Experience and procedural efficacy of pulmonary vein isolation using the fourth and second generation cryoballoon: The shorter, the better?

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Abstract

**Background:** The second-generation cryoballoon (CB2) provides effective and durable pulmonary vein isolation (PVI) associated with encouraging clinical outcome. The novel fourth-generation cryoballoon (CB4) incorporates a 40% shorter distal tip. This design change may translate into an increased rate of PVI real-time signal recording, facilitating an individualized ablation strategy using the time to effect (TTE).

**Methods and Results:** Three hundred consecutive patients with paroxysmal or persistent atrial fibrillation were prospectively enrolled. The first 150 consecutive patients underwent CB2 based PVI (CB2 group) and the last 150 consecutive patients were treated with the CB4 (CB4 group). A total of 594/594 (100%, CB4) and 589/594 (99.2%, CB2) pulmonary veins (PVs) were successfully isolated utilizing the CB4 and CB2, respectively ($p = .283$). The real-time PVI visualization rate was 47% (CB4) and 39% (CB2; $p = .005$) and the mean freeze cycle duration 200 ± 90 s (CB4) and 228 ± 110 s (CB2; $p < .001$), respectively. The total procedure time did not differ between the groups (CB4: 64 ± 32 min) and (CB2: 62 ± 29 min, $p = .370$). No differences in periprocedural complications were detected.

**Conclusions:** A higher rate of real-time electrical PV recordings are seen using the CB4 as compared to CB2, which may facilitate an individualized ablation strategy using the TTE.

**Keywords**
acute efficacy, atrial fibrillation, cryoballoon, pulmonary vein isolation
1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults. Current AF guidelines recommend the rhythm control strategy for symptoms and quality of life improvement in patients, stating that pulmonary vein isolation (PVI) performed using either radiofrequency (RF), or cryoballoon (CB) catheters should be the standard choice. For the treatment of patients with paroxysmal AF (PAF), the FIRE AND ICE trial demonstrated noninferiority of CB-based PVI versus RF-based PVI in terms of efficacy and safety. Different CB ablation strategies may apply a fixed freeze cycle duration of 180–240 s, often followed by a bonus-freeze cycle. However, ablation protocols have recently been modified aiming at shorter and fewer CB applications and demonstrated comparable clinical outcomes. The latest strategies introduced the time to effect (TTE), defining the time to PVI, as an essential indicator for durable PVI. By preventing a proximal positioning of the circular mapping catheter, the long distal tip of the second-generation cryoballoon (CB2) limits the optimal recording of PV signals, possibly leading to a limited use of the TTE strategy. To increase the rate of real-time PV recordings, the third-generation cryoballoon (CB3; Arctic Front Advance ST; Medtronic Inc.) was designed with a 40% shorter tip, facilitating a more proximal spiral catheter position. In consequence, several studies demonstrated a significantly higher rate of real-time PV recordings when utilizing the CB3 compared to CB2. However, acute and 1-year efficacy was similar for both systems. Thus, the CB3 did not pass the limited market release. The novel fourth-generation CB (CB4; Artic Front Advance Pro; Medtronic Inc.), also with a 40% shortened tip compared to the CB2, aims at better catheter maneuverability and improved recording of PV signals. The purpose of this prospective analysis was to assess the procedural efficacy and ablation characteristics of the CB4 in comparison to the CB2 for PVI in a large data setting.

2 | METHODS

2.1 | Inclusion and exclusion criteria

Three hundred consecutive patients with symptomatic, drug-refractory PAF or persistent AF were consented for CB-based PVI and prospectively enrolled. The first 150 consecutive patients treated with the CB2 (CB2 group) served as a control group, the last 150 consecutive patients were treated with the CB4 (CB4 group). The patients were not randomized. Exclusion criteria were prior left atrial (LA) ablation attempts, an LA diameter >60 mm, severe valvular heart disease or contraindications to postinterventional oral anticoagulation. Transesophageal echocardiography was performed in all patients before PVI to rule out intracardiac thrombi and to assess the LA diameter. No further preprocedural imaging was performed. In patients on vitamin K antagonists the procedure was performed under therapeutic INR values of 2–3. In patients on new oral anticoagulants the morning dose on the day of the procedure was omitted. All patients gave written informed consent and all patient information was anonymized. The study was approved by the local ethics committee (Lübeck ablation registry ethical review board number: WF-028/15) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

2.2 | Intraprocedural management

Our intraprocedural management has been described in detail before. Briefly, the procedure was performed under deep sedation using midazolam, fentanyl, and propofol. Two ultrasound guided right femoral vein punctures were performed and two 8F short sheaths were inserted. Before transseptal puncture (TSP) a diagnostic catheter (7F, Biosense Webster, Inc.) was introduced via the right femoral vein and positioned in the coronary sinus. A single TSP was performed under fluoroscopic guidance using a modified Brockenbrough technique and an 8.5F transseptal sheath (SL1; St. Jude Medical, Inc.). After TSP injection of contrast medium was performed to confirm LA access. Selective PV angiography was then performed to identify the pulmonary vein (PV) ostia utilizing a 7F multipurpose catheter or directly via the transseptal sheath. The transseptal sheath was exchanged over a guidewire for the 15F Flexcath Advance sheath. The sheath was continuously flushed with heparinized saline (20 ml/h). After TSP heparin boluses were administered targeting an activated clotting time of >300 s. In all patients, an esophageal temperature probe (Sensitherm; St Jude Medical, Inc. or CIRCA S-CATH™) was inserted and positioned according to the individual CB position to facilitate esophageal temperature monitoring during energy delivery. The intraluminal esophageal temperature cut-off was set at 15°C. During energy delivery along the septal PVs, continuous phrenic nerve pacing at maximum output and pulse width (12 mA, 2.9 ms) at a cycle length of 1000 ms was performed, using a diagnostic catheter positioned in the superior vena cava. Phrenic nerve capture was monitored by intermittent fluoroscopy and by tactile feedback of diaphragmatic contraction by the operator’s hand positioned on the patient’s abdomen. In addition, the continuous motor action potential (CMAP) was monitored. Refrigerant delivery was stopped immediately if weakening or loss of diaphragmatic movement, or the reduction of CMAP amplitude was noted. If phrenic nerve palsy (PNP) occurred, no additional freeze cycle was applied along the septal PVs.

2.3 | Cryoballoon-based PVI

The 28 mm CB2 was advanced into the LA via the 15 French steerable sheath and a spiral mapping catheter (20 mm diameter; Achieve, Medtronic, Inc.) was advanced into the target PV to record electrical activity. The occlusion of the PV ostium was verified by contrast dye injections. A pop-out phenomenon was defined by the observation of a balloon dislodgement from the PV ostium after initializing the freezing process.
This was evaluated by a second injection of contrast medium and fluoroscopy 5–10 s after initializing the freezing process. If stable occlusion was verified, the freeze cycle was continued; if the occlusion was not perfect the balloon was slightly repositioned and a third contrast dye injection was utilized to verify occlusion or the freeze cycle was stopped and a further attempt was made. The minimum CB cut-off temperature was set at −60°C.

The PVs were treated following a clockwise sequence (LSPV, LIPV, RIPV, RSPV). A gentle pull-down maneuver was performed for LIPV and RIPV after 70 s of freezing time. A time-to-effect based ablation protocol was utilized for both CB systems. The standard freeze cycle duration was 180 s. If the TTE could be recorded and was measured at <60 s the freeze cycle duration was set at 180 s and a bonus freeze application of 180 s was performed. If no TTE was measured a standard 180 s bonus freeze cycle was performed (Figure 2). The procedural endpoint was the disappearance of PV signals verified via the circular mapping catheter after the freeze cycle. A pop-out phenomenon was defined by the observation of a balloon dislocation from the PV ostium after initializing the freezing process. This was evaluated by a second injection of contrast medium and fluoroscopy 5–10 s after initializing the freezing process.

In patients demonstrating AF at the time of the procedure, electrical CV was performed after the final freeze cycle and PVI was reconfirmed in sinus rhythm. Cavotricuspid isthmus ablation using an open irrigated RF catheter (Celsius ThermoCool or ThermoCool SF, Biosense Webster) was only performed in patients with documented or induced common type atrial flutter.

### 2.4 Postprocedural care

A figure-of-eight suture and a pressure bandage were used to prevent femoral bleeding. The pressure bandage was removed after 4 h and the figure-of-eight suture was removed the next day. Following ablation, all patients underwent transthoracic echocardiography immediately, after 2 h, and at day 1 to rule out a pericardial effusion. Low molecular-weight heparin was administered in patients on vitamin K antagonists and an INR < 2.0 until a therapeutic INR of 2–3 was achieved. New oral anticoagulants were reinitiated 6 h post ablation. Anticoagulation was continued for at least 3 months and continued thereafter based on the individual CHA2DS2-VAASc score. Previously ineffective antiarrhythmic drugs or a new antiarrhythmic drug was prescribed and continued for 3 months post ablation. All patients were treated with proton-pump inhibitors for 6 weeks.

### 2.5 Statistical analysis

Continuous variables are presented as means and SDs; they were compared using Student’s t test. Categorical variables are presented as absolute and relative frequencies; they were compared using the \( \chi^2 \) test or Fisher’s exact test (in case of small expected cell frequencies). All \( p \) values are two-sided and a \( p \)-value < .05 was considered statistically significant. All calculations were performed with the statistical analysis software SAS (version 9.3; SAS Institute Inc.).

### 3 RESULTS

#### 3.1 Patient characteristics

A total of 300 consecutive patients underwent 28 mm CB-based PVI utilizing the CB2 (\( n = 150 \)) or CB4 (\( n = 150 \)). Patient baseline characteristics are depicted in Table 1. No demographic differences were apparent between the groups.

| TABLE 1 | Baseline patient characteristics |
|----------|---------------------------------|
|          | CB4    | CB2    | \( p \) |
| Patients (n) | 150    | 150    | .263  |
| Age (years)  | 67 ± 11 | 66 ± 11 | .132  |
| CHA2DS2-VAASc score | 1.9 ± 0.8 | 2.0 ± 1.0 | .989  |
| LA volume index (ml/m²) | 38 ± 16 | 37 ± 11 | .636  |
| Female gender | 61 (41) | 57 (38) | .728  |
| Paroxysmal AF | 69 (46) | 66 (44) | .380  |
| Congestive heart failure | 26 (17) | 32 (21) | .322  |
| Arterial hypertension | 106 (71) | 98 (65) | .497  |
| Diabetes mellitus type 2 | 22 (15) | 18 (12) | .892  |
| Coronary artery disease | 36 (24) | 35 (23) | .259  |
| AF duration (month) | 27 ± 35 | 30 ± 43 | .259  |

Note: Values are counts (n), \( n \) (%), or mean ± SD. Abbreviations: AF, atrial fibrillation; LA, left atrium.
3.2 | Acute ablation results

All PVs were successfully isolated using the CB4 (n = 594/594, 100%), whereas with the CB2 99.2% (n = 589/594) were isolated (p = .283). Real-time PVI was visualized in 47% of PVs using the CB4 and 39% of patients using the CB2 (p = .005) (Figure 1). Total freezing time was found to be statistically different between the groups (p < .001). There was a significant difference with regard to the mean minimum CB temperatures reached using the CB4 and CB2 (−46.6°C vs. −47.5°C, p = .031). However, no difference was found for the mean total number of CB freeze cycles per PV until PVI, the mean time to PVI, the total freeze time applied, or the mean minimum esophageal temperature (Table 2). Furthermore, no difference was observed for the mean procedure duration and mean fluoroscopy time. All procedures were performed by four operators highly experienced in CB ablation procedures. No differences were observed between CB2 and CB4 concerning catheter maneuverability and catheter stability along the targeted PVs.

3.3 | Acute ablation results per individual PV

Ablation data per individual PV is summarized in Table 3. Applying a TTE-guided ablation strategy, shorter mean freeze cycle durations were noted for the CB4 targeting the LIPV (191 ± 61 s vs. 226 ± 88 s, p < .001), the RSPV (192 ± 97 s vs. 235 ± 137 s, p = .002), and the RIPV (209 ± 95 s vs. 239 ± 121 s, p = .018); no difference was found for the LSPV. The rate of TTE recordings was statistically different for the RSPV utilizing the CB4 (62% vs. 29%, p = .002), whereas for the LSPV, LIPV, and RIPV no differences were found.

3.4 | Peri- and postprocedural complications

Major complications were defined as complications with surgical or interventional treatment, the necessity of blood transfusion due to low hemoglobin blood levels or patients sequela. Minor complications were defined as complications with no additional treatment patients sequela. Major complications occurred in two patients (1.3%) of the CB4 group and 0 patients (0%) of the CB2 group (p = .874). Details of periprocedural complications are shown in Table 3. Transient PNP occurred in 3/150 (2%) patients in the CB4 group during energy delivery targeting the RSPV, with full recovery of nerve function after 15 min. For the CB2 group 3/150 (2%) experienced PNP. Minor complications occurred in four patients (2.7%) of the CB4 group and eight patients (5.3%) of the CB2 group (p = .239). All pericardial effusions were asymptomatic and resolved during follow-up without sequelae. No cardiac tamponade, symptomatic PV stenosis or atrioesophageal fistula was observed.
The total freezing time was significantly shorter in the CB4 compared to the CB2. The rate of TTE recordings was significantly higher when using the CB4. The current study sought to compare the procedural efficacy and overall safety of CB2 and CB4. The new CB4 catheter, which was designed to improve the TTE recording rate, also showed a statistically significant increase in the percentage of live PV recordings using the novel catheter as compared to CB2. The present study confirms that the mean number of freeze cycles until PVI is similar for both CB2 and CB4-guided ablation procedures. With its shorter catheter length (8 vs. 13 mm) and similar technical properties, including the cooling specifications, when compared to CB2, the newer catheter failed to demonstrate any statistically significant differences in the 1-year clinical outcomes. The new CB4 catheter, which was designed to improve the TTE recording rate, also showed a statistically significant increase in the percentage of live PV recordings using the novel catheter as compared to CB2, but without reaching statistical significance. In our analysis, the CB4 group showed a statistically significant increase in the percentage of TTE recordings in comparison to the control group, which translated into a shorter total freezing time when using a TTE-based protocol. When analyzing the individual PVs, the significantly shorter total freezing time for the CB4 group was observed for the right PVs and the left inferior PV, while the increased rate of PV potential recordings is an essential prerequisite for the personalized TTE-guided ablation protocols. To achieve this requirement, the CB3 introduced the new catheter design. Even if the incidence of PVs with real-time signal recording was significantly higher when using CB3 compared to CB2, the newer catheter failed to demonstrate any statistically significant differences in the 1-year clinical outcomes. CB3 was taken from the European market, because of observed differences in minimal CB freeze temperatures most likely due to a changed position of the temperature probe of the CB3 to a more proximal position, which causes a minimally longer distance of the returning gas to the temperature probe and therefore higher returning gas temperatures.

The present study confirms that the mean number of freeze cycles until PVI is similar for both CB2 and CB4-guided ablation procedures. With its shorter catheter design, the CB4 allows better maneuverability, has recently been introduced into clinical practice. It provides a 40% shortened distal tip (8 vs. 13 mm) and similar technical properties, including the cooling specifications, when compared to CB2. The present study confirms that the mean number of freeze cycles until PVI is similar for both CB2 and CB4-guided ablation procedures. With its shorter catheter design, the CB4 allows better maneuverability, has recently been introduced into clinical practice. It provides a 40% shortened distal tip (8 vs. 13 mm) and similar technical properties, including the cooling specifications, when compared to CB2. The present study confirms that the mean number of freeze cycles until PVI is similar for both CB2 and CB4-guided ablation procedures. With its shorter catheter design, the CB4 allows better maneuverability, has recently been introduced into clinical practice. It provides a 40% shortened distal tip (8 vs. 13 mm) and similar technical properties, including the cooling specifications, when compared to CB2. The present study confirms that the mean number of freeze cycles until PVI is similar for both CB2 and CB4-guided ablation procedures. With its shorter catheter design, the CB4 allows better maneuverability, has recently been introduced into clinical practice. It provides a 40% shortened distal tip (8 vs. 13 mm) and similar technical properties, including the cooling specifications, when compared to CB2. The present study confirms that the mean number of freeze cycles until PVI is similar for both CB2 and CB4-guided ablation procedures. With its shorter catheter design, the CB4 allows better maneuverability, has recently been introduced into clinical practice. It provides a 40% shortened distal tip (8 vs. 13 mm) and similar technical properties, including the cooling specifications, when compared to CB2. The present study confirms that the mean number of freeze cycles until PVI is similar for both CB2 and CB4-guided ablation procedures. With its shorter catheter design, the CB4 allows better maneuverability, has recently been introduced into clinical practice. It provides a 40% shortened distal tip (8 vs. 13 mm) and similar technical properties, including the cooling specifications, when compared to CB2. The present study confirms that the mean number of freeze cycles until PVI is similar for both CB2 and CB4-guided ablation procedures. With its shorter catheter design, the CB4 allows better maneuverability, has recently been introduced into clinical practice. It provides a 40% shortened distal tip (8 vs. 13 mm) and similar technical properties, including the cooling specifications, when compared to CB2. The present study confirms that the mean number of freeze cycles until PVI is similar for both CB2 and CB4-guided ablation procedures. With its shorter catheter design, the CB4 allows better maneuverability, has recently been introduced into clinical practice. It provides a 40% shortened distal tip (8 vs. 13 mm) and similar technical properties, including the cooling specifications, when compared to CB2.
procedure time and total fluoroscopy time, the total amount of contrast was significantly lower in the CB4 group.

Characteristic complications of CB-based PVI such as PNP or a significant drop in intraluminal esophageal temperatures potentially resulting in esophageal thermal injury typically occur at later stages of the freeze cycles. In the current study, even though the total freezing time was significantly shorter in the CB4 group, the major and minor complications incidence was similar for both catheters. Thus, we confirm that the safety profile of CB4 is similar to that of the CB2. Further analyses should be conducted to assess the long-term effectiveness of the novel cryoballoon.

All procedures were performed by four highly experienced operators and no differences were observed with regard to catheter maneuverability and stability. Straube et al. analysed a total of 76 patients treated with the CB4. Although a high rate of real time recordings was observed (84.8%) they reported the necessity to exchange the spiral mapping catheter to a stiff wire in case of instable balloon positioning. They used the latest version of the Achieve catheter (Achieve Advance; Medtronic Inc), which is more flexible in its handling when compared to the previous version (Achieve; Medtronic). Since we only used the Achieve catheter, there was no need to use a stiff wire to improve CB alignment or stability. These findings are in line with other reports on the CB4 procedural characteristics.

### LIMITATIONS

The current study represents a single-center experience in a limited number of patients. However, this is the largest analysis focusing on the acute efficacy and safety of the CB4 compared to the CB2. No randomization has been performed. Yet, consecutive patients were prospectively evaluated in this study. Only acute efficacy and safety data are provided, while long-term clinical outcome will need future assessment.

### CONCLUSIONS

To the best of our knowledge this is the largest study reporting on the acute results of CB4-based PVI as compared to CB2. While demonstrating an identical acute efficacy for PVI, the CB4 provides a significantly increased rate of real-time PV-recordings and thus facilitates individual ablation strategies considering the TTE.

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### AUTHOR CONTRIBUTIONS

Concept/design, data collection, data analysis and interpretation, and drafting article: Christian-Hendrik Heeger. Critical revision and approval: Roza Meyer-Sarai, Vanessa Sciacca, Jan-Eric Bohnen.

| Table 3 Procedural details—Individual pulmonary veins | CB4 | CB2 | p |
|-----------------------------------------------------|-----|-----|---|
| LSPV | 144 | 144 | |
| Total CB cycles until PVI | 1.0 ± 0.2 | 1.1 ± 0.4 | .365 |
| Total CB cycles | 1.2 ± 0.5 | 1.2 ± 0.4 | .715 |
| Minimum CB temperature (°C) | −47.7 ± 5.7 | −49.2 ± 6.2 | .694 |
| Minimum esophageal temperature (°C) | 32.4 ± 4.8 | 32.6 ± 4.8 | .821 |
| Time to PVI (s) | 42.6 ± 19.9 | 42.5 ± 21.4 | .973 |
| TTE recordings | 92 (64) | 79 (55) | .199 |
| Total freezing time (s) | 210 ± 100 | 212 ± 86 | .902 |
| LIPV | 144 | 144 | |
| Total CB cycles until PVI | 1.0 ± 0.1 | 1.2 ± 0.4 | .377 |
| Total CB cycles | 1.1 ± 0.3 | 1.2 ± 0.4 | .107 |
| Minimum CB temperature (°C) | −44.3 ± 5.4 | −45.5 ± 6.2 | .264 |
| Minimum esophageal temperature (°C) | 30.2 ± 6.9 | 30.8 ± 6.8 | .124 |
| Time to PVI (s) | 33.8 ± 16.2 | 39.6 ± 22.5 | .288 |
| TTE recordings | 76 (53) | 66 (46) | .239 |
| Total freezing time (s) | 191 ± 61 | 226 ± 88 | <.001 |
| RSPV | 150 | 150 | |
| Total CB cycles until PVI | 1.1 ± 0.3 | 1.2 ± 0.5 | <.001 |
| Total CB cycles | 1.2 ± 0.5 | 1.3 ± 0.7 | .06 |
| Minimum CB temperature (°C) | −47.9 ± 9.7 | −48.5 ± 6.8 | .235 |
| Minimum esophageal temperature (°C) | 34.2 ± 6.1 | 34.4 ± 3.2 | .405 |
| Time to PVI (s) | 43.9 ± 33.1 | 36.1 ± 23 | .167 |
| TTE recordings | 62 (41) | 43 (29) | .021 |
| Total freezing time (s) | 192 ± 97 | 235 ± 137 | .002 |
| RIPV | 150 | 150 | |
| Total CB cycles until PVI | 1.1 ± 0.5 | 1.3 ± 0.5 | .081 |
| Total CB cycles | 1.2 ± 0.4 | 1.3 ± 0.6 | .012 |
| Minimum CB temperature (°C) | −45.7 ± 6.3 | −46.8 ± 7.0 | .176 |
| Minimum esophageal temperature (°C) | 33.4 ± 4.5 | 33.4 ± 4.4 | .829 |
| Time to PVI (s) | 55.7 ± 29.7 | 46.8 ± 28.7 | .169 |
| TTE recordings | 45 (30) | 40 (27) | .522 |
| Total freezing time (s) | 209 ± 95 | 239 ± 121 | .018 |

Note: Values are counts, n (%), mean ± SD.

Abbreviations: CB, cryoballoon; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PV, pulmonary vein; PVI, pulmonary vein isolation; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; temp., temperature; TTE, time to effect.
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**DATA AVAILABILITY STATEMENT**

The data will be available on request.

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**REFERENCES**

1. Hindricks G, Potpara T, Dagres N, et al. 2020. ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2020;42(5):373-498.

2. Kuck KH, Brugada J, Fünkranz A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med*. 2016;374(23):2235-2245.

3. Kuck KH, Fünkranz A, Chun KRJ, et al. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: rehospitalization, quality-of-life outcomes in the FIRE AND ICE trial. *Eur Heart J*. 2016;37(38):2858-2865.

4. Heeger CH, Wisser E, Wohlmuth P, et al. Bonus-freeze: benefit or risk? Two-year outcome and procedural comparison of a “bonus-freeze” and “no bonus-freeze” protocol using the second-generation cryoballoon for pulmonary vein isolation. *Clin Res*. 2016;105(9):774-782.

5. Chun KR, Stch M, Fünkranz A, et al. Individualized cryoballoon energy pulmonary vein isolation guided by real-time pulmonary vein recordings, the randomized ICE-T trial. *Heart Rhythm*. 2017;14(4):495-500.

6. Metzner A, Reissmann B, Rausch P, et al. One-year clinical outcome after pulmonary vein isolation using the second-generation 28-mm cryoballoon. *Circ Arrhythm Electrophysiol*. 2014;7(2):288-292.

7. Wisser E, Heeger CH, Grah H, et al. One-year clinical success of a “no bonus-freeze” freeze protocol using the second-generation 28 mm cryoballoon for pulmonary vein isolation. *Europace*. 2015;17(8):1236-1240.

8. Ciccone G, Asmundis Cde, Sieira J, et al. Single 3-minute freeze for second-generation cryoballoon ablation: one-year follow-up after pulmonary vein isolation. *Heart Rhythm*. 2015;12(4):673-680.

9. Reissmann B, Wisser E, Deiss S, et al. First insights into cryoballoon-based pulmonary vein isolation taking the individual time-to-isolation into account. *Europace*. 2017;19(10):1676-1680.

10. Chun KRJ, Fünkranz A, Köster I, et al. Two versus one repeat freeze-thaw cycle(s) after cryoballoon pulmonary vein isolation: the alster extra pilot study. *J Cardiovasc Electrophysiol*. 2012;23(8):814-819.

11. Heeger CH, Wisser E, Mathew S, et al. Short tip-big difference? First-in-man experience and procedural efficacy of pulmonary vein isolation using the third-generation cryoballoon. *Clin Res*. 2016;105(6):482-488.

12. Su W, Aryana A, Passman R, et al. Cryoballoon best practices II: practical guide to procedural monitoring and dosing during atrial fibrillation ablation from the perspective of experienced users. *Heart Rhythm*. 2018;15(9):1348-1355.

13. Aryana A, Mugnai G, Singh SM, et al. Procedural and biophysical indicators of durable pulmonary vein isolation during cryoballoon ablation of atrial fibrillation. *Heart Rhythm*. 2016;13(2):424-432.

14. Aryana A, Singh SM, Mugnai G, et al. Pulmonary vein reconnection following catheter ablation of atrial fibrillation using the second-generation cryoballoon versus open-irrigated radiofrequency: results of a multicenter analysis. *J Interv Card Electrophysiol*. 2016;47(3):341-348.

15. Pott A, Petscher K, Messener M, Rottbauer W, Dahme T. Increased rate of observed real-time pulmonary vein isolation with third-generation short-tip cryoballoon. *J Interv Card Electrophysiol*. 2016;47(3):333-339.

16. Chierchia GB, Mugnai G, Ströker E, et al. Incidence of real-time recordings of pulmonary vein potentials using the third-generation short-tip cryoballoon. *Europace*. 2016;18(8):1158-1163.

17. Mugnai G, de Asmundis C, Hünük B, et al. Improved visualisation of real-time recordings during third generation cryoballoon ablation: a comparison between the novel short-tip and the second generation device. *J Interv Card Electrophysiol*. 2016;46(3):307-314.

18. Heeger CH, Schuette C, Seitelberger V, et al. Time-to-effect guided pulmonary vein isolation utilizing the third-generation versus second-generation cryoballoon: one year clinical success. *Cardiol J*. 2019;26(4):368-374.

19. Straube F, Dorwarth U, Pongratz J, et al. The fourth cryoballoon generation with a shorter tip to facilitate real-time pulmonary vein potential recording: feasibility and safety results. *J Cardiovasc Electrophysiol*. 2019;30(6):918-925.

20. Heeger CH, Abdin A, Mathew S, et al. Efficacy and safety of cryoballoon ablation in patients with heart failure and reduced left ventricular ejection fraction: a multicenter study. *Circ J*. 2019;83(8):1653-1659.

21. Lyam E, Yalin K, Abdin A, et al. Mechanism, underlying substrate and predictors of atrial tachycardia following atrial fibrillation ablation using the second-generation cryoballoon. *J Cardiol*. 2019;73(6):497-506.

22. Su W, Kowal R, Kowalski M, et al. Best practice guide for cryoballoon ablation in atrial fibrillation: the compilation experience of more than 3000 procedures. *Heart Rhythm*. 2015;12(7):1658-1666.

23. Franceschi F, Koutbi L, Gitenay E, et al. Electromyographic monitoring for prevention of phrenic nerve palsy in second-generation cryoballoon procedures. *Circ Arrhythm Electrophysiol*. 2015;8(2):303-307.

24. Heeger CH, Wisser E, Mathew S, et al. Once isolated, always isolated? Incidence and characteristics of pulmonary vein reconnection after second-generation cryoballoon-based pulmonary vein isolation. *Circ Arrhythm Electrophysiol*. 2015;8(5):1088-1094.

25. Rottner L, Fink T, Heeger CH, et al. Is less more? Impact of different ablation protocols on periprocedural complications in second-generation cryoballoon based pulmonary vein isolation. *Europace*. 2017;20(9):1459-1467.

26. Tilz RR, Sano M, Vogler J, Fink T, Eitel C, Heeger CH. Fourth-generation cryoablation based left atrial appendage isolation for the treatment of persistent atrial fibrillation: first case report. *Am J Case Reports*. 2019;20:1830-1836.

27. Metzner A, Heeger CH, Wohlmuth P, et al. Two-year outcome after pulmonary vein isolation using the second-generation 28-mm cryoballoon: lessons from the bonus freeze protocol. *Clin Res*. 2016;105(1):72-78.

28. Heeger CH, Rexha E, Maack S, et al. Reconnection after second-generation cryoballoon-based pulmonary vein isolation—impact of different ablation strategies. *Circ J*. 2020;84(6):902-910.

29. Heeger CH, Wisser E, Knöll M, et al. Three-year clinical outcome after second-generation cryoballoon-based pulmonary vein isolation for the treatment of paroxysmal and persistent atrial fibrillation—a 2-center experience. *Circ J*. 2017;81(7):974-980.

30. Reddy VY, Sediva L, Petru J, et al. Durability of pulmonary vein isolation with cryoballoon ablation: results from the sustained PV
isolation with arctic front advance (SUPIR) study. J Cardiovasc Electrophysiol. 2015;26(5):493-500.

31. Rottner L, Mathew S, Reissmann B, et al. Feasibility, safety, and acute efficacy of the fourth-generation cryoballoon for ablation of atrial fibrillation: another step forward? Clin Cardiol. 2020;43(4):394-400.

32. Miyazaki S, Kajiyama T, Watanabe T, et al. Characteristics of phrenic nerve injury during pulmonary vein isolation using a 28-mm second-generation cryoballoon and short freeze strategy. J Am Heart Assoc. 2018;7(7):e008249.

33. Mathew S, Rottner L, Warneke L, et al. Initial experience and procedural efficacy of pulmonary vein isolation using the fourth-generation cryoballoon—a step forward? Acta Cardiol. 2020;8(75):754-759.

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