Once Isolated, Always Isolated? Incidence and Characteristics of Pulmonary Vein Recondution after Second-Generation Cryoballoon-Based Pulmonary Vein Isolation

Running title: Heeger et al.: PV reconduction after cryoballoon-based PVI

Christian-Hendrik Heeger, MD*; Erik Wissner, MD*; Shibu Mathew, MD;
Sebastian Deiss, MD; Christine Lemes, MD; Andreas Rillig, MD; Peter Wohlmuth, PhD;
Bruno Reissmann, MD; Roland Richard Tilz, MD; Feifan Ouyang, MD; Karl-Heinz Kuck, MD;
Andreas Metzner, MD

Department of Cardiology, Asklepios Klinik St. Georg, Hamburg, Germany
*contributed equally

Correspondence:
Andreas Metzner, MD
Aklepios-Klinik St. Georg
Department of Cardiology
Lohmühlenstr. 5
20099 Hamburg
Germany
Tel: ++49-(0)40-1818 852305
Fax: ++49-(0)40-1818 854435
E-mail: AndreasMetzner1@web.de

Journal Subject Terms: Catheter Ablation and Implantable Cardioverter-Defibrillator
Abstract

**Background** - The second-generation cryoballoon (CB) delivers effective pulmonary vein isolation (PVI) associated with superior 1-year clinical outcome. However, data on reconduction of previously isolated pulmonary veins (PV) is sparse.

**Methods and Results** - A total of 421 patients underwent second-generation 28mm CB-based PVI in two centers (“St. George’s hospital” and “Harburg hospital”, Hamburg, Germany) between 06/2012 and 05/2015. Sixty-six out of 421 (16%) patients (39/66, 59% female, mean age 63±10 years, mean LA diameter 45±6 mm) with a history of paroxysmal (40/66, 61%) or persistent atrial fibrillation (AF) and atrial tachyarrhythmia recurrences despite previous successful second-generation 28mm CB-based PVI were included in this analysis. During the index PVI the standard freeze cycle duration was 240 seconds. After successful PVI, a bonus freeze cycle of 240 seconds was applied in the first 15/66 (23%) patients, while no bonus freeze cycle was applied in the remaining patients. Repeat procedures were performed after a median of 205 (131-357) days following the index ablation. Electrical reconduction was assessed for all PVs and re-ablation was performed using radiofrequency energy. Persistent electrical isolation was noted in 178/258 (69%) PVs. In 17/66 (26%) patients all previously targeted PVs remained isolated. A significant difference towards highest reconduction-rate for the postero-inferior segment of the right inferior PV (RIPV) was found (p – 0.0002).

**Conclusions** - Second-generation CB ablation is associated with a high rate of persistent PVI. The postero-inferior segment of the RIPV showed the highest reconduction rate and seems to be a predilection site for PV reconduction.

**Key words:** atrial fibrillation; pulmonary vein isolation, cryoballoon, electrical reconduction, clinical follow-up
Introduction

The second-generation cryoballoon (CB) provides homogeneous cooling of the complete distal balloon hemisphere and has proven highly effective for acute pulmonary vein isolation (PVI), while demonstrating encouraging 1-year clinical outcome in patients with paroxysmal atrial fibrillation (PAF) or persistent atrial fibrillation (AF). The reported one-year clinical success rates range from 80 to 84% for PAF and up to 69% for persistent AF. The first 2-year outcome data approved this finding with 73% of patients showing stable SR. One explanation for these encouraging success rates may be a persistent high rate of PVI over time. In this regard, the present study set out to evaluate the rate of electrical reconduction in patients presenting for re-ablation due to recurrence of atrial tachyarrhythmias (ATA) following initial 28mm CB-based PVI.

Methods

Inclusion and exclusion criteria

Consecutive patients with initial drug-refractory PAF or persistent AF and recurrent symptomatic and documented ATA after previous second-generation 28mm CB-based PVI were admitted for re-ablation and included in the study. Transesophageal echocardiography was performed prior to ablation in all patients to rule out intracardiac thrombi. No additional pre-procedural imaging was performed. All patients gave written informed consent and all patient information was anonymized. All data was evaluated retrospectively. The study was approved by the local ethical review board.

Intraprocedural management

All procedures were performed in deep sedation using midazolam, fentanyl, and propofol. Triple puncture of the right femoral vein was performed and two diagnostic catheters were positioned...
inside the coronary sinus and along the His-bundle, respectively. A single (index ablation) or double (repeat ablation) transseptal puncture was performed under fluoroscopic guidance using a modified Brockenbrough technique and one or two 8.5F transseptal sheaths (TS; SL1, St. Jude Medical, Inc., St. Paul, MN, USA). Heparin was given to maintain an activated clotting time of \( \geq 300 \) seconds. In order to identify the PV ostia, selective pulmonary vein (PV) angiography was performed.

**Index-PVI using the second-generation 28mm cryoballoon**

The regular TS was exchanged over a guidewire for a 12F steerable TS (Flexcath Advance, Medtronic, Inc., Minneapolis, MN, USA). The second-generation 28mm CB was advanced into the LA and directed towards the target PV via a spiral mapping catheter (20 mm diameter; Achieve\textsuperscript{TM}, Medtronic, Inc.). The CB was inflated proximal to the PV ostium and pushed against the PV ostium aiming for complete antral PV occlusion as verified by contrast medium injections distal to the balloon. Freeze cycle duration was set at 240 seconds. An additional bonus freeze cycle of the same duration was applied after successful PVI in the first 12 consecutive patients, while the extra freeze cycle was omitted in the remaining patients (“no-bonus” freeze protocol).\(^6\)

In all patients, an esophageal temperature probe (Sensitherm, St. Jude Medical, Inc.) was inserted to monitor intraluminal esophageal temperatures during energy delivery. The intraluminal esophageal temperature cut-off was set to 10°C according to previous evaluations.\(^9\)

During ablation of the septal PVs, continuous phrenic nerve (PN) pacing at maximum output and pulse width (12mA, 2.9ms) at a cycle length of 1200ms was performed using a diagnostic catheter positioned in the superior vena cava. PN capture was monitored by tactile feedback of diaphragmatic contraction and registration of the compound motoric activation potential (CMAP) of the right diaphragm.\(^10,11\) Energy delivery was stopped immediately in case
of weakening or loss of diaphragmatic movement or if the CMAP amplitude decreased by 30%.

**Repeat procedures**

In patients admitted for a repeat procedure due to ATA recurrence, an electroanatomical LA-map (Carto 3™, Biosense Webster, Inc., Diamond Bar, CA, USA) was generated and the PV ostia tagged on the LA map. Persistent PVI or electrical reconduction of previously isolated PVs was assessed by the presence or absence of electrical activity inside each PV using a spiral mapping catheter (Lasso™, Biosense-Webster). Identified reconduction gaps were assigned to 4 segments (antero-superior, antero-inferior, postero-superior, postero-inferior) and closed by radiofrequency (RF) ablation using a 3.5mm irrigated-tip catheter (Biosense Webster, Navi-Star™, ThermoCool™). In patients with persistent isolation of all PVs admitted in SR, fractionated ostial potentials along previously performed ablation lines were identified and ablated and/or linear lesion sets were applied. In patients admitted in AF or atrial tachycardia (AT) and persistent isolation of all PVs, ostial potentials were identified and ablated followed by ablation of complex fractionated atrial electrograms (CFAE) and deployment of linear lesion sets in case of conversion to an AT.12-15

**Postprocedural care**

Following ablation, all patients underwent transthoracic echocardiography to rule out 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. Novel oral anticoagulants were re-initiated 6 hours post ablation at half the regular dose and at full dose the following day. Anticoagulation was continued for at least 3 months and thereafter based on the individual CHA2DS2-VASc score. Previously ineffective antiarrhythmic drugs were continued for 3 months.
Follow-up after index and repeat ablation

Following a blanking period of 3 months, patients completed outpatient clinic visits at 3, 6 and 12 months with 24h-Holter ECGs recorded at each visit. In addition, symptoms suggestive for ATA recurrence prompted an additional outpatient clinic visit.

Statistical analysis

Differences of continuous variables between two groups were analyzed with t-tests, if the data were normally distributed, and with Wilcoxon-Mann Whitney tests otherwise. Differences between categorical variables were evaluated with the Chi-square test or with Fisher’s exact test in case of small expected cell frequencies. PVI data are analyzed using mixed models. Linear mixed models are used for continuous data (minimal temperature). The outcome data are log-transformed if appropriate (time to PVI). Generalized linear mixed models are used if the response variables are binary or count data are analyzed. For binary data (bonus freeze yes/no) a hierarchical logistic regression model is applied. For count data (number of CB cycles) a poisson distribution is assumed. The number of gaps in superior and inferior PV are analyzed with Wilcoxon signed ranks test. To test for differences between reconduction rates for different PVs post-hoc tests using the Bonferroni method (adjustment for multiplicity) were performed. All p-values are two-sided and a p-value < 0.05 was considered significant. All calculations were performed with the statistical analysis software SAS (SAS Institute Inc., version 9.3, Cary, NC, USA).

Results

Patient characteristics

Between 06/2012 and 05/2015 a total of 421 patients underwent second-generation 28mm CB-based PVI in two centers (“St. George’s hospital” and “Harburg hospital”, both Hamburg,
Germany). A repeat procedure due to ATA recurrence was performed in 66/421 (16%) patients (figure 1). The patients’ baseline characteristics are shown in table 1. Repeat procedures were performed after a median of 205 (131-357) days following the index ablation.

**Index pulmonary vein isolation**

A total of 258 PVs were identified in 66 patients (66 right superior PVs [RSPV], 66 right inferior PVs [RIPV], 60 left superior PVs [LSPV], 60 left inferior PVs [LIPV] and 6 left common PVs [LCPV]). All PVs (258/258, 100%) were successfully isolated during the index PVI (table 2). Successful PVI during the initial freeze cycle was achieved in 54/66 (82%) RSPVs, 53/66 (80%) RIPVs, 49/60 (82%) LSPVs, 53/60 (88%) LIPVs, and 4/6 (67%) LCPVs, respectively. In the first 15/66 (23%) patients a “bonus” freeze cycle was applied, which was omitted in the remaining 51/66 (77%) patients. The mean number of CB applications per PV is listed in table 3. The average procedure and fluoroscopy time was 136±41 min and 21±8 min including a 30-minute waiting period after the final freeze cycle.

**Findings during re-ablation procedures**

In a total of 80/258 (31%) PVs, LA-to-PV reconduction was demonstrated while persistent PVI was documented in 178/258 (69%) PVs. The LA-to-PV reconduction rate was comparable for patients with PAF (47/156 PVs, 30%) and persistent AF (33/102 PVs, 32%) (p = 0.58). In 17/66 (26%) patients all PVs were still isolated. LA-to-PV reconduction of single PV was noted in 28/66 (42%) patients, whereas 2 and 3 recovered PVs were identified in 14/66 (21%) and 5/66 (8%) patients, respectively. Two patients (3%) demonstrated electrical reconduction of all 4 PVs. LA-to-PV reconduction was seen in 16/66 (24%) RSPVs, 31/66 (47%) RIPVs, 17/60 (28%) LSPVs, 14/60 (23%) LIPVs and 2/6 (33%) LCPVs. Significant differences were found comparing reconduction rates for different PVs (p = 0.006). Post-hoc tests between all PVs
showed significant differences between RIPV and RSPV (p = 0.042) as well as RIPV and LIPV (p = 0.013). Differences between RIPV and LSPV (p = 0.071), LSPV and LIPV (p > 0.99), RSPV and LIPV (p > 0.99), RSPV and LSPV (p > 0.99) were not significant.

In 43/49 (88%) patients demonstrating LA-to-PV reconduction a detailed description of the location of each gap was provided, while in 6/49 (12%) patients the exact location of the gap was unknown. In total, 77 reconduction gaps were identified in 43 patients and distributed as shown in figure 2. Of note, only one gap was found along the inter-PV section. In 24/43 (56%) patients a single gap was found, while in 11/43 (26%) and in 7/43 (16%) patients 2 and 3 gaps were identified, respectively. In one patient 4 gaps (2%) and in a further patient 5 gaps (2%) were found. No statistical difference (p = 0.88) was found between the number of reconduction gaps for patients with PAF (46/77, 60%) and persistent AF (31/77, 40%). When comparing all PV segments, a significant difference towards highest reconduction-rate for the postero-inferior segment of the RIPV was found (22/77 (29%), p = 0.0002). When comparing patients with PAF and persistent AF concerning the reconduction rate for the postero-inferior segment of the RIPV no differences were found (p = 0.48). The reconduction rate for inferior PVs was similar to superior PVs (34% versus 25%, p = 0.11). When performing a subgroup analysis for patients with PAF only, no significant difference was found between the reconduction rate for inferior and superior PVs (30% versus 26%, p = 0.60).

Reablation results

In 49/66 (74%) patients electrical reconduction of previously isolated PVs was identified. Re-isolation of all PVs was successfully performed using RF energy. In 10/49 (20%) patients, complete circumferential ablation lines around the ipsilateral PVs were applied. In addition, ablation of ostial potentials was performed in 13/49 (27%) patients, CFAE ablation in 2/49 (4%)
patients, and of linear lesions ablation in 9/49 (18%) patients (n = 2 mitral isthmus lines, n = 7 anterior lines).

In 6/17 (35%) patients with persistent isolation of all PVs admitted in SR, ostial potentials were targeted for ablation. In two patients (12%) a roof line was deployed. In 4/17 (24%) patients presenting in AF, ablation of ostial potentials was followed by CFAE ablation. An additional 6/17 (35%) patients underwent ablation of CFAE and converted from AF to an AT followed by ablation of linear lesions (n = 3 mitral isthmus line, n = 3 anterior lines). In one patient ablation of an anterior line and mitral isthmus line resulted in isolation of the left atrial appendage. Ablation of the right isthmus was performed in 15/66 (23%) patients because of documented typical cavotricuspid-dependent atrial flutter. Periprocedural stroke occurred in 1/66 (1.5%) patient. One further patient received a procedure related hematoma of the right groin without surgical treatment or blood transfusion. No additional complications were documented. Mean procedure and fluoroscopy time was 131±46 min and 15±9 min, respectively.

Predictors of pulmonary vein reconduction
No statistically significant predictors of PV reconduction were identified analyzing procedural characteristics during the index ablation procedure such as total CB-applications per PV, number of CB-applications until PVI, application of a bonus freeze cycle and mean freeze time until PVI (“time-to-effect”). Yet a statistical difference could be identified for the mean minimal CB temperature (table 3). Concerning patients’ baseline characteristics no statistical differences were found (table 4).

Follow-up
Follow-up after re-ablation was completed in 63/66 (95%) patients, while 3/66 (5%) patients were lost to follow-up. After a median follow-up of 135 (16-377) days, 50/63 (79%) patients

DOI: 10.1161/CIRCEP.115.003007
were in stable SR, 13/63 (21%) patients developed ATA recurrence in the form of AF in 8/13 (62%) patients and AT in 5/13 (38%) patients. In 9/13 (69%) patients a third ablation procedure was performed. In 8/9 (89%) patients all PVs were still isolated while one patient showed reconduction of the RIPV and LSPV. Therefore a total of 34/36 (94%) identified PVs were still isolated after the second procedure.

Discussion
The current study sought to assess the incidence and location of PV-reconduction following initial second-generation 28mm CB-based PVI. The major findings are that 1) 69% of PVs were still isolated during the repeat procedure, 2) in 26% of patients all PVs demonstrated persistent isolation, 3) a higher rate of electrical reconduction was found for the postero-inferior segment of the RIPV, and 4) the majority of PVs demonstrating electrical reconduction had only a single reconduction gap.

Compared to the first generation, the second-generation CB offers better cooling characteristics resulting in homogeneous cooling of the distal balloon hemisphere.1, 3 These cooling properties translate into a high rate of acute PVI and improved clinical outcome. The 1-year clinical success rate following second-generation CB-based PVI in patients suffering from PAF ranges between 80% to 84%.2, 3, 5, 6 Promising 1-year success rates were also reported for persistent AF with freedom from ATA recurrence in up to 69% of patients.4, 7, 16 However, better cooling characteristics and clinical efficacy may in turn be associated with a higher incidence of damage to extra-cardiac structures such as the esophagus or the phrenic nerve.9, 10, 17, 18 Recently reported endoluminal esophageal temperature cut-offs have resulted in a significant reduction in thermal esophageal injury, while the development and evaluation of multiple safety algorithms to prevent phrenic nerve palsy such as CMAP pacing or the “double-stop” technique have further
improved the safety profile of the second-generation CB.\textsuperscript{11, 17, 19, 20}

It had yet to be evaluated whether the greater clinical efficacy of the second-generation CB is due to a higher rate of permanently isolated PVs. Using the first-generation CB the rate of electrical reconduction was 54\%.\textsuperscript{21} For the second-generation CB only a single study evaluated the incidence of PV reconduction.\textsuperscript{22} In 18 patients admitted for re-ablation due to recurrent ATA, persistent electrical isolation was demonstrated in 55/71 (77\%) previously isolated PVs, while in 6/18 (33\%) patients all 4 PVs were still isolated.\textsuperscript{22} The current study confirms these results in a larger patient cohort of 66 patients with 69\% of PVs persistently isolated and 26\% of patients demonstrating isolation of all 4 PVs.

During follow-up, we did not assess a higher incidence of AF recurrences in patients with persistent isolation of all 4 PVs and initially persistent AF (1/7, 14\%) as compared to patients with initially PAF (1/10, 10\%), (p = 0.331). However, the number of patients included into our analysis is too small to find differences. It can be speculated that in patients with initially persistent AF and persistent isolation of all PVs the recurrence rate would be higher than in patients with history of PAF.

In the present analysis the right inferior PVs, exhibited the highest rate of electrical reconduction. This may be explained by imperfect alignment of the ablation system with the course of the right inferior PVs resulting in suboptimal mechanical stability and a less effective durable lesion formation. In addition, CB temperatures also depend on the size of the target PV. Since the inferior PVs are usually smaller in diameter, a greater portion of the balloon surface is surrounded by blood counteracting optimal tissue cooling. Less effective cooling may result in a higher rate of PV reconduction. The low incidence of gaps along the ridge is on one hand due to the very effective cooling profile of the second-generation CB. On the other hand, there is an
overlay of ablation lesions between the superior and the inferior lateral PVs since they are usually in close anatomical proximity. Consequently the ridge, which is characterized by thick muscular tissue, should be very effectively ablated.

The current study included patients treated with or without a bonus freeze cycle following successful PVI. A comparison of persistently isolated PVs versus reconnected PVs failed to show a significant difference for the selected ablation strategy (p = 0.93) and may argue in favor of a “no bonus” freeze protocol. Nevertheless the observed patients population is relatively small. Therefore randomized trials with larger patient numbers and different ablation protocols will be necessary to draw final conclusions.

The high proportion of patients with recurrent ATA and persistent isolation of all PVs raises the question regarding the best treatment strategy during the repeat procedure. In patients demonstrating electrical PV reconduction repeat PVI was performed.

As described, in a high proportion of patients (26%) all PVs were isolated despite recurrence of AF. In these patients, we especially checked for ostial potentials along the previously performed ablation lines, since these spots might serve as potential triggers for induction of AF. Some patients might also have triggers outside the PV. However, in our standard ablation protocol we do not explicitly check for extra-PV triggers if they are not apparent during procedure.

In patients admitted in SR and persistent isolation of all PVs, ablation of ostial potentials and additional ablation of linear lesions was performed, while in patients presenting in AF identification and ablation of CFAE was followed by ablation of linear lesions, if necessary. Nevertheless, independent of the ablation technology used, in patients presenting with persistent isolation of all PVs and ATA recurrence the optimal ablation strategy is currently unknown and
demands further investigation.

Limitations

The presented findings are based on a two-center experience enrolling a limited number of patients. The follow-up was limited to 24h-Holter ECGs. This might overestimate the success rate after repeat ablation procedures as closer follow-up (e.g. via implantable loop recorders) may have detected a higher number of ATA recurrences. Furthermore not all patients with ATA recurrences agreed for a repeat ablation procedure. Therefore the included patients represent only a subgroup of all patients with ATA recurrence after second-generation CB-based PVI. Different ablation protocols (bonus freeze cycle versus no bonus freeze cycle) were used during the index ablation procedure. Due to low patients number subgroup analyses are not powered enough to evaluate outcomes of patients with and without a bonus freeze applications. Repeat ablation procedures were scheduled and performed at individual points in time after the index ablation procedure. Furthermore, not all patients with proven LA-to-PV reconduction underwent detailed gap-analysis. The optimal ablation strategy for patients with persistent isolation of all PVs during the repeat procedure is currently unknown and requires further clarification.

Conclusions

Following second-generation CB-based PVI, a high rate of persistent PVI was demonstrated in patients with recurrent ATA presenting for a repeat ablation procedure. Electrical PV reconduction was more frequently demonstrated for the postero-inferior segment of the RIPV. Overall, these findings are in support of previous studies reporting better clinical efficacy using the second-generation CB for PVI.

Conflict of Interest Disclosures: A Metzner received speaker's honoraria from Medtronic. E
Wissner received speaker's honoraria from Medtronic and is member of Medtronic’s advisory board. KH Kuck received a research grant and speaker's honoraria from Medtronic. All other authors have no relevant disclosures.

References:


Table 1: Baseline characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>66</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63±10</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>39 (59)</td>
</tr>
<tr>
<td>LA* - size (mm)</td>
<td>45±6</td>
</tr>
<tr>
<td>Paroxysmal AF†, n (%)</td>
<td>40 (61)</td>
</tr>
<tr>
<td>Short-term persistent AF†, n (%)</td>
<td>26 (39)</td>
</tr>
<tr>
<td>Duration of AF†, months</td>
<td>34±32</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>54±3</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>40 (61%)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>6 (9%)</td>
</tr>
</tbody>
</table>

*LA = left atrium, †AF = atrial fibrillation
Table 2: Procedural characteristics of index cryoballon based pulmonary vein isolation

<table>
<thead>
<tr>
<th></th>
<th>RSPV*</th>
<th>RIPV†</th>
<th>LSPV‡</th>
<th>LIPV§</th>
<th>LCPV‖</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PVs#, n</td>
<td>66</td>
<td>66</td>
<td>60</td>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>Isolated PVs#, n (%)</td>
<td>66/66 (100)</td>
<td>66/66 (100)</td>
<td>60/60 (100)</td>
<td>60/60 (100)</td>
<td>6/6 (100)</td>
</tr>
<tr>
<td>Isolation during first CB** cycle, n (%)</td>
<td>54/66 (82)</td>
<td>53/66 (80)</td>
<td>49/60 (82)</td>
<td>53/60 (88)</td>
<td>4/6 (67)</td>
</tr>
<tr>
<td>Mean number of CB** cycles, mean±SD</td>
<td>1.4±0.6</td>
<td>1.5±0.8</td>
<td>1.5±0.7</td>
<td>1.4±0.6</td>
<td>1.8±0.8</td>
</tr>
<tr>
<td>Number of PVs# with bonus freeze cycle, n (%)</td>
<td>15/66 (23)</td>
<td>15/66 (23)</td>
<td>15/60 (25)</td>
<td>15/60 (25)</td>
<td>2/6 (33)</td>
</tr>
<tr>
<td>Mean minimal CB** temperature, mean±SD (°C)</td>
<td>-50±7</td>
<td>-47±6</td>
<td>-49±5</td>
<td>-44±5</td>
<td>-49±9</td>
</tr>
</tbody>
</table>

* RSPV = Right superior PV, † RIPV = Right inferior PV, ‡ LSPV = Left superior PV, § LIPV = Left inferior PV, ‖ LCPV = Left common PV, # PVs = Pulmonary veins, ** CB = cryoballoon
Table 3: Analysis of procedural parameters during the index ablation procedure comparing isolated versus reconnected pulmonary veins

<table>
<thead>
<tr>
<th></th>
<th>Isolated PVs*</th>
<th>Reconnected PVs*</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PVs*, n</td>
<td>178</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Total CB† cycles per PV*, mean±SD</td>
<td>1.5±0.7</td>
<td>1.4±0.6</td>
<td>0.94</td>
</tr>
<tr>
<td>Total CB† cycles per PV* until PVI‡, mean±SD</td>
<td>1.2±0.5</td>
<td>1.2±0.6</td>
<td>0.46</td>
</tr>
<tr>
<td>Number of PVs* with bonus freeze cycle, n (%)</td>
<td>39 (21)</td>
<td>19 (25)</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean minimal CB† temperature, mean±SD (°C)</td>
<td>-48±6</td>
<td>-46±7</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean time to PVI‡, mean±SD (sec.)</td>
<td>55±35</td>
<td>61±43</td>
<td>0.66</td>
</tr>
</tbody>
</table>

* PV(s) = Pulmonary vein(s), † CB = cryoballoon, ‡ PVI = pulmonary vein isolation
Table 4: Analysis of patients’ characteristics according to isolated versus reconnected pulmonary veins

<table>
<thead>
<tr>
<th></th>
<th>Patients with isolated PVs*</th>
<th>Patients with reconnected PVs*</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients, n</td>
<td>17</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>66±10</td>
<td>61±10</td>
<td>0.12</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>8 (47)</td>
<td>28 (63)</td>
<td>0.24</td>
</tr>
<tr>
<td>Paroxysmal AF†, n (%)</td>
<td>10 (59)</td>
<td>30 (61)</td>
<td>0.86</td>
</tr>
<tr>
<td>LA‡ size, mean±SD (mm)</td>
<td>46±6</td>
<td>44±6</td>
<td>0.32</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>10 (59)</td>
<td>30 (61)</td>
<td>0.86</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1 (6)</td>
<td>5 (10)</td>
<td>0.59</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>1 (6)</td>
<td>6 (12)</td>
<td>0.46</td>
</tr>
<tr>
<td>With bonus freeze cycle, n (%)</td>
<td>4 (24)</td>
<td>11 (22)</td>
<td>0.93</td>
</tr>
<tr>
<td>Mean procedure time, mean±SD (min)</td>
<td>127±40</td>
<td>140±42</td>
<td>0.27</td>
</tr>
<tr>
<td>Time until repeat PVI§, (median – 25th, 75th percentile) [days]</td>
<td>172 (115-321)</td>
<td>211 (136-362)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

* PV(s) = Pulmonary vein(s), † AF = atrial fibrillation, ‡ LA = left atrium, § PVI = pulmonary vein isolation. Values expressed as n (%), mean± standard deviation or median (25th, 75th percentiles).
Figure Legends:

**Figure 1:** Patients flow chart for repeat ablation

AF = atrial fibrillation, AT = atrial tachycardia, Aflutter = atrial flutter, PAF = paroxysmal AF,
PersAF = persistent AF, PV(s) = Pulmonary vein(s), PVI = Pulmonary vein isolation

**Figure 2:** Location of electrical reconduction gaps in previously isolated pulmonary veins.

Septal and lateral pulmonary vein ostia are divided into four segments (antero-superior, antero-inferior, postero-superior, postero-inferior). Numbers express the number of reconduction gaps found in each segment. Only one gap was found within the inter pulmonary vein area between ipsilateral pulmonary veins. Data for a left common pulmonary vein (n = 6) is not shown. RSPV = Right superior pulmonary vein, RIPV = Right inferior pulmonary vein, LSPV = Left superior pulmonary vein, LIPV = Left inferior pulmonary vein
Pulmonary vein isolation (PVI) procedures with second-generation 28mm Cryoballon
06/2012 - 05/2015
N = 421

N = 66/421 (16%) patients with repeat procedures:
Median: 205 (129-357) days after initial PVI

Repeat procedures due to:
- PAF: n = 26/66 (39%)
- PersAF: n = 26/66 (39%)
- AT: n = 10/66 (15%)
- Aflutter: n = 4/66 (6%)

Repeat Procedures:
In total n = 258 PVs
N = 80 (31%) PVs showed reconduction
N = 178 (69%) PVs were still isolated

Follow-up:
N = 50/63 (79%) patients with stable sinus rhythm
after a median of 135 (16-377) days
Once Isolated, Always Isolated? Incidence and Characteristics of Pulmonary Vein Reconduction after Second-Generation Cryoballoon-Based Pulmonary Vein Isolation
Christian-Hendrik Heeger, Erik Wissner, Shibu Mathew, Sebastian Deiss, Christine Lemes, Andreas Rillig, Peter Wohlmuth, Bruno Reissmann, Roland Richard Tilz, Feifan Ouyang, Karl-Heinz Kuck and Andreas Metzner

Circ Arrhythm Electrophysiol. published online September 3, 2015;
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/early/2015/09/03/CIRCEP.115.003007

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Arrhythmia and Electrophysiology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Arrhythmia and Electrophysiology is online at:
http://circep.ahajournals.org/subscriptions/