High rate of durable pulmonary vein isolation after second-generation cryoballoon ablation: analysis of repeat procedures

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Aims Pulmonary vein isolation (PVI) using the first-generation cryoballoon (CB1) was characterized by a high rate of recovered pulmonary vein (PV) conduction along with a typical conduction gap pattern in patients with recurrent atrial tachyarrhythmia (ATa). Second generation (CB2) enables more uniform freezing. However, the rate of chronic PVI and PV conduction gap pattern is unknown.

Methods and results All patients with ATa recurrence undergoing a second procedure after CB2 or (historical) CB1 PVI (28 mm) were enrolled. In all patients, a left atrial three-dimensional electroneatomic reconstruction was performed. The rates of chronic PVI and localization of PV conduction gaps were determined and compared between CB1 and CB2. Antral PV re-isolation was performed using irrigated-tip radiofrequency current energy ablation. Of 206 patients (CB2), 18 patients underwent the repeat procedure after 192 (75:245) days. In 6 of 18 (33%) patients, all PVs were electrically isolated whereas in the remaining 12 patients (66%) at least one PV was electrically isolated. Of 71 PVs [1 left common PV (LCPV)], 55 PVs (77%) were chronically isolated. The right superior PV (RSPV) was characterized by the lowest rate of chronic PVI (RSPV: 56%, LSPV: 76%, RIPV: 83%, LIPV: 94%, LCPV: 100%). Compared with CB1, CB2 resulted in a significantly higher rate of chronic PVI (CB2: 77% vs. CB1: 32%; P < 0.0001) with the greatest improvement along both inferior PVs.

Conclusion Second-generation cryoballoon atrial fibrillation ablation is associated with a high rate of durable PVI in patients with ATa recurrence. The RSPV represents the PV with the greatest risk for left atrium—pulmonary vein reconnection.

Keywords Atrial fibrillation • Cryoablation • PV reconnection

Introduction Pulmonary vein isolation (PVI) represents the cornerstone in paroxysmal atrial fibrillation (AF) ablation.1 Traditionally, radiofrequency current (RFC) energy ablation encircling point by point the ipsilateral pulmonary veins (PVs) has been proposed as the standard ablation strategy. However, this approach is limited by a long individual learning curve and high technical complexity. The cryoballoon (CB) system has been introduced to facilitate in obtaining the procedural endpoint of PVI. Importantly, all currently utilized ablation energy sources and ablation strategies are characterized by high rates of recovered PV conduction along ablation lesions.2–4 Therefore, multiple ablation procedures may be often required to obtain chronic PVI.5

The first-generation CB (CB1) was characterized by a non-homogeneous cooling along the equator region. Therefore, despite feasibility of acute PVI, CB1 ablation was characterized by a high rate of AF recurrence along with resumed PV conduction during follow-up. Interestingly, a typical reconduction gap pattern predominantly along inferior PVs has been described.3 In contrast, the second-generation CB (CB2) enables homogeneous cooling of the distal portion of the balloon (‘north pole’) resulting in improved...
What’s New?

- The new generation cryoballoon (CB2) is associated with a better mid- and long-term follow-up compared with the first-generation cryoballoon (CB1).
- We first compared CB1 vs. CB2 in terms of durable pulmonary vein isolation (PVI) in symptomatic patients undergoing a second ablation procedure.
- CB2 was associated with a 77% rate of durable PVI.
- The significant improvement compared with CB1 was related to a better durable isolation of inferior PVs.
- The right superior PV is the vein with the highest rate of PV reconnection using CB2.

procedural parameters and resulting in ca. 80% SR after 12 months clinical follow-up.6–10 CB2 is also associated with a low acute reconnection rate after adenosine challenge.11 However, the rate of chronic PVI and the conduction gap pattern remains undetermined.

Methods

All AF ablation procedural data have been collected in the CCB database since May 2010. All CB2 PVI patients undergoing a repeat procedure have been identified. Procedural data from the repeat procedures after CB2 ablation have been analysed. A historical cohort of CB1 ablation repeat procedures from the same institution served as a control group. All the patients gave written consent, and the study was approved by the Institutional Review Board.

Index second-generation cryoballoon ablation

The simplified single big cryoballoon technique has been described elsewhere.7 In brief, after a single transseptal puncture using the modified Brockenbrough technique (BRK-1 needle, 8.5F SL1 transseptal sheath, St Jude Medical), PV angiographies were performed. The CB delivery sheath (12F, Flex Cath Advance, Medtronic) was advanced into the left atrium (LA). The second generation 28 mm CB was used in conjunction with a multipolar spiral catheter (SC—Achieve, Medtronic) (Arctic Front Advance—CB2, Medtronic) allowing registration of PV conduction and determination of the moment of PVI. Pulmonary vein occlusion was assessed by contrast medium injection through the distal CB lumen. Cryoballoon freeze duration was set to 240 s. The delivery of a bonus application after acute PVI was optional. During ablation of both septal PVs, an octopolar diagnostic catheter (7F ParaHis —Biosense Webster) stimulated the phrenic nerve (PN) from the superior vena cava (12V, 2.9 ms, 1000 ms) to early identify PN dysfunction. A temperature probe (SensiTherm, St Jude Medical) was inserted into the oesophagus to monitor the luminal oesophageal temperature (LET). All relevant procedural data such as minimal CB temperature and LET have been systematically collected.

Repeat ablation procedure after second-generation cryoballoon ablation

All patients with documented recurrence of atrial tachyarrhythmias (ATa) lasting >30 s were offered a repeat AF ablation procedure. All repeat procedures were performed under conscious sedation (midazolam, propofol, and fentanyl boluses followed by a propofol infusion). After double transseptal puncture, a three-dimensional (3D) electroanatomical (EA) LA map (Carto 3, Biosense Webster) was performed using a 3.5 mm irrigated-tip radiofrequency (RF) catheter (ThermoCool Navistar, Biosense Webster). Selective PV angiograms were performed and both ipsilateral PV ostia were tagged in the LA CARTO map as previously described.12 A decapolar spiral catheter (Lasso 15/20 mm, Biosense Webster) was positioned within the proximal PV ostium to assess potential LA–PV reconnection. If LA–PV reconnection was present, the PV spike sequence was analysed to identify the earliest PV activation site. Radiofrequency ablation was guided by PV activation sequence and local map potential along the tagged PV ostium level (figure 1). Gap location was defined as the site of successful re-isolation of the PV or the site of clear change in the PV electric activation pattern, as previously published.7 All PVs were divided into four quadrants [antero-superior (AS); antero-inferior (AI); postero-inferior (PI); postero-superior (PS)] to categorize the gap location. In patients presenting with AF as the type of ATa recurrence, only re-PVI was performed. In patients presenting with atrial tachycardia (AT), the underlying tachycardia mechanism was elucidated combining 3D EA-mapping with conventional electrophysiological (EP) information such as entrainment manoeuvres. After AT termination, re-PVI was performed in SR.

Comparison: first-generation cryoballoon vs. second-generation cryoballoon

Pulmonary vein reconduction data after CB1 procedure were obtained from our centres CB cohort of the recently published ‘Laser vs. Cryostudy’.3 This historical CB1 group served as the comparator.

Follow-up

After the ablation procedure, all patients were seen in our outpatient clinic at 3, 6, 9, and 12 months and in 6 months intervals thereafter and obtained a 72 h Holter-ECG. In case of symptoms suggestive of an ATa recurrence, patients received an external event monitor. Atrial tachyarrhythmia recurrence has been defined as documented episodes lasting >30 s.

Objectives and endpoints

Primary endpoint

To characterize LA–PV reconnection rates and localization of PV conduction gaps after CB2 PV isolation.

Secondary endpoints

To compare LA–PV reconnection after CB1 and CB2 PVI ablation. To identify procedural parameters predicting LA–PV reconnection after CB2 ablation. To analyse repeat procedural parameters, complications, and patient outcome.

Statistical analysis

All quantitative variables with a normal distribution were reported as mean ± standard deviation, and compared using the Student’s t-test. For the descriptive variables comparison, the Pearson’s χ² test or the Fisher’s exact test wherever appropriate was used. An odds ratio with 95% confidence interval (CI) was computed to compare PV isolation rates after PVI using the CB1 and CB2.

Results

Patients and procedure

A repeat AF ablation procedure was performed in 18 of 206 patients (9%) after 192 (75–245) days post-index CB2. The historical CB1 control group consisted of 22 of 70 patients in which the repeat
procedure was performed after 139 (89–327) days post-index CB1 (Figure 2). Patients demographic and baseline characteristics have been summarized in Table 1.

Primary endpoint
Pulmonary vein reconduction pattern and gap localization after second-generation cryoballoon ablation

A total of 71 PVs have been identified including one left common PV (LCPV). Overall, durable electrical PVI was documented in 55 of 71 (77%) PVs. Recovered PV conduction was present in 16 of 71 PVs (23%). Different rates of chronic PVI based on PV location have been observed: LCPV: 100%; LIPV: 94%; LSPV: 77%; RIPV: 83.3%; RSPV: 55.5% (Figure 3). In all reconnected PVs, PV conduction gaps were confined to one sector; the spatial distribution pattern of PV conduction gaps after CB2 ablation is given in Figure 4. Eight out of 16 PV (50%) conduction gaps were localized at the RSPV, thus representing the PV with the highest risk for LA–PV reconnection.
Secondary endpoints

Pulmonary vein reconduction: second-generation vs. first-generation cryoballoon ablation

The rate of chronic PVI was significantly increased while comparing CB2 vs. CB1 ablation: (55 of 71, 77% PVs vs. 27 of 85, 32% PVs; \( P < 0.0001 \)). This significant improvement in lesion durability after CB2 compared with CB1 was strongly dependent on an increased rate of permanent isolation of both inferior PVs (Figure 3). Of note, after CB1 ablation not a single patient (0 of 22 patients, 0%) came back with all PVs isolated whereas after CB2 ablation 6 of 18 patients (33%) demonstrated chronic isolation of all PVs (\( P = 0.048 \)). Therefore, the use of the CB2 vs. CB1 was associated with a significantly higher probability for patients to receive durable PVI for all veins. Further details are given in Table 2.

Predictors of pulmonary vein reconduction after second-generation cryoballoon ablation

A detailed analysis comparing index and repeat procedural data revealed that reconnected PVs were in trend associated with warmer CB2 temperatures compared with chronically isolated PVs (\(-47.2 \pm 1.1 \text{ vs. } -50.1 \pm 0.7 ^\circ\text{C}, \ P = 0.05\)). There was a higher rate of bonus freeze in PVs with reconnection (\( P = 0.046 \)). The other procedural aspects such as total number of CB freezes, single shot isolation, real-time PV recording visualization, and time to isolation were not statistically significantly different (Table 3).

Atrial tachyarrhythmia recurrence and ablation

The type of clinical ATa recurrence was grouped into AF or AT (Figure 2). Atrial fibrillation was present after CB1 and CB2 in 17 of 22 patients (77%, CB1) vs. 12 of 18 patients (67%, CB2). Atrial tachycardia was present in 5 of 22 patients (23%, CB1) vs. 6 of 18 patients (33%, CB2), respectively (Table 1). All AT recurrences in CB1 were associated with PV reconnection. In CB2, four out of six patients with AT recurrence had all PV persistently isolated. In all patients with PV reconnection re-PVI was performed: CB1—22 of 22 patients (100%) vs. CB2—12 of 18 patients (66%). Additional ablation beyond re-PVI was performed in CB1: anterior line —5 of 22 patients (23%), right atrial cavo-tricuspid line —6 of 22 patients.

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### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>CB1</th>
<th>CB2</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>22</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>22 (100%)</td>
<td>14 (78%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Male (%)</td>
<td>14 (63%)</td>
<td>9 (50%)</td>
<td>0.522</td>
</tr>
<tr>
<td>Age</td>
<td>62 ± 13</td>
<td>69 ± 11</td>
<td>0.068</td>
</tr>
<tr>
<td>Years of AF</td>
<td>3.0 ± 2.0</td>
<td>4.0 ± 4.0</td>
<td>0.351</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>41 ± 4</td>
<td>41 ± 4</td>
<td>0.917</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>63 ± 5</td>
<td>61 ± 6</td>
<td>0.296</td>
</tr>
<tr>
<td>Time to repeat procedure (days)</td>
<td>139 (89–327)</td>
<td>192 (75–245)</td>
<td>0.009</td>
</tr>
<tr>
<td>Type of recurrence</td>
<td>AF</td>
<td>17/22 (77%)</td>
<td>0.497</td>
</tr>
<tr>
<td></td>
<td>AT</td>
<td>5/22 (23%)</td>
<td>0.497</td>
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</tbody>
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**Figure 2** Flowchart displaying arrhythmia recurrence type and ablations performed in the second procedure.
Compared with CB2: anterior line —8 of 18 patients (44%), right atrial cavo-tricuspid line —2 of 18 patients (11%), and roof line —5 of 18 patients (28%). One patient in the CB2 group presented with a trigger from the left atrial appendage (LAA) and therefore received three linear lesions (anterior, roof, and mitral isthmus), resulting in electrical isolation of the LAA.

Procedural parameters and complications

Procedural time and fluoroscopy time of the repeat procedures were similar in CB1 and CB2 groups: 103 $\pm$ 27 vs. 103 $\pm$ 55 ($P = 0.98$) and 13 $\pm$ 4 vs. 12 $\pm$ 5 ($P = 0.35$), respectively.

The repeat procedure was complicated by one transient ischaemic attack and one false aneurysm in the CB2 group, and no complications occurred in CB1 repeat procedures. Pulmonary vein stenosis was ruled out in all patients after the index CB PVI by angiograms.

Follow-up

The median follow-up after the RFC re-ablation was 190 days (Q1–Q3: 106–450 days) for CB1 and 182 days (Q1–Q3: 105–261 days) for CB2: 3 of 22 patients in CB1 and 2 of 18 patients in CB2 experienced documented ATa recurrences after the repeat procedure ($P = 1.00$).
by higher chronic isolation rates of inferior PVs. Previously, it has been established that CB1 PVI is associated with a typical PV reconduction gap pattern along inferior PVs: specifically, inferior PV sectors have been in contact with the ‘warmer’ surface of the CB1 resulting in typical sites of PV conduction recovery. In contrast, the CB2 permits freezing of the entire PV antrum with increased energy, resulting in a faster cryo-lesion formation and in an enhanced rate of ‘single-shot’ acute PV isolation. The inferior sectors of the PV antrum are also in contact with the coolest CB2 surface, explaining the high rate of permanent PVI recorded in the repeat procedures. Interestingly, improved CB2 cardiac lesion quality has been recently suggested by animal data as well as human biomarker findings. In addition, according to our data only discrete PV conduction gaps reappeared after CB2 PVI, which could be successfully closed by focal RFC ablation. Moreover, RFC-induced re-PVI was obtained along the level of PV ostia tagged for antral wide area circumferential RFC ablation, indicating a comparable anatomic level of ablation lesions. This observation needs to be confirmed in a prospective study.

In the CB1 group, no patient (0%) demonstrated chronic PVI of all PVs and merely a low rate of chronic PVI (32% PVs) has been observed. In contrast, after CB2, a significantly higher rate of durable PVI has been found (CB2: 77% vs. CB1: 32%, P < 0.0001). The risk of PV reconnection (‘per PV’ and ‘per patient’) was significantly lower in CB2 vs. CB1 (odds ratio: 0.042; CI: 0.002–0.824). These new observations may represent the EP basis explaining improved clinical outcome after CB2 AF ablation. The interesting question whether these findings may also help to define the role of chronic PVI in persistent AF remains to be determined in future studies.

A detailed analysis of our data shows that superior PVs do merely show a non-significant improvement of chronic PVI after CB2. First of all, both superior PVs already did show relatively high chronic isolation rates after CB1. Therefore, an absolute but non-significant increase of chronic PVI could be observed after CB2. The majority of recovered PV conduction gaps have been located along the anterior RSPV (50% of all reconnected PVs). This may be explained by different mechanisms: (i) continuous PN stimulation during the initial phase of RSPV ablation may counteract adequate balloon–tissue contact and lead to a non-transmural freeze; (ii) early freeze termination to preserve PN function may also result in increased risks of non-transmural cryo-lesions and increased risk of PV reconduction; (iii) non-alignment of sheath and CB after transseptal LA access, resulting in a lower contact force along the anterior sector of the RSPV. However, in the present series, we observed no PN weakening during RSPV ablation so the correlation between PNP and RSPV conduction recovery could not be studied.

Predictors of pulmonary vein reconduction

Analyzing index procedural data, no factor predicting recovered PV reconduction could be identified (Table 3). There was just a trend (P = 0.052) towards lower CB temperatures in chronically isolated PVs. Electrophysiological parameters such as ‘real-time PVI’ and ‘time to PVI’ were also statistically not different. In the present data, PVI durability was not related to the application of a bonus freeze. Reconnected PVs had a non-significant longer time to PVI, eventually leading the operator to add a bonus application. Whether a larger
number of recovered PVs may have resulted in statistically significant differences remains open. The clinical importance of an empirical bonus freeze even on PVI durability is still open and is currently under investigation in the prospective, randomized ICE-T Trial (DRKS 0004937).

Atrial tachycardia after second-generation cryoballoon

The considerable rate of chronic PVI after CB2 ablation may explain why a relatively high rate of AT instead of AF has been observed as the second clinical arrhythmia. Typically, AF recurrence is linked to recovered PV conduction. Therefore, high rates of chronic PVI may separate PVI responders from PVI non-responders.

Complications

Increasing cryoblation power may result in unwanted collateral damage. Importantly, the CB2 has been linked to oesophageal lesions if no temperature limit has been set.13 The optimal dosing strategy of CB2 ablation remains unclear and is currently under evaluation.

Limitations

The major limitation of this study refers to the fact that only selected patients with symptomatic ATa recurrence after CB PVI have been investigated. Therefore, the rate of recovered PV conduction in the overall patient population remains unknown. Patients were not randomized, hence we report a sequence of patients treated either with CB1 or CB2. A potential impact of a learning curve for the CB2 is unlikely but cannot be excluded. In general, single-centre studies do not reflect real-world settings. However, if two devices are compared in an identical setting, this could be regarded as a strength rather than limitation of a study. Patient selection could also play a role in the presented findings. Since the introduction of CB2, even short-persistent AF patients enrolled for CB ablation may be impacting the rate of non-PV responder in our population. Adenosin testing was not performed after isolation in the index procedures; whether this test as recently described13 could have predicted chronic reconnection in our series remains unknown. No data about rewarming time as previously described14 were collected; whether these data could correlate with PV reconnection rate in our series remains unknown.

Conclusions

Second-generation cryoballoon AF ablation is associated with a high rate of durable PVI in patients with ATa recurrence. The RSPV represents the PV with the greatest risk for LA–PV reconnection.

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