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

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

Methods and Results—A total of 421 patients underwent second-generation 28-mm cryoballoon-based PVI in 2 centers (St. George’s hospital and Harburg hospital, Hamburg, Germany) between June 2012 and May 2015. Sixty-six of 421 (16%) patients (39/66, 59% women; mean age, 63±10 years, mean left atrium diameter, 45±6 mm) with a history of paroxysmal atrial fibrillation (40/66, 61%) or persistent atrial fibrillation and atrial tachyarrhythmia recurrences despite previous successful second-generation 28-mm cryoballoon-based PVI were included in this analysis. During the index PVI, the standard freeze cycle duration was 240 s. After successful PVI, a bonus freeze cycle of 240 s was applied in the first 15 of 66 (23%) patients, whereas 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. Electric reconduction was assessed for all PVs, and reablation was performed using radiofrequency energy. Persistent electric isolation was noted in 178 of 258 (69%) PVs. In 17 of 66 (26%) patients, all previously targeted PVs remained isolated. A significant difference toward highest reconduction rate for the posteroinferior segment of the right inferior PV was found (P=0.0002).

Conclusions—The second-generation cryoballoon ablation is associated with a high rate of persistent PVI. The posteroinferior segment of the right inferior PV showed the highest reconduction rate and seems to be a predilection site for PV reconduction. (Circ Arrhythm Electrophysiol. 2015;8:1088-1094. DOI: 10.1161/CIRCEP.115.003007.)

Key Words: atrial fibrillation ■ cryosurgery ■ pulmonary veins ■ recurrence ■ tachycardia, supraventricular

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), whereas demonstrating encouraging 1-year clinical outcome in patients with paroxysmal atrial fibrillation (PAF) or persistent atrial fibrillation (AF). The reported 1-year clinical success rates range from 80% to 84% for PAF and ≤69% for persistent AF. One explanation for these encouraging success rates may be a persistent high rate of PVI over time. In this regard, this study set out to evaluate the rate of electric reconduction in patients presenting for reablation because of recurrence of atrial tachyarrhythmias (ATA) following initial 28-mm 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 28-mm CB-based PVI were admitted for reablation and included in the study. Transesophageal echocardiography was performed before ablation in all patients to rule out intracardiac thrombi. No additional preprocedural imaging was performed. All patients gave written informed consent, and all patient information was anonymized. All data were 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 2 diagnostic catheters were positioned inside the coronary sinus and along the His-bundle, respectively. A single (index ablation) or double (repeat ablation) transeptal puncture was performed under fluoroscopic guidance using a modified Brockenbrough technique and 1 or 2 8.5F transeptal sheaths (TS; SL1, St. Jude Medical Inc, St. Paul, MN). Heparin was given to maintain an activated clotting time of ≥300 s. To identify the PV ostia, selective PV angiography was performed.

Index PVI Using the Second-Generation 28-mm Cryoballoon
The regular TS was exchanged over a guidewire for a 12F steerable TS (Flexcath Advance, Medtronic Inc., Minneapolis, MN). The
WHAT IS KNOWN

- Catheter-based pulmonary vein isolation is an established treatment option for patients with symptomatic atrial fibrillation, as stated in the current guidelines.
- The second-generation cryoballoon has proven safe and effective for pulmonary vein isolation with a high rate of freedom from recurrent atrial fibrillation during 1 and 2-year clinical follow-up.

WHAT THE STUDY ADDS

- In 26% of patients durable isolation of all pulmonary veins is noted during a repeat procedure for recurrent atrial fibrillation after initial second-generation cryoballoon-based pulmonary vein isolation. Overall, 69% of pulmonary veins demonstrated durable electrical isolation.
- Electric reconduction gaps are most commonly located along the posteroinferior portion of the right inferior pulmonary vein.

Repeat Procedures

In patients admitted for a repeat procedure because of ATA recurrence, an electroanatomical LA map (Carto 3, Biosense Webster Inc., Diamond Bar, CA) was generated and the PV ostia tagged on the LA map. Persistent PVI or electric reconnection of previously isolated PVs was assessed by the presence or absence of electric activity inside each PV using a spiral mapping catheter (Lasso, Biosense-Webster). Identified reconduction gaps were assigned to 4 segments (anteroseptal, anterolateral, posteroseptal, and posterolateral) and closed by radiofrequency ablation using a 3.5-mm irrigated tip catheter (Biosense Webster, Navi-Star, Thermo-Cool). In patients with persistent isolation of all PVs admitted in SR, fractionated ostial potentials along previously performed ablation lines were identified, and ablated and 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 (CFAEs) and deployment of linear lesion sets in case of conversion to an AT.12–25

Postprocedural Care

After 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 international normalized ratio (INR) <2.0 until a therapeutic INR of 2 to 3 was achieved. Novel oral anticoagulants were reinitiated 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

After a blanking period of 3 months, patients completed outpatient clinic visits at 3, 6, and 12 months with 24-hour 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 2 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 χ² test or with Fisher 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 is analyzed with Wilcoxon signed-rank 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 2-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).

Results

Patient Characteristics

Between June 2012 and May 2015, a total of 421 patients underwent second-generation 28-mm CB-based PVI in 2 centers (St. George’s Hospital and Harburg Hospital, both Hamburg, Germany). A repeat procedure because of ATA recurrence was performed in 66 of 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 PVI

A total of 258 PVs were identified in 66 patients (66 right superior PVs [RSPVs], 66 right inferior PVs [RIPVs], 60 left superior PVs [LSPVs], 60 left inferior PVs [LIPVs], and 6 left common PVs [LCPVs]). 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 of 66 (82%) RSPVs, 53 of 66 (80%) RIPVs, 49 of 60 (82%) LSPVs, 53/60 (88%) LIPVs, and 4 of 6 (67%) LCPVs. In the first 15 of 66 (23%) patients, a bonus freeze cycle was applied, which was omitted in the remaining 51 of 66 (77%) patients. The mean number of CB applications per PV is listed in Table 3. The average procedure and fluoroscopy time were 136±41 and
21±8 minutes, including a 30-minute waiting period after the final freeze cycle.

Findings During Reablation Procedures

In a total of 80 of 258 (31%) PVs, LA-to-PV reconduction was demonstrated, whereas persistent PVI was documented in 178 of 258 (69%) PVs. The LA-to-PV reconduction rate was comparable for patients with PAF (47 of 156 PVs, 30%) and persistent AF (33 of 102 PVs, 32%; P=0.58). In 17 of 66 (26%) patients, all PVs were still isolated. LA-to-PV reconstruction of single PV was noted in 28 of 66 (42%) patients, whereas 2 and 3 recovered PVs were identified in 14 of 66 (21%) and 5 of 66 (8%) patients, respectively. Two patients (3%) demonstrated electric reconduction of all 4 PVs. LA-to-PV reconduction was seen in 16 of 66 (24%) RSPVs, 31 of 66 (47%) RIPVs, 17 of 60 (28%) LSPVs, 14 of 60 (23%) LIPVs, and 2 of 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), and RSPV and LSPV (P>0.99) were not significant.

In 43 of 49 (88%) patients demonstrating LA-to-PV reconduction, a detailed description of the location of each gap was provided, whereas in 6 of 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 of 43 (56%) patients, a single gap was found, whereas in 11 of 43 (26%) and in 7 of 43 (16%) patients, 2 and 3 gaps were identified, respectively. In 1 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 toward highest reconduction rate for the posteriorinferior segment of the RIPV was found (22/77 [29%], P=0.0002). When comparing patients with PAF and persistent AF about the reconduction rate for the posteriorinferior 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 of 66 (74%) patients, electric reconduction of previously isolated PVs was identified. Reisolation of all PVs was successfully performed using radiofrequency energy. In 10 of 49 (20%) patients, complete circumferential ablation lines around the ipsilateral PVs were applied. In addition, ablation of ostial potentials was performed in 13 of 49 (27%) patients, CFAE ablation in 2 of 49 (4%) patients, and of linear lesions ablation in 9 of 49 (18%) patients (n=2 mitral isthmus lines, n=7 anterior lines).

In 6 of 17 (35%) patients with persistent isolation of all PVs admitted in SR, ostial potentials were targeted for ablation. In 2 patients (12%), a roof line was deployed. In 4 of 17 (24%) patients presenting in AF, ablation of ostial potentials was followed by CFAE ablation. An additional 6 of 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 1 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 of 66 (23%) patients because of documented typical cavotricuspid-dependent atrial flutter. Periprocedural stroke occurred in 1 of 66 (1.5%) patients. 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 were 131±46 and 15±9 minutes, respectively.

Predictors of PV 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 reablation was completed in 63 of 66 (95%) patients, whereas 3 of 66 (5%) patients were lost to follow-up. After a median follow-up of 135 (16–377) days, 50 of 63 (79%) patients were in stable SR, 13 of 63 (21%) patients developed ATA recurrence in the form of AF in 8 of 13 (62%) patients and AT in 5 of 13 (38%) patients. In 9 of 13 (69%) patients, a third ablation procedure was performed. In 8 of 9 (89%) patients, all PVs were still isolated, whereas 1 patient showed reconduction of the RIPV and LSPV. Therefore, a total of 34 of 36 (94%) patients identified that PVs were still isolated after the second procedure.

Discussion
This study sought to assess the incidence and location of PV reconduction after initial second-generation 28-mm 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 electric reconduction was found for the posteroinferior segment of the RIPV, and (4) the majority of PVs demonstrating electric reconduction had only a single reconduction gap.

Compared with 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 after second-generation CB-based PVI in patients having PAF ranges between 80% and 84%.2,3,5,6 Promising 1-year success rates were also reported for persistent AF with freedom from ATA recurrence in ≤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 extracardiac structures, such as the esophagus or the phrenic nerve.9,10,17,18 Recently reported endoluminal esophageal temperature cutoffs have resulted in a significant reduction in thermal esophageal injury, whereas the development and evaluation of multiple safety algorithms to prevent phrenic nerve palsy, such as compound motoric activation potential pacing or the double-stop technique, have further improved the safety profile of the second-generation CB.11,17,19,20

It had yet to be evaluated whether the greater clinical efficacy of the second-generation CB is because of a higher rate of permanently isolated PVs. Using the first-generation CB, the rate of electric reconduction was 54%.21 For the second-generation CB, only a single study evaluated the incidence of PV reconduction.22 In 18 patients admitted for reablation

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**Table 2. Procedural Characteristics of Index CB-Based PV 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>No. of PVs, n</td>
<td>66</td>
<td>66/66 (100)</td>
<td>60/60 (100)</td>
<td>60/60 (100)</td>
<td>6/6 (100)</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>53/66 (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>

CB indicates cryoballoon; LCPV, left common PV; LIPV, left inferior PV; LSPV, left superior PV; RIPV, right inferior PV; and RSPV, right superior PV.

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**Table 3. Analysis of Procedural Parameters During the Index Ablation Procedure Comparing Isolated Versus Reconnected PVs**

<table>
<thead>
<tr>
<th></th>
<th>Isolated PVs</th>
<th>Reconnected PVs</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 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>No. 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 (s)</td>
<td>55±35</td>
<td>61±43</td>
<td>0.66</td>
</tr>
</tbody>
</table>

CB indicates cryoballoon; and PVI, pulmonary vein isolation.
because of recurrent ATA, persistent electric isolation was demonstrated in 55 of 71 (77%) previously isolated PVs, whereas in 6 of 18 (33%) patients, all 4 PVs were still isolated. 

This study confirms that 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%) when compared with 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 RIPVs exhibited the highest rate of electric reconduction. This may be explained by imperfect alignment of the ablation system with the course of the RIPVs 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. Because 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 because of the effective cooling profile of the second-generation CB. However, there is an overlay of ablation lesions between the superior and the inferior lateral PVs because they are usually in close anatomic proximity. Consequently, the ridge, which is characterized by thick muscular tissue, should be effectively ablated.

This study included patients treated with or without a bonus freeze cycle after 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 about the

| Table 4. Analysis of Patients’ Characteristics According to Isolated Versus Reconnected PVs |
|-----------------------------------------------|-----------------------------------------------|-----------------|
| Patients With Isolated PVs | Patients With Reconnected PVs | P Value |
| No. of patients, n | 17 | 49 | 0.12 |
| Age, y | 66±10 | 61±10 | 0.24 |
| Female sex, n (%) | 8 (47) | 28 (63) | 0.24 |
| Paroxysmal AF, n (%) | 10 (59) | 30 (61) | 0.86 |
| LA size, mean±SD, mm | 46±6 | 44±6 | 0.32 |
| Arterial hypertension, n (%) | 10 (59) | 30 (61) | 0.86 |
| Diabetes mellitus, n (%) | 1 (6) | 5 (10) | 0.59 |
| Coronary artery disease, n (%) | 1 (6) | 6 (12) | 0.46 |
| With bonus freeze cycle, n (%) | 4 (24) | 11 (22) | 0.93 |
| Mean procedure time, mean±SD (min) | 127±40 | 140±42 | 0.27 |
| Time until repeat PVI, (median: 25th, 75th percentile), d | 172 (115–321) | 211 (136–362) | 0.46 |

Values expressed as n (%), mean±SD, or median (25th, 75th percentiles). AF indicates atrial fibrillation; LA, left atrium; and PVI, pulmonary vein isolation.
best treatment strategy during the repeat procedure. In patients demonstrating electric PV, reconnection 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 because 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, whereas in patients presenting with 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 2-center experience enrolling a limited number of patients. The follow-up was limited to 24-hour Holter ECGs. This might overestimate the success rate after repeat ablation procedures as closer follow-up (eg, 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. Because of low patients number, subgroup analyses are not powered enough to evaluate outcome 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 reconnection 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

After second-generation CB-based PVI, a high rate of persistent PV was demonstrated in patients with recurrent ATA presenting for a repeat ablation procedure. Electric PV reconnection was more frequently demonstrated for the posterior-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.

Disclosures

Dr Metzner received speaker’s honoraria from Medtronic. Dr Wisser received speaker’s honoraria from Medtronic and is a member of Medtronic’s advisory board. Dr Kuck received a research grant and speaker’s honoraria from Medtronic. The other authors report no conflicts.

References


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Circ Arrhythm Electrophysiol. 2015;8:1088-1094; originally published online September 3, 2015;
doi: 10.1161/CIRCEP.115.003007

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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