One-year clinical outcome after pulmonary vein isolation in persistent atrial fibrillation using the second-generation 28 mm cryoballoon: a retrospective analysis

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Aims

The purpose of this study was to determine efficacy of pulmonary vein isolation (PVI) using the 28 mm cryoballoon (CB) in patients with persistent atrial fibrillation (AF). Superior acute and 1-year outcome has been demonstrated following PVI, using the second-generation CB in patients with paroxysmal AF. Data on the outcome in patients with persistent AF are sparse.

Methods and results

Forty-nine patients (20 female, mean age 63 ± 10 years, mean left atrial diameter 46 ± 5 mm) with persistent AF [median AF duration since first diagnosis: 48 (20:192) months] underwent second-generation 28 mm CB-based PVI. The freeze cycle duration was set at 240 s. After successful PVI, a bonus freeze cycle of 240 s was applied in the first 11/49 (22%) patients, and no bonus freeze cycle was used in the remaining 38/49 (78%) patients. Follow-up (FU) was based on outpatient clinic visits at 3, 6, and 12 months, which included Holter electrocardiograms and telephone interviews. Recurrence was defined as an episode of symptomatic and/or documented atrial tachyarrhythmia ≥ 30 s beyond the 3-month blanking period. A total of 193 pulmonary veins (PVs) were identified and 193/193 (100%) PVs were successfully isolated. No phrenic nerve paralysis occurred. Follow-up was obtained in 49/49 (100%) patients with a mean FU duration of 416 ± 178 days. After the 3-month blanking period, antiarrhythmic medication was discontinued in 33/49 (67%) patients. Thirty-four of 49 (69%) patients remained in stable sinus rhythm.

Conclusions

In patients with persistent AF, use of the second-generation 28 mm CB was associated with a 69% 1-year clinical success rate.

Keywords

Persistent atrial fibrillation • Pulmonary vein isolation • Cryoballoon • Long-term follow-up

Introduction

The second-generation cryoballoon (CB, Artic Front Advance, Medtronic, Inc., Minneapolis, MN, USA) has proved clinically effective for pulmonary vein isolation (PVI), demonstrating a good safety profile in patients with paroxysmal atrial fibrillation (PAF).1–8 In this patient population, the reported 1-year clinical success rates ranging from 80 to 84%.9,10 However, outcome data in patients suffering from persistent atrial fibrillation (AF) are sparse. A recent study reported a 1-year clinical success rate of 60%.11

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The present study reports on the 1-year clinical outcome following PVI, using the second-generation 28 mm CB in patients with persistent AF.

Methods

Inclusion and exclusion criteria
Consecutive patients with symptomatic, drug-refractory persistent AF were admitted and consented for PVI, using the second-generation 28 mm CB. Exclusion criteria were prior left atrial (LA) ablation, LA diameter >60 mm, severe valvular heart disease, or contraindications to post-interventional oral anticoagulation. Transoesophageal echocardiography was performed prior to PVI in all patients to assess the LA diameter and to rule out intracardiac thrombi. No additional pre-procedural imaging was performed.

All patients gave written informed consent. All data were evaluated retrospectively. Only patients with available follow-up (FU) were included into the analysis.

Intraprocedural management
All procedures were performed under deep sedation using midazolam, fentanyl, and propofol. Two diagnostic catheters were introduced via the right femoral vein and positioned according to the individual CB position to facilitate electrical activity inside the PVs. The CB was inflated proximal to the PV ostium and positioned according to the individual CB position to facilitate PV ostium angiography. In all patients, an oesophageal temperature probe (Sensitherm, St Jude Medical, Inc., St Paul, MN, USA) was inserted and positioned according to the individual CB position to facilitate oesophageal temperature monitoring during energy delivery. The intraluminal oesophageal temperature cut-off was set to 10°C.6

Pulmonary vein isolation using the second-generation 28 mm cryoballoon
The second-generation 28 mm CB was advanced into the LA via the 12 French steerable sheath and a spiral mapping catheter (20 mm diameter; AchieveTM, Medtronic, Inc.) was advanced into the target PV to record electrical activity. The CB was inflated proximal to the PV ostium and gently pushed against the PV ostium to facilitate complete antral sealing. Contrast medium injected through the central lumen of the CB was used to verify complete occlusion of the PV ostium. Each freeze cycle duration lasted 240 s. One additional bonus freeze cycle with a duration of 240 s was applied after successful PVI in the first 11 patients. In the remaining 38 patients, the bonus freeze cycle was omitted. In patients demonstrating AF at the time of the procedure, electrical cardioversion (CV) was performed after the final freeze cycle and PVI was re-confirmed in sinus rhythm (SR).

Phrenic nerve pacing
During energy delivery along the septal PVs, continuous phrenic nerve (PN) pacing at maximum output and pulse width (12 mA, 2.9 ms) at a cycle length of 1200 ms was performed, using a diagnostic catheter positioned in the superior vena cava (7 French, Webster TM, Biosense Webster, Inc.). Phrenic nerve capture was monitored by intermittent fluoroscopy and by tactile feedback of diaphragmatic contraction when the operator’s hand was placed on the patient’s abdomen. In addition, the continuous motor action potential (CMAP) was monitored.12,13 Refrigerant delivery was stopped immediately if weakening or loss of diaphragmatic movement was noted or the amplitude of the CMAP decreased by 30%. If PN palsy occurred, no additional freeze cycle was applied along the septal PVs.

Post-procedural care
Following ablation, all patients underwent transthoracic echocardiography to rule out a 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 re-initiated 6 h 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. To prevent early recurrences of AF, patients continued previously ineffective antiarrhythmic medications for at least 3 months.

Repeat procedures
In patients admitted for a repeat procedure due to atrial tachyarrhythmia (ATA) recurrence, venous access and two transseptal punctures were performed as described above. The presence or absence of electrical activity inside the PVs was assessed using a spiral mapping catheter. An electroanatomical LA map (CartoTM, Biosense Webster) was generated and the PV ostia were tagged. Identified gaps along the previously performed ablation lines were closed by irrigated radiofrequency ablation, using a 3.5 mm irrigated-tip catheter (Biosense Webster, Navi-StarTM, ThermocooolTM).

Follow-up
Following a blanking period of 3 months, patients completed outpatient clinic visits at 3, 6, and 12 months with 24 h-Holter electrocardiograms recorded at each visit. In addition, regular telephone interviews were performed. Symptoms suggestive of recurrent ATA prompted additional outclinic visits.

Endpoints
The primary endpoint was ATA recurrence, defined as a symptomatic and/or documented episode >30 s. Secondary endpoints were defined as procedure-related complications such as PN palsy, pericardial effusion/tamponade, or cerebral embolism.

Statistical analysis
Continuous data are shown as mean and standard deviation or otherwise as median and quartiles. Survival curves were generated with the Kaplan–Meier technique. All P-values are two-sided and a P-value <0.05 was considered statistically significant.

What’s new?
• Superior acute and 1-year outcome has been demonstrated following pulmonary vein isolation (PVI), using the second-generation cryoballoon (CB) in patients with paroxysmal atrial fibrillation (AF).
• These are new data on the outcome in patients with persistent AF.
Results

Patient characteristics

During the recruitment period, ~350 patients underwent catheter ablation for persistent AF. A subgroup of 49 patients (20 female, mean age 63 ± 10 years, mean LA diameter 46 ± 5 mm) with a history of drug-refractory persistent AF [median AF duration since first diagnosis: 48 (20:192) months] underwent second-generation 28 mm CB-based PVI. Arterial hypertension was present in 33/49 (67%) patients, stable coronary artery disease in 6/49 (18%) patients, and diabetes mellitus in 6/49 (12%) patients. None of the patients had a previous history of TIA/stroke (Table 1). At admission, 31/49 (63%) patients were in AF. A total of 18/49 (37%) patients were successfully isolated using the second-generation 28 mm CB-based PVI procedure including a 30-min waiting period and the mean fluoroscopy time was 213 ± 6.7 min.

Complications

No major complications such as PN palsy, pericardial effusion, pericardial tamponade, symptomatic PV stenosis, cerebral embolism, or atrioesophageal fistula were noted. A minor complication occurred in 1/49 (2%) patients in the form of a pseudoaneurysm in the right groin.

Clinical follow-up

Clinical FU was completed in 49/49 (100%) patients. In 9/49 (18%) patients, ATA recurrences during the blanking period were documented and successful CV was performed in 8/9 (89%) patients, 1/9 (11%) patients spontaneously converted to SR. During a mean FU time of 416 ± 178 (range 188–744) days and following a single second-generation 28 mm CB-based PVI procedure including a 3-month blanking period, 34/49 (69%) patients remained in stable SR without symptomatic and/or documented episodes of ATA (Figure 1). A symptomatic and/or documented atrial arrhythmia recurrence was observed in 15/49 (31%) patients. Thirteen of 15 (86%) patients presented with ATA recurrence. In the remaining 2/15 (13%) patients, a left atrial tachycardia (AT) and typical counterclockwise cavo-tricuspid isthmus-dependent atrial flutter were recorded, respectively. At the time of FU, 5/49 (10%) patients were on amiodarone [3/5 (60%) patients with ATA recurrence], another 11/49 (22%) patients on flecainide [4/11 (36%) patients with ATA recurrence]. Despite recommendation, antiarrhythmic medication was discontinued in only 33/49 (67%) patients following the 3-month blanking period.

Repeat procedures

A total of 9/15 (60%) patients suffering from ATA recurrence underwent a second ablation procedure after a mean of 225 ± 139 days following the index procedure. In 1/9 (11%) patients, the repeat procedure was performed during the blanking period because electrical CV failed despite still being under antiarrhythmic medication. In 3/9 (33%) patients, all PVs were still isolated. Ostial potentials along the lateral PVs were ablated in one patient, while in the second patient complex fractionated atrial electrogram (CFAE) ablation was performed in the LA. In the third patient with typical atrial flutter documentation only, a cavo-tricuspid isthmus line was placed resulting in bidirectional isthmus block. In 5/9 (56%) patients, LA-to-PV reconnection in 10/20 (50%) previously isolated PVs (3 RSPV, 2 RIPV, 2 LSPV, and 3 LIPV) occurred and repeat PVI was performed. In 1/9 (11%)

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Age (years)</th>
<th>Female gender, n (%)</th>
<th>LA size (mm)</th>
<th>Hypertension, n (%)</th>
<th>Coronary artery disease, n (%)</th>
<th>Diabetes mellitus, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>63 ± 10</td>
<td>20 (41)</td>
<td>46 ± 5</td>
<td>33 (67)</td>
<td>9 (18)</td>
<td>6 (12)</td>
</tr>
</tbody>
</table>

LA, left atrium.

Table 2 Acute ablation results

<table>
<thead>
<tr>
<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>49</td>
<td>49</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Isolated PVs, n (%)</td>
<td>49/49 (100)</td>
<td>49/49 (100)</td>
<td>46/46 (100)</td>
<td>46/46 (100)</td>
</tr>
<tr>
<td>Isolation during first freeze cycle, n (%)</td>
<td>40/49 (82)</td>
<td>41/49 (83)</td>
<td>37/46 (80)</td>
<td>42/46 (91)</td>
</tr>
<tr>
<td>Number of freeze cycles until PVI, mean ± SD</td>
<td>1.2 ± 0.5</td>
<td>1.3 ± 0.7</td>
<td>1.3 ± 0.8</td>
<td>1.1 ± 0.3</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.
patients, no information on PV-reconduction was available since the re-procedure was performed in a different medical centre. For the repeat procedures, the mean procedure and fluoroscopy time were 115 ± 59 and 17 ± 12 min, respectively.

In the first 11 patients treated with a bonus freeze after successful PVI, ATA recurrence was noted in 5/11 (45%) patients. In 2/5 (40%) patients, a repeat procedure was performed. One patient demonstrated PV reconduction of all PVs, while all PVs remained isolated in the second patient.

Discussion

The present study demonstrates that the use of the second-generation 28 mm CB in patients with persistent AF results in (i) a 100% acute PVI rate and (ii) a 1-year clinical success rate of 69%. In addition, in a majority of patients with ATA recurrence, electrical PV reconduction of ≥1 previously isolated PVs was noted during the repeat procedure.

The second-generation CB incorporates a modified refrigerant injection system resulting in improved cooling of the complete distal balloon hemisphere. Initial studies on the use of the second-generation CB mainly focused on patients suffering from PAF demonstrating high acute PVI rates and improved long-term clinical results compared with the first-generation CB, with success rates ranging from 80 to 84%. However, more effective cooling has resulted in an increased incidence of oesophageal thermal lesions that may be avoided if the operator adheres to a critical oesophageal cut-off temperature. Fünnkranz et al. reported that an endoluminal oesophageal safety cut-off temperature of 15 °C resulted in a 1.5% incidence of oesophageal thermal lesions. Furthermore, using the second-generation CB for PVI, the incidence of PN palsy was 3.5%. Employing precautionary measures such as oesophageal temperature monitoring and CMAP recording in addition to PN pacing complication rates are comparable with the first-generation CB.

Currently, the best ablative strategy to treat patients with persistent AF is unknown. Results from the STAR-AF II study suggest that outcome after PVI only in patients with persistent AF, using radiofrequency ablation in conjunction with a 3D mapping-system, is not inferior to more extensive ablation strategies such as ablation of CFAEs or placement of linear lesions in addition to PVI. These results re-emphasize the importance of durable PVI even in patients with persistent AF and may justify use of second-generation CB for ablation of persistent AF. Importantly, the bigger 28 mm CB will result in a greater area of energy delivery, hence modifying a larger potentially arrhythmogenic, antral substrate. Nevertheless, PVI in persistent AF using the first-generation CB was associated with only moderate 1-year clinical success rates of 45%. Importantly, ATA recurrence correlated with a high number of previously isolated PVs demonstrating electrical reconduction. Whether the use of the second-generation CB in patients with persistent AF translates into an increased rate of durable PVI has yet to be proven. The first study assessing the outcome in patients with persistent AF, using the second-generation 28 mm CB demonstrated a 1-year success rate of 60%. In the present study, the 1-year single-procedure clinical success rate was 69%. However, both studies are based on a rather low number of patients. Further studies including higher patient numbers will be mandatory before final conclusions can be drawn. Electrical PV reconduction may serve as the main cause for arrhythmia recurrence in patients with persistent AF (as was demonstrated for the first-generation CB), since in the present patient cohort electrical PV reconduction of ≥1 previously isolated PVs was noted in the majority (56%) of patients. However, an extrapulmonary arrhythmic substrate should be considered if patients present with arrhythmia recurrence and persistence of PVI during a repeat procedure as was seen in 3/9 (33%) patients.

A bonus freeze cycle was applied after successful PVI in the initial 11/49 (22%) patients followed by 38/49 (78%) patients in whom the bonus freeze was omitted. Foregoing the bonus freeze cycle may be an attractive strategy because of further reduction of total procedure and fluoroscopy times and an improved safety profile. Furthermore, we previously reported that in 4/115 (3.5%) patients suffering from PN palsy, half of affected patients experienced decline in PN function during delivery of a bonus freeze cycle targeting the RSPV. In addition to an increased risk of PN palsy, there may be a cumulative cooling effect within the oesophagus during application of a bonus freeze cycle. Consequently, foregoing the extra freeze cycle may not only prevent the development of PN palsy but also limit the rate of oesophageal thermal lesions.

A future step towards an individualized ablation strategy would utilize electrical information gleaned from the spiral mapping catheter (Achieve™, Medtronic, Inc.) to assess the time-to-PVI. As shown by Fünnkranz et al., PV electrical signals can be recorded in 76% of targeted PVs. Whether continuation of the freeze cycle following live verification of PVI for a fixed duration (e.g. 120 s) is equally effective than the standard freeze cycle duration of 240 s and/or use of a bonus freeze cycle will have to be evaluated.

Limitations

The present study represents a single-centre retrospective experience reporting on a limited number of patients. The ablation protocol was modified in that the initial patient cohort received a bonus freeze.
cycle that was omitted later on. Despite recommendation, antiarrhythmic medication was discontinued after the 3-month blanking period in only 33/49 (67%) patients. Nevertheless, this is one of the very first reports assessing the 1-year clinical outcome in patients with persistent AF treated with the second-generation 28 mm CB.

Conclusions

The use of the second-generation 28 mm CB in patients with persistent AF resulted in a 69% 1-year freedom from recurrent ATAs. Future prospective studies enrolling a greater number of patients and assessing various individualized ablation protocols are needed to further define the role of the second-generation CB for the treatment of persistent AF.

Conflict of interest: A.M. received speaker’s honoraria from Medtronic. E.W. received speaker’s honoraria from Medtronic and is a member of Medtronic’s advisory board. K.-H.K. received a research grant and speaker’s honoraria from Medtronic. C.L. received travel grants from Medtronic.

References