± 4 mm, right inferior PV 18 ± 4 mm and in case of a left common trunk, which was present in 17 patients, we measured a mean diameter of 25 ± 9 mm. Acute procedural success, defined as entrance and exit block of all PVs, was achieved in all patients. The mean freezing duration per vein was 234 ± 92 s. The complication rate requiring intervention was low (1.92%): we observed one arteriovenous fistula and one mediastinal hematoma caused by a bleeding from the right pulmonary veins with self-tamponade. Of note, permanent palsy of the phrenic nerve and severe PV stenosis did not occur.

3.4 | Follow-up and freedom from arrhythmia recurrence

After 12 months of follow-up the recurrence rate was 8% (6/93). Regarding the whole follow-up period of 2.6 ± 2 years (median: 15 months, interquartile range: 11 months), 77/93 (83%) of the patients remained in stable sinus rhythm, of whom 6 (8%) were still on antiarrhythmic drug treatment. Of the patients with recurrence, 32% suffered of persistent AF. The Kaplan–Meier analysis revealed an estimated 1-year recurrence rate of 13%, and 25% for 5 years (Figure 1). In both univariate and multivariate analysis, an enlargement of the left atrium was associated with a significant higher risk of recurrence (univariate: hazard ratio [HR]: 1.10, 95% confidence interval [CI]: [1.02, 1.18]; multiple: HR: 1.15, 95% CI: [1.04, 1.26]; Tables 2 and 3). Persistent AF was associated with a nearly doubled risk of AF recurrence (HR: 1.83, [0.43, 7.74]). Only n = 2 of patients with recurrence showed a progression from paroxysmal AF to persistent AF. In contrast to the majority of patients, they initially presented with signs and symptoms of arrhythmia-induced cardiomyopathy and potential remodeling and/or fibrosis of the left atrium. The remainder maintained the same type of AF after recurrence compared with their baseline.

3.5 | Predictors for arrhythmia recurrence after successful PVI

In addition to the Cox models, we also performed an exploratory analysis of our data using a variable selection technique (Elastic Net) to further identify risk factors for recurrence. Using this penalized variable selection method, male sex, and persistent AF were identified as risk factors for recurrence in addition to an enlarged LA diameter.

3.6 | Comparison with historical control group

We performed a propensity matched analysis using logistic regression of age on relevant clinical parameters with a historical control group consisting of CB patients older than 45 years. Characteristics of the control group are depicted in Table 4. The difference of the LA diameter was accepted given the fact that both values are within the normal range.

The recurrence rate in the control group was 27% in contrast to a recurrence rate of 15% in the younger patients. Increasing age was
associated with an HR of 1.16 (95% CI: [0.60, 2.23]) for recurrence. The recurrence-free survival within the first 12 months following the index procedure is depicted in Figure 2. Due to a high number of censored results, the logrank test did not reach statistical difference ($p = .16$), however, the graph shows the statistical trend toward a beneficial outcome in the young.

## 4 | DISCUSSION

### 4.1 | Major findings

In this observational study we analyzed the efficacy and safety of PVI using the second-generation CB in young adults suffering from AF. We report three major findings:

First, PVI using the CB technique is safe and effective in young patients. Second, short- and long-term success rate by means of freedom from any AF/AT recurrence following CB-guided PVI is relatively high (~80%) and may therefore be suggested as a first-line ablation approach in this specific patient cohort. Third, young AF adults with findings suggestive of LA remodeling, such as a dilated LA diameter, are more likely to develop recurrent AF/AT following CB-guided PVI.

### 4.2 | Trigger arrhythmias, mechanisms, and substrates in young AF patients

An EP study was performed before AF ablation in most patients. An SVT was detected and successfully ablated in 7% of patients. Supraventricular arrhythmias triggering the initiation or maintenance of AF is a relatively common phenomenon in young adults and has been reported in up to 39% of young AF patients. Although it is still possible, that non-PV triggers were responsible for AF initiation in our patient cohort, a PV-dependent mechanism is the most likely mechanism. This might be a possible explanation for the acute and long-term success rate of CB ablation in these patients.

### 4.3 | Procedural considerations performing CB-guided PVI in young adults

Focusing on procedural data, procedure duration and freezing cycle length was comparable to other clinical studies, whereas the fluoroscopy time was lower than usually reported. This might be due to the widespread use of ICE to guide catheter ablation in our

### TABLE 1 Baseline characteristics and comparison of patients with and without recurrence

|                  | All  | No recurrence | Recurrence | $p$ Value |
|------------------|------|---------------|------------|-----------|
| Age (years)      | 35 ± 7 | 35 ± 0.5 | 33 ± 8 | .31 |
| BMI              | 28 ± 4 | 28 ± 5 | 28 ± 4 | .94 |
| Female sex       | 15 (16%) | 14 (18%) | 1 (6%) | .42 |
| Persistent AF    | 20 (22%) | 15 (20%) | 5 (31%) | .48 |
| Follow-up (months) | 24 ± 19 | 23 ± 19 | 30 ± 18 | .17 |
| Procedure time (min) | 111 ± 39 | 111 ± 40 | 115 ± 31 | .62 |
| Fluoroscopy time (min) | 9.8 ± 7.0 | 9.7 ± 7.1 | 10.1 ± 7.0 | .85 |
| Left atrial diameter (mm) | 36.0 ± 6.6 | 35.5 ± 6.1 | 38.7 ± 8.3 | .18 |
| Ejection fraction (%) | 53.7 ± 5.3 | 53.7 ± 5.6 | 53.8 ± 3.2 | .91 |
| Congestive heart failure | 9 (10%) | 7 (9%) | 2 (13%) | 1 |
| Arterial hypertension | 12 (13%) | 11 (14%) | 1 (6%) | .64 |
| Diabetes         | 1 (1%) | 1 (1%) | 0 (0%) | 1 |
| Stroke           | 3 (3%) | 3 (4%) | 0 (0%) | .98 |
| Vascular disease | 1 (1%) | 1 (1%) | 0 (0%) | 1 |
| CHA2DS2-Vasc score | 0.3 ± 0.7 | 0.3 ± 0.7 | 0.13 ± 0.3 | .31 |
| Beta-blockers    | 40 (43%) | 30 (39%) | 10 (63%) | .15 |
| Chronic phenprocoumon | 4 (4%) | 3 (6%) | 1 (4%) | 1 |
| Chronic DOAC     | 19 (20%) | 13 (17%) | 6 (38%) | .13 |

Note: The table contains means, standard errors, and $p$ values for comparing the patients with recurrence and without recurrence. Exploratory $p$ values were calculated by t-tests for metric and $\chi^2$ tests for categorical variables, for some of the variables no test could be calculated due to small sample sizes in one group.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; DOAC, direct oral anticoagulant.
Of note, CB-guided ablation was conducted with the 28-mm CB in most patients irrespective of the PV anatomy or diameter. Today, there is no clear evidence that PV anatomy has an important impact on predicting the success of a CB-guided PVI. As our study led to conclusive results regarding the short-term outcomes of CB-guided PVI, we aimed at comparing potential predictors of recurrence in this patient cohort in terms of univariate and multivariate regression analyses.

### Table 2: Univariate Regression Analysis of Potential Predictors

| Covariate                        | Hazard Ratio | 95% CI       | p Value |
|----------------------------------|--------------|--------------|---------|
| Female                           | 0.26         | [0.03, 2.00] | .20     |
| Age                              | 0.98         | [0.92, 1.05] | .62     |
| BMI                              | 1.02         | [0.92, 1.13] | .71     |
| Type of AF                       | 2.65         | [0.88, 8.00] | .08     |
| Left atrial diameter             | 1.10         | [1.02, 1.18] | .01*    |
| Left common pulmonary vein diameter | 0.84      | [0.61, 1.61] | .30     |
| Arterial hypertension            | 0.35         | [0.05, 2.71] | .32     |
| Congestive heart failure         | 2.19         | [0.48, 10.06] | .31     |
| CHA2DS2-Vasc score               | 0.52         | [0.14, 1.92] | .33     |

Note: LA diameter remained as a significant predictor of recurrence. Hazard ratios, 95% confidence intervals, and exploratory p values were obtained from the respective logrank tests.

### Table 3: Multivariate Regression Model

| Covariate                        | HR           | 95% CI         | p Value | p Value (BH) |
|----------------------------------|--------------|----------------|---------|--------------|
| Female                           | 0.32         | [0.04, 2.69]   | .29     | .41          |
| Age                              | 0.94         | [0.87, 1.02]   | .12     | .36          |
| BMI                              | 0.94         | [0.82, 1.07]   | .35     | .41          |
| Type of AF                       | 1.83         | [0.43, 7.74]   | .41     | .41          |
| Left atrial diameter             | 1.15         | [1.04, 1.26]   | .01     | .04*         |
| CHA2DS2-Vasc score               | 0.39         | [0.10, 1.58]   | .19     | .38          |

Note: Age and left atrial diameter remained as significant predictors for recurrence. Hazard ratios, 95% confidence intervals, unadjusted p values, and Benjamini–Hochberg adjusted p values.

Abbreviations: AF, atrial fibrillation; BH, Benjamini–Hochberg; BMI, body mass index; CI, confidence interval; HR, hazard ratio; *, significant.
and long-term outcome by means of freedom from AF/AT recurrence, the isolation of the PVs using a CB with a standardized size appears to be safe and feasible in young patients irrespective of the individual PV anatomy. This might be an advantage in contrast to RF-guided ablation, in which the PV anatomy can significantly influence procedural success.16

The overall complication rate was low, with no phrenic nerve palsy observed in our cohort. The frequency of this complication has been reported ranging from 4% to 13%.13,17 The reason for this low rate in our study is not entirely clear. One explanation could be that the phrenic nerve is more resistant to the effects of freezing in younger patients or that it recovers quickly after a transient or asymptomatic palsy immediately after abortion of the freeze cycle.

Furthermore, no PV stenosis was observed in our study. The mechanism of PV stenosis following CB ablation is caused by a combination of cellular damage, vascular damage, and immunologic phenomenon.18 According to the literature, the incidence of PV stenosis following CB ablation ranges between 0% and 7%.13,19 PV stenosis were related to a larger ostial diameter and a more distal application site in a study by Narui et al.20 There might be two possible explanations for this observation in our study. First, the utilization of ICE ensures a proximal application site in most freezing cycles. Second, considering that most PV stenosis following CB ablation remain asymptomatic,21 it simply might not have been detected.

### 4.4 When are single-shot devices useful in young AF patients?

This study reports a very good success rate of CB-guided AF ablation in young adults. Considering the whole observational period, 83% of the patients were free of any AT/AF recurrence. The 1-year recurrence rate was 8%. This is a relatively low rate compared with previously published data and could be explained by the fact that any underlying trigger arrhythmia was ruled out or treated before AF ablation, or by the performance of ablation at an early stage of AF. The vast majority of patients with arrhythmia recurrence suffered from AF. Of these patients (n=16), three received a second CB-guided PVI, six patients were scheduled for RF-guided PVI using a 3D mapping system and n=6 were treated with antiarrhythmic drug therapy. In all except one patient undergoing reablation, PV reconnection of at least one PV was observed. The remainder suffered from a scar-related and roof-dependent atrial macroreentrant tachycardia. Out of the patients with reablation, we noted three patients with recurrence, the remainder were free from arrhythmias since the last procedure. With a recurrence rate around 30% after 12 months, previous publications reported comparable midterm results of CB-guided AF ablation compared with conventional RF ablation.2,9,12,17 This might be explained by our relatively healthy patient cohort with low comorbidities and fibrotic burden. In a recent analysis by Saguner et al.,22 the 1-year success rate after CB-guided ablation in young patients was comparable (86%) too. However, only seven patients received CB-guided PVI in their study and this subgroup was too small to draw further conclusions. Two studies exist reporting the success of CB ablation in young patients.23,24 Moran et al.25 demonstrated a success rate of 88% from CB-guided PVI after a median follow-up of 18 months and De Regibus et al.23 showed a 1-year success rate of >90%. These reported results are in line with our findings from >100 patients and a follow-up time of 2 years. However, being only of borderline significance, our data indicates a favorable outcome in younger patients when compared with a matched control group of older age. This observation needs further prospective evaluation in a larger population warranting a sufficient event rate. In this context, our analysis added valuable information regarding the efficacy and success of CB-guided ablation in young patients, arrhythmia mechanism and substrate may differ in the general AF population.

Several observations have led to new insights in AF management and arrhythmia-associated cardiac remodeling. AF is a progressive disease that is not only a consequence of structural, hemodynamic, and electrophysiological remodeling, but also a cause of the same processes.4 One of the markers of LA remodeling is the dilation of the atrial structure in AF patients, which was also found to be a positive predictor of AF/AT recurrence in our study. LA fibrosis, a hallmark of atrial remodeling, has been discriminated as a relevant predictor of AF recurrence after successful catheter ablation.25 In this context, the recent study by Gramlich et al.26 demonstrated that

#### TABLE 4 Comparison of the control group with the matched cohort

|                  | All  | Controls | p Value |
|------------------|------|----------|---------|
| Age              | 35 ± 7 | 58 ± 7  | <.001*  |
| BMI              | 28 ± 4 | 27 ± 4  | .43     |
| Female sex       | 15 (16%) | (28%)  | .06     |
| Persistent AF    | 20 (22%) | (19%)  | .36     |
| Procedure time (min) | 111 ± 39 | 112 ± 37 | .91     |
| Fluoroscopy time (min) | 9.8 ± 7.0  | 15 ± 7  | <.001*  |
| Left atrial diameter (mm) | 36.0 ± 6.6 | 38 ± 5 | .03*    |
| Ejection fraction (%) | 53.7 ± 5.3 | 54 ± 3 | .30     |
| CHA2DS2-Vasc score | 0.3 ± 0.7  | 0.98 ± 0.9 | <.001* |
| Beta-blockers    | 40 (43%) | 51 (45%) | .91     |
| Chronic phenprocoumon | 4 (4%)    | 11 (10%) | .23     |
| Chronic DOAC     | 19 (20%) | 26 (23%) | .81     |

Note: The table contains means, standard errors, and p values for comparing the patient cohort with the matched control group. Exploratory p values were calculated by t-tests for metric and χ² tests for categorical variables.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; DOAC, direct oral anticoagulant; *, significant.
the presence of LA low-voltage areas significantly affected the success of CB-guided PVI.

A potential limitation of our analysis is the absence of evaluation of LA fibrosis extent in our patients before catheter ablation. Our analysis demonstrates that in young AF patients with a low arrhythmia burden and few comorbidities, a high success rate of AF ablation can be expected using a single-shot device, even without additional information from electroanatomical mapping. Irrespective of this observation, it remains of utmost importance to identify other trigger arrhythmias causing or maintaining AF in young patients. Our results fill the gap of evidence in terms of efficacy, safety, and long-term success of CB-guided AF ablation, exclusively in young patients.

5 | CONCLUSION

PVI using the second generation CB is safe and effective in young adults. A general utilization of a single-shot device as first-line therapy in this certain AF population might be considered, warranting further prospective evaluation.

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REFERENCES

1. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *EP Europace*. 2018;20(1):157-208.
2. Murray MI, Arnold A, Younis M, Varghese S, Zeiher AM. Cryoballoon versus radiofrequency ablation for paroxysmal atrial fibrillation: a meta-analysis of randomized controlled trials. *Clin Res Cardiol*. 2018;107(8):658-669.
3. Oyen N, Ranthe MF, Carstensen L, et al. Familial aggregation of lone atrial fibrillation in young persons. *J Am Coll Cardiol*. 2012;60(10):917-921.
4. Sohns C, Marrouche NF. Atrial fibrillation and cardiac fibrosis. *Eur Heart J*. 2020;41(10):1123-1131.
5. Hayashi K, An Y, Nagashima M, et al. Importance of nonpulmonary vein foci in catheter ablation for paroxysmal atrial fibrillation. *Heart Rhythm*. 2015;12(9):1918-1924.
6. Hung Y, Lo LW, Lin YJ, et al. Characteristics and long-term catheter ablation outcome in long-standing persistent atrial fibrillation.
patients with non-pulmonary vein triggers. Int J Cardiol. 2017;241:205-211.

7. Mohanty S, Mohanty P, Di Biase L, et al. Long-term follow-up of patients with paroxysmal atrial fibrillation and severe left atrial scarring: comparison between pulmonary vein antrum isolation only or pulmonary vein isolation combined with either scar homogenization or trigger ablation. J Am Coll Cardiol. 2017;69(24):2864-2876.

8. Neumann T, Vogt J, Schumacher B, et al. Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. J Am Coll Cardiol. 2008;52(4):273-278.

9. Vogt J, Heintze J, Gutleben KJ, Muntean B, Horstkotte D, Nölker G. Long-term outcomes after cryoballoon pulmonary vein isolation. J Am Coll Cardiol. 2013;61(16):1707-1712.

10. Nölker G, Heintze J, Gutleben K-J, et al. Cryoballoon pulmonary vein isolation supported by intracardiac echocardiography: integration of a nonfluoroscopic imaging technique in atrial fibrillation ablation. J Cardiovasc Electrophysiol. 2010;21(12):1325-1330.

11. Ceresnak SR, Liberman L, Silver ES, et al. Lone atrial fibrillation in the young—perhaps not so “lone”? J Pediatr. 2013;162(4):827-831.

12. Boveda S, Metzner A, Nguyen DQ, et al. Single-procedure outcomes and quality-of-life improvement 12 months post-cryoballoon ablation in persistent atrial fibrillation: results from the multicenter CRYO4PERSISTENT AF Trial. JACC Clin Electrophysiol. 2018;4(11):1440-1447.

13. Kuck K-H, Brugada J, Fürnkranz A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med. 2016;374(23):2235-2245.

14. Neumann T, Wójcik M, Berkowitsch A, et al. Cryoballoon ablation of paroxysmal atrial fibrillation: 5-year outcome after single procedure and predictors of success. Europace. 2013;15(8):1143-1149.

15. Khoueiry Z, Albenque JP, Providencia R, et al. Outcomes after cryoablation vs. radiofrequency in patients with paroxysmal atrial fibrillation: impact of pulmonary veins anatomy. Europace. 2016;18(9):1343-1351.

16. Sohns C, Sohns JM, Bergau L, et al. Pulmonary vein anatomy predicts freedom from atrial fibrillation using remote magnetic navigation for circumferential pulmonary vein ablation. Europace. 2013;15(8):1136-1142.

17. 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(16):1713-1723.

18. Avitall B, Kalinski A. Cryotherapy of cardiac arrhythmia: from basic science to the bedside. Heart Rhythm. 2015;12(10):2195-2203.

19. Matsuda J, Miyazaki S, Nakamura H, et al. Pulmonary vein stenosis after second-generation cryoballoon ablation. J Cardiovasc Electrophysiol. 2017;28(3):298-303.

20. Narui R, Tokuda M, Matsushima M, et al. Incidence and factors associated with the occurrence of pulmonary vein narrowing after cryoballoon ablation. Circ Arrhythm Electrophysiol. 2017;10(6):e004588.

21. Tokutake K, Tokuda M, Yamashita S, et al. Anatomical and procedural factors of severe pulmonary vein stenosis after cryoballoon pulmonary vein ablation. JACC Clin Electrophysiol. 2019;5(11):1303-1315.

22. Saguner AM, Maurer T, Wissner E, et al. Catheter ablation of atrial fibrillation in very young adults: a 5-year follow-up study. Europace. 2018;20(1):58-64.

23. De Regibus V, Mugnai G, Moran D, et al. Second-generation cryoballoon ablation in the setting of lone paroxysmal atrial fibrillation: single procedural outcome at 12 months. J Cardiovasc Electrophysiol. 2016;27(6):677-682.

24. Moran D, De Regibus V, de Asmundis C, et al. Second generation cryoballoon ablation for atrial fibrillation in young adults: midterm outcome in patients under 40 years of age. Europace. 2018;20(2):295-300.

25. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA. 2014;311(5):498-506.

26. Gramlich M, Maleck C, Marquardt J, et al. Cryoballoon ablation for persistent atrial fibrillation in patients without left atrial fibrosis. J Cardiovasc Electrophysiol. 2019;30(7):999-1004.

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