One-Year Clinical Outcome After Pulmonary Vein Isolation Using the Second-Generation 28-mm Cryoballoon

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Background—The use of second-generation cryoballoon for pulmonary vein isolation in patients with paroxysmal atrial fibrillation has demonstrated encouraging acute and mid-term results. Long-term outcome data are not yet available.

Methods and Results—Fifty patients (18 women; mean age, 61±11 years; mean left atrial diameter, 43±5 mm) with paroxysmal (36 of 50 patients; 72%) or short-standing (<3-month duration) persistent atrial fibrillation (14 of 50 patients; 28%) underwent cryoballoon-based pulmonary vein isolation. Freeze cycle duration was 240 seconds. After successful pulmonary vein isolation, a bonus freeze was applied. Follow-up was based on outpatient clinic visits at 3, 6, and 12 months including Holter-ECGs and telephonic interviews. Recurrence was defined as a symptomatic or documented arrhythmia episode >30 seconds excluding a 3-month blanking period. A total of 192 pulmonary veins were identified, and 191 of 192 (99%) pulmonary veins were successfully isolated. Phrenic nerve palsy occurred in 1 of 50 (2%) patients. Follow-up was available for 49 of 50 (98%) patients with a mean follow-up duration of 440±39 days. Thirty-nine of 49 (80%) patients remained in stable sinus rhythm. Of 8 of 10 patients with arrhythmia recurrence, a second procedure using radiofrequency ablation demonstrated left atrial to pulmonary vein reconnection.

Conclusions—The use of second-generation 28-mm cryoballoon for pulmonary vein isolation results in an 80% 1-year success rate. (Circ Arrhythm Electrophysiol. 2014;7:288-292.)

Key Words: ablation ■ atrial fibrillation ■ follow-up studies

The cryoballoon (Artic Front Advance; Medtronic Inc, Minneapolis, MN) has gained increasing acceptance as an effective ablation tool for pulmonary vein isolation (PVI). Although the first-generation cryoballoon demonstrated moderate long-term clinical efficacy combined with an acceptable safety profile,1-3 the second-generation cryoballoon has been optimized for better performance. Despite an identical outer shape, modifications to the refrigerant injection system allow for improved cooling of the distal balloon hemisphere. Initial acute and mid-term clinical results have been published, reporting an improvement in efficacy compared with the first-generation cryoballoon.4,5 Furthermore, the rate of phrenic nerve (PN) palsy6,7 and esophageal thermal injury8,9 has been described. However, 1-year clinical outcome after PVI using the second-generation 28-mm cryoballoon has not yet been reported.

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Methods

Inclusion and Exclusion Criteria

Consecutive patients with symptomatic, drug-refractory paroxysmal atrial fibrillation (PAF) or short-standing persistent AF (duration ≤3 months) were admitted and consented for cryoballoon-based PVI. Exclusion criteria were previous left atrial (LA) ablation, LA diameter >60 mm, severe valvular heart disease, or contraindications to postinterventional oral anticoagulation. Transesophageal echocardiography was performed before PVI to assess the LA diameter and to rule out intracardiac thrombi. No additional preprocedural imaging was performed.

The study was approved by our institutional review committee. All patients gave written informed consent.

Intraprocedural Management

In brief, the procedure was performed under deep sedation using midazolam, fentanyl, and propofol. Before transseptal puncture, 2 diagnostic catheters were introduced via the right femoral vein and positioned within the coronary sinus and along the His-bundle. Single transseptal puncture was performed via the right femoral vein under fluoroscopic guidance using a modified Brockenbrough technique and an 8.5-F transseptal sheath (SL1; St Jude Medical, Inc, St Paul, MN). The transseptal sheath was exchanged over a guidewire for a 12-F steerable sheath (Flexcath Advance, Medtronic Inc). A heparin bolus was administered targeting an activated clotting time >300 seconds. Subsequently, selective PV angiography was performed to identify the individual PV ostia. A temperature probe (Sensitherm; St Jude Medical) was placed within the esophagus at the level of the individual cryoballoon position to monitor esophageal temperatures during the freeze cycle. The intraluminal esophageal temperature cut-off was set at 10°C.7

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PVI Using the Second-Generation 28-mm Cryoballoon

The 28-mm cryoballoon was advanced into the LA via the 12-F steerable sheath using a spiral mapping catheter (15 or 20 mm diameter; Achieve; Medtronic Inc) as a guidewire. The cryoballoon was inflated proximal to the PV ostium followed by gentle push aiming for complete sealing at the antral aspect of the PV. Contrast medium injected through the central lumen of the cryoballoon was used to verify complete occlusion of the PV ostium. This was followed by a freeze cycle of 240 seconds. After successful PVI, 1 additional bonus freeze of 240 ms duration was applied.

The procedural end point was defined as persistent PVI verified by spiral mapping catheter recordings 30 minutes after the last energy application.

Phrenic Nerve Pacing

During cryoenergy application along the septal PVs, continuous pacing of the PN was performed using a diagnostic catheter positioned within the superior vena cava (7 F; Webster TM; Biosense Webster, Inc). Pacing was set at maximum output and pulse width (12 mA, 2.9 ms) at a cycle length of 1200 ms. PN capture was monitored by intermittent fluoroscopy and tactile feedback placing the operator’s hand on the patient’s abdomen. Refrigerant delivery was immediately stopped, if weakening or loss of diaphragmatic movement was noted. In case of catheter dislodgement, the pacing catheter was repositioned until PN capture was achieved. No further cryoenergy was delivered along the septal PVs, if PN palsy had occurred.

Postprocedural Care

After ablation, all patients underwent transesophageal echocardiography to rule out pericardial effusion. All patients were treated with proton pump inhibitors twice daily for 6 weeks. Low-molecular-weight heparin was administered in patients on vitamin K antagonists and an international normalized ratio <2.0 until a therapeutic international normalized ratio was achieved. An anticoagulation regimen was continued for ≥3 months and continued thereafter based on the individual CHA2DS2-VASC score. Previously ineffective antiarrhythmic drugs were continued for 3 months.

Repeat Procedures

In patients admitted for a repeat procedure because of AF recurrence, venous access and transseptal puncture were performed as previously described. The presence or absence of electric activity inside the PVs was assessed using a spiral mapping catheter. An electroanatomical LA map (Carto; Biosense Webster) was generated and the PV ostia were tagged. Identified gaps within the previously performed ablation lines were closed by irrigated radiofrequency ablation using a 3.5-mm irrigated tip catheter (Navi-Star and Thermo-Cool; Biosense Webster). The procedural end point was complete electric PVI.

Follow-Up

After a blanking period of 3 months, patients completed outpatient clinic visits at 3, 6, and 12 months including 24-hour Holter-ECGs. In addition, regular telephonic interviews were performed. Additional outpatient clinic visits were immediately initiated in case of symptoms suggestive of recurrent arrhythmia.

End Points

The primary end point was AF recurrence, defined as a documented episode of AF >30 seconds, either symptomatic or asymptomatic, on Holter-ECG or 12-lead ECG. Secondary end points were defined as procedure-related complications such as PN palsy, cerebral embolism, or atrioesophageal fistula.

Statistical Analysis

Continuous data are shown as mean and standard deviation. Survival curves were generated with the Kaplan–Meier technique. All P values are 2-sided, and a P<0.05 was considered significant.

Results

Patient Characteristics

A total of 50 patients (18 women; mean age, 61±11 years; mean LA diameter, 43±5 mm) with a history of PAF (36 of 50 patients; 72%) or short-standing persistent AF (14 of 50 patients; 28%) underwent 28-mm cryoballoon-based PVI. Atrial hypertension was present in 37 of 50 (74%) patients, stable coronary artery disease in 6 of 50 (12%) patients, and diabetes mellitus in 8 of 50 (16%) patients, respectively (Table 1).

Acute Ablation Results

In our cohort of 50 patients, 192 PVs were identified (50 right superior PVs [RSPVs], 50 right inferior PVs [RIPVs], 42 left superior PVs [LSPVs], 42 left inferior PVs [LIPVs], and 8 left common PVs [LCPVs]). A total of 191 of 192 (99%) PVs were successfully isolated using the second-generation 28-mm cryoballoon. Because of loss of PN capture during energy application along the RSPV, 1 of 50 (2%) RIPVs was not targeted. During the first cryoballoon application, electric PVI was achieved in 46 of 50 (92%) RSPVs, 41 of 50 (82%) RIPVs, 37 of 42 (88%) LSPVs, 42 of 42 (100%) LIPVs, and in 4 of 8 (50%) LCPVs. The mean number of cryoapplications resulting in PVI was 1.1±0.5, 1.3±0.6, 1.1±0.3, 1.0±0, and 1.5±0.5 for the RSPV, RIPV, LSPV, LIPV, and LCPV, respectively. A single bonus cryoapplication was applied after successful PVI. Hence, the average total number of cryoballoon applications including the bonus freeze cycle was 2.2±0.5, 2.2±0.7, 2.1±0.3, 2.0±0, and 2.5±0.5 for the RSPV, RIPV, LSPV, LIPV, and LCPV, respectively (Table 2).

Mean procedure duration was 140±28 minutes including a waiting period of 30 minutes. Mean fluoroscopy time was 25±8 minutes.

Complications

As the only complication, PN palsy occurred in 1 of 50 (2%) patients during cryoblation along the RSPV. PN palsy was persistent throughout the hospital stay and during fluoroscopic reevaluation at 3 and 6 months postablation. However, PN palsy completely resolved 10 months postablation.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±11</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>18 (36)</td>
</tr>
<tr>
<td>LA size, mm</td>
<td>43±5</td>
</tr>
<tr>
<td>Paroxysmal AF, n (%)</td>
<td>36 (72)</td>
</tr>
<tr>
<td>Short-term persistent AF, n (%)</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>37 (74%)</td>
</tr>
<tr>
<td>Coronary artery disease, n</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>8 (16)</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; and LA, left atrium.
No pericardial effusion, pericardial tamponade, symptomatic PV stenosis, cerebral embolism, or atrioesophageal fistula occurred in any of the remaining patients.

Clinical Follow-Up
Clinical long-term follow-up was obtained in 49 of 50 (98%) patients, whereas 1 of 50 (2%) patients was lost to follow-up. During a mean follow-up time of 440±39 days and after a single second-generation 28-mm cryoballoon-based PVI procedure including a 3-month blanking period, 39 of 49 (80%) patients (29 of 36 [81%] patients with PAF, 10 of 13 [77%] patients with short-term persistent AF) were in stable sinus rhythm without symptomatic or documented episode of AF (see the Figure). A symptomatic or documented atrial arrhythmia recurrence was observed in 10 of 49 (20%) patients (7 of 36 [19%] patients with PAF, 3 of 13 [23%] patients with short-term persistent AF). Five out of 7 (71%) patients with PAF presented with PAF on recurrence, whereas the remaining 2 of 7 (29%) patients presented with an atrial tachycardia. Two of 3 (67%) patients with short-term persistent AF presented with persistent AF and 1 of 3 (33%) patients with PAF.

Repeat Procedures
A total of 8 of 10 (80%) patients with arrhythmia recurrence underwent a second ablation procedure using radiofrequency ablation 207±119 days after the index procedure. LA to PV reconnection in at least 1 right-sided PV was found in 7 of 8 (88%) patients and in at least 1 left-sided PV in 6 of 8 (75%) patients. In 1 of 8 (13%) patients with PAF, 2 focal atrial tachycardias were mapped and ablated within the LA in addition to reisolation of the PVs. In a second patient with PAF, an additional anterior line, a roofline, and a posterior line were deployed within the LA due a macro-reentrant atrial tachycardia.

For the second procedure, the mean procedure time was 160±50 minutes using a mean fluoroscopy time of 19±10 minutes.

Discussion
This is the first study to report 1-year follow-up outcome after PVI using the second-generation 28-mm cryoballoon. The current study found that (1) 1-year clinical success rate was 80% (81% for PAF, 77% for short-term persistent AF) and thus superior to reported long-term follow-up using the first-generation cryoballoon; (2) all patients with tachyarrhythmia recurrence had at least 1 PV demonstrating LA to PV reconnection as a potential source for arrhythmia recurrence; and (3) the peri- and postinterventional complication rate was low.

The first-generation cryoballoon has demonstrated acute and long-term clinical results comparable to radiofrequency ablation with a similar safety profile.\textsuperscript{1,3,11,12} A freeze cycle of 300 seconds resulting in acute PVI was typically followed by a bonus freeze of the same duration. Applying a second bonus freeze failed to demonstrate additional benefit and was associated with an increase in complications.\textsuperscript{13} Via a spiral mapping catheter (Achieve) introduced through the central lumen of the

Table 2. Acute Ablation Results

<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>50</td>
<td>50</td>
<td>42</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Isolated PVs, n (%)</td>
<td>50/50 (100)</td>
<td>49/50 (98)</td>
<td>42/42 (100)</td>
<td>42/42 (100)</td>
<td>8/8 (100)</td>
</tr>
<tr>
<td>Isolation during first cryoapplication, n (%)</td>
<td>46/50 (92)</td>
<td>41/50 (82)</td>
<td>37/42 (88)</td>
<td>42/42 (100)</td>
<td>4/8 (50)</td>
</tr>
<tr>
<td>No. of cryoapplications until PVI, mean±SD</td>
<td>1.1±0.5</td>
<td>1.3±0.6</td>
<td>1.1±0.3</td>
<td>1.0±0.0</td>
<td>1.5±0.5</td>
</tr>
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LCPV indicates left common pulmonary vein (PV); LIPV, left inferior PV; LSPV, left superior PV; RIPV, right inferior PV; RSPV, right superior PV; and PVI, PV isolation.
catheter, PV signals could be recorded allowing for live verification of PVI in ≈49% of targeted PVs.4

By contrast, the second-generation cryoballoon incorporates a modified refrigerant injection system providing homogeneous cooling of the complete distal balloon hemisphere resulting in extensive ice formation on the balloon surface.10 Initial studies demonstrated an improvement in procedural efficacy compared with the first-generation balloon with an 84% acute isolation rate during the first freeze cycle.4 Furthermore, the rate of live registration of electric PVI via the spiral mapping catheter increased from 49% to 76% when comparing both cryoballoon generations.4 In turn, an increase in acute efficacy has led to a higher rate of injury to adjacent noncardiac anatomic structures such as the esophagus or PN. The incidence of esophageal thermal injury after PVI using the 28-mm second-generation cryoballoon ranges between 12% and 19%.64 Based on these results, safety cut-offs for the intraluminal esophageal temperature were developed to reduce the risk of esophageal thermal injury.63 The incidence of PN palsy during second-generation cryoballoon-based PVI was reported as high as 19.5%.6 At our center, the rate is 3.5%7 and thus comparable to the first-generation cryoballoon.3

In our electrophysiology laboratories, only the 28-mm cryoballoon is used because of 2 reasons: first, our rate of acute PVI using only the 28-mm cryoballoon is 99%; second, the 28-mm cryoballoon is usually bigger than a normal-sized PV. This leads to an ablation lesion covering a substantial portion of the potentially arrhythmogenic PV antrum. Using the 23-mm cryoballoon increases the risk of ablation inside the PV, thus increasing the potential risk for PN paralysis when ablating the right superior or the right inferior PV. Also the risk of PV stenosis and esophageal thermal injury may be higher using a cryoballoon of smaller diameter.

Only 6-month clinical outcome data using the second-generation 28-mm cryoballoon have been reported to date.4 Applying a single 180-second freeze cycle, 82% of patients remained in sinus rhythm.4 In the current study, freeze cycle duration was 240 seconds, and after successful PVI, a bonus freeze of the same duration was applied. Using this protocol, the 1-year clinical success rate was 80%. Compared with published results from our center using the first-generation 28-mm cryoballoon in patients with PAF applying a 300-second freeze cycle, the 1-year success rate improved from 52% to 80%.13

The encouraging results reported in the present study raise the question whether a bonus freeze cycle after successful PVI is actually necessary. Although 6-month results after a single freeze application are encouraging, long-term outcome data will have to provide more data to support a single-shot strategy. In view of the high rate of live verification of successful PVI using the Achieve catheter, future studies may focus on time to effect, that is, adjusting freeze cycle duration to the individual patient depending on the time to isolation.4 A reduction in the number or duration of individual freeze cycles per PV may also contribute to shorter procedure and fluoroscopy times while further decreasing the risk for adverse events.

In the current study, all patients with arrhythmia recurrence who underwent a second radiofrequency ablation procedure demonstrated electric LA to PV reconnection into at least 1 PV. The precise evaluation of the quantity and location of reconnection gaps needs further evaluation and will be the focus of upcoming studies.

Limitations
The present study represents the experience of a single center. No comparison group was included. However, results are compared with the outcome of a patient cohort from our center previously published using the first-generation 28-mm cryoballoon and a similar ablation protocol (1 bonus freeze cycle, 300-second freeze duration).11,13

Conclusions
The use of second-generation 28-mm cryoballoon for PVI results in an 80% 1-year success rate. Future studies will need to evaluate whether forgoing a bonus freeze would result in similar encouraging long-term outcome.

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

References


**CLINICAL PERSPECTIVE**

The cryoballoon (Artic Front Advance; Medtronic, Inc, Minneapolis, MN) has gained increasing acceptance as an effective ablation tool for pulmonary vein isolation (PVI). Although the first-generation cryoballoon demonstrated moderate long-term clinical efficacy combined with an acceptable safety profile, the second-generation cryoballoon has been optimized for better performance. Despite an identical outer shape, modifications to the refrigerant injection system allow for improved cooling of the distal balloon hemisphere. Initial acute and mid-term clinical results have been published, reporting an improvement in efficacy compared with the first-generation cryoballoon. This is the first study to report 1-year follow-up outcome after PVI using the second-generation 28-mm cryoballoon. A total of 50 patients (18 women; mean age, 61±11 years; mean left atrial [LA] diameter, 43±5 mm) with a history of paroxysmal atrial fibrillation (PAF; 36 of 50 patients; 72%) or short-standing persistent AF (14 of 50 patients; 28%) underwent 28-mm cryoballoon-based PVI. A total of 192 PVs were identified and 191 of 192 (99%) PVs were successfully isolated. The 1-year clinical success rate was 80% (81% for PAF, 77% for short-term persistent AF) and thus superior to reported long-term follow-up using the first-generation cryoballoon. All patients with tachyarrhythmia recurrence had at least 1 PV demonstrating LA to PV reconduction as a potential source for arrhythmia recurrence. The peri- and postinterventional complication rate was low.
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