One-Year Clinical Outcome after Pulmonary Vein Isolation using the Second-Generation 28mm Cryoballoon

Running title: Metzner et al.; One-year outcome after novel cryoballoon-based PVI

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Abstract:

**Background** - Use of the second-generation cryoballoon (CB) for pulmonary vein isolation (PVI) in patients with paroxysmal atrial fibrillation (AF) has demonstrated encouraging acute and mid-term results. Long-term outcome data is not yet available.

**Methods and Results** - Fifty patients (18 female, mean age 61±11 years, mean LA-diameter 43±5mm) with paroxysmal (36/50 [72%] patients) or short-standing (<3 months duration) persistent AF (14/50 [28%] patients) underwent CB-based PVI. Freeze cycle duration was 240 sec. After successful PVI 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 and/or documented arrhythmia episode >30 sec excluding a 3-month blanking period. A total of 192 pulmonary veins (PV) were identified and 191/192 (99%) PVs were successfully isolated. Phrenic nerve palsy occurred in 1/50 (2%) patients. Follow-up was available for 49/50 (98%) patients with a mean follow-up duration of 440±39 days. Thirty-nine of 49 (80%) patients remained in stable sinus rhythm. Of 8/10 patients with arrhythmia recurrence, a second procedure using radiofrequency ablation demonstrated left atrial to PV reconnection.

**Conclusions** - Use of the second-generation 28mm CB for PVI results in an 80% 1-year success rate.

**Keywords:** atrial fibrillation, atrial fibrillation arrhythmia, pulmonary vein isolation, cryoballoon, follow-up
Introduction

The cryoballoon (CB, Artic Front Advance, Medtronic, Inc., Minneapolis, MN, USA) has gained increasing acceptance as an effective ablation tool for pulmonary vein isolation (PVI). While the first-generation CB demonstrated moderate long-term clinical efficacy combined with an acceptable safety profile, the second-generation CB 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 midterm clinical results have been published reporting an improvement in efficacy if compared to the first-generation CB. Furthermore, the rate of phrenic nerve (PN) palsy and esophageal thermal injury has been described. However, 1-year clinical outcome following PVI using the second-generation CB has not yet been reported.

Methods

Inclusion and exclusion criteria

Consecutive patients with symptomatic, drug-refractory paroxysmal AF or short-standing persistent AF (duration of ≤ 3 months) were admitted and consented for CB-based PVI. Exclusion criteria were prior left atrial (LA) ablation, LA diameter >60 mm, severe valvular heart disease or contraindications to postinterventional oral anticoagulation. Transesophageal echocardiography was performed prior to 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. Prior to transseptal puncture (TP), two diagnostic catheters were introduced via the right femoral vein and positioned within the coronary sinus and along the His-bundle. Single TP was performed via the right femoral vein under fluoroscopic guidance using a modified Brockenbrough technique and an 8.5F transseptal sheath (SL1, St. Jude Medical, Inc., St. Paul, MN, USA). The transseptal sheath was exchanged over a guidewire for a 12F steerable sheath (Flexcath Advance, Medtronic, Inc., Minneapolis, MN, USA). A heparin bolus was administered targeting an activated clotting time of >300 sec. Subsequently, selective PV angiography was performed to identify the individual pulmonary vein (PV) ostia. A temperature probe (Sensitherm, St. Jude Medical) was placed within the esophagus at the level of the individual CB position to monitor esophageal temperatures during the freeze cycle. The intraluminal esophageal temperature cut-off was set at 10°C.7

**PVI using the second-generation 28mm CB**

The 28mm CB was advanced into the LA via the 12F steerable sheath using a spiral mapping catheter (15 mm or 20 mm diameter; Achieve™, Medtronic, Inc., Minneapolis, MN, USA) as a guidewire. The CB 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 CB was used to verify complete occlusion of the PV ostium. This was followed by a freeze cycle of 240 seconds. After successful PVI one additional bonus freeze of 240ms duration was applied.

The procedural endpoint was defined as persistent PVI verified by spiral mapping catheter recordings 30 min 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 (7F, Webster TM, Biosense Webster, Inc.). Pacing was set at maximum output and pulse width (12mA, 2.9ms) at a cycle length of 1200ms. 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**

Following ablation, all patients underwent transthoracic 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 INR <2.0 until a therapeutic INR of 2-3 was achieved. Novel oral anticoagulants were reinitiated 6 hours post ablation. Anticoagulation was continued for at least 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 due to AF recurrence, venous access and TP were performed as previously described. The presence or absence of electrical 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 RF ablation using a 3.5 mm irrigated-tip catheter (Biosense Webster, Navi-Star™, Thermo-Cool™). The procedural endpoint was complete electrical PVI.
Follow-up

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

Endpoints

The primary endpoint was AF recurrence, defined as a documented episode of AF >30sec, either symptomatic or asymptomatic, on Holter-ECG and/or 12-lead ECG. Secondary endpoints 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 two-sided and a p<0.05 was considered significant.

Results

Patient characteristics

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

Acute ablation results

In our cohort of 50 patients, 192 PVs were identified (50 right superior PVs [RSPV], 50 right inferior PVs [RIPV], 42 left superior PVs [LSPV], 42 left inferior PVs [LIPV] and 8 left
common PVs [LCPV]). A total of 191/192 (99%) PVs were successfully isolated using the second-generation 28mm CB. Due to loss of PN capture during energy application along the RSPV, 1/50 (2%) RIPVs was not targeted. During the first CB-application electrical PVI was achieved in 46/50 (92%) RSPVs, 41/50 (82%) RIPVs, 37/42 (88%) LSPVs, 42/42 (100%) LIPVs, and in 4/8 (50%) LCPVs, respectively. The mean number of cryo applications 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 CB 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 min including a waiting period of 30 min. Mean fluoroscopy time was 25±8 min.

Complications

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

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 FU was obtained in 49/50 (98%) patients, while 1/50 (2%) patients was lost to FU. During a mean FU time of 440±39 days and following a single second-generation 28mm CB-based PVI procedure including a 3-month blanking period, 39/49 (80%) patients (29/36 [81%] patients with PAF, 10/13 [77%] patients with short-term persistent AF) were in stable SR.
without symptomatic and/or documented episode of AF (figure 1). A symptomatic and/or documented atrial arrhythmia recurrence was observed in 10/49 (20%) patients (7/36 [19%] patients with PAF, 3/13 [23%] patients with short-term persistent AF). Five out of 7 (71%) patients with PAF presented with PAF upon recurrence while the remaining 2/7 (29%) patients presented with an atrial tachycardia (AT). Two out of 3 (67%) patients with short-term persistent AF presented with persistent AF and 1/3 (33%) patients with PAF.

**Repeat procedures**

A total of 8/10 (80%) patients suffering from arrhythmia recurrence underwent a second ablation procedure using RF 207±119 days after the index procedure. LA to PV reconduction in at least one right-sided PV was found in 7/8 (88%) patients and in at least one left-sided PV in 6/8 (75%) patients, respectively. In 1/8 (13%) patients with PAF, 2 focal ATs were mapped and ablated within the LA in addition to re-isolation 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 AT.

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

**Discussion**

This is the first study to report one-year FU outcome following PVI using the second-generation 28mm CB. The current study found that (1) the 1-year clinical success rate was 80% (81% for paroxysmal AF, 77% for short-term persistent AF) and thus superior to reported long-term FU using the first generation CB; (2) all patients with tachyarrhythmia recurrence had at least one PV demonstrating LA to PV reconduction as a potential source for arrhythmia recurrence, and (3) the peri- and postinterventional complication rate was low.
The first-generation CB has demonstrated acute and long-term clinical results comparable to RF ablation with a similar safety profile.\textsuperscript{1-3,11,12} A freeze cycle of 300 sec in duration 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 catheter PV signals could be recorded allowing for live verification of PVI in approximately 49\% of targeted PVs.\textsuperscript{4}

By contrast, the second-generation CB incorporates a modified refrigerant injection system providing homogeneous cooling of the complete distal balloon hemisphere resulting in extensive ice formation on the balloon surface.\textsuperscript{10} Initial studies demonstrated an improvement in procedural efficacy compared to the first-generation balloon with an 84\% acute isolation rate during the first freeze cycle.\textsuperscript{4} Furthermore, the rate of live registration of electrical PVI via the spiral mapping catheter increased from 49\% to 76\% when comparing both CB generations.\textsuperscript{4} In turn, an increase in acute efficacy has led to a higher rate of injury to adjacent non-cardiac anatomical structures such as the esophagus or PN. The incidence of esophageal thermal injury following PVI using the 28mm second-generation CB ranges between 12\% to 19\%.\textsuperscript{8,9} Based on these results, safety cut-offs for the intra luminal esophageal temperature were developed to reduce the risk of esophageal thermal injury.\textsuperscript{8,9} The incidence of PN palsy during second-generation CB based PVI was reported as high as 19.5\%.\textsuperscript{6} At our center the rate is 3.5\% \textsuperscript{7} and thus comparable to the first-generation CB.\textsuperscript{3}

In our electrophysiology laboratories only the 28mm CB is used because of two reasons: First, our rate of acute PVI using only the 28mm CB is 99\%. Second, the 28mm CB 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 23mm CB 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 the smaller diameter CB.

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

The encouraging results reported in the present study raise the question whether a bonus freeze cycle after successful PVI is actually necessary. While 6-month results following 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. 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, RF ablation procedure demonstrated electrical LA-to-PV reconduction into at least 1 PV. The precise evaluation of the quantity and location of reconduction 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 28mm CB and a similar ablation protocol (one bonus freeze cycle, 300 sec freeze duration).\textsuperscript{11,13}

Conclusions

Use of the second-generation 28mm CB for PVI results in an 80% 1-year success rate. Future studies will need to evaluate whether forgoing a bonus freeze results in similar encouraging long-term outcome.

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.

References:


### Table 1. Baseline Characteristics

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<table>
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<tbody>
<tr>
<td>Patients (n)</td>
<td>50</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61±11</td>
</tr>
<tr>
<td>Female Gender, n (%)</td>
<td>18 (36)</td>
</tr>
<tr>
<td>LA-size (mm)</td>
<td>43±5</td>
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<tr>
<td>Paroxysmal AF, n (%)</td>
<td>36 (72)</td>
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<tr>
<td>Short-term persistent AF, n (%)</td>
<td>14 (28)</td>
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<td>Hypertension, n (%)</td>
<td>37 (74%)</td>
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<td>Coronary Artery Disease, n (%)</td>
<td>6 (12%)</td>
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<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>8 (16)</td>
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AF = Atrial Fibrillation; LA = Left Atrium

### 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>
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<tbody>
<tr>
<td>No. of PVs (n)</td>
<td>50</td>
<td>50</td>
<td>42</td>
<td>42</td>
<td>8</td>
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<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>
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<tr>
<td>Isolation during first cryo-appl. 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</td>
<td>1.5±0.5</td>
</tr>
</tbody>
</table>

PV = Pulmonary Vein; PVI = PV Isolation; RSPV = Right Superior PV; RIPV = Right Inferior PV; LSPV = Left Superior PV; LIPV = Left Inferior PV; LCPV = Left Common PV
Figure Legends:

**Figure 1.** Kaplan–Meier curve demonstrating the relative proportion of patients in stable sinus rhythm following initial pulmonary vein isolation using the second-generation 28mm cryoballoon during a follow-up period of 440±39 days including a 3-month blanking period.
One-Year Clinical Outcome after Pulmonary Vein Isolation using the Second-Generation 28mm Cryoballoon
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