Effect of Cryoballoon Ablation vs. Radiofrequency Ablation on Left Atrial Ganglionated Plexi in Patients with Atrial Fibrillation

Keiko Takahashi1, Ichiro Watanabe1, Yasuo Okumura1, Koichi Nagashima1, Ryuta Watanabe1, Masaru Arai1, Kazuki Iso1, Sayaka Kurokawa1, Kimie Okubo1, Toshiko Nakai1, Atsushi Hirayama1, Kazumasa Sonoda2 and Toshimasa Tosaka2

1Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan
2Division of Cardiology, Department of Medicine, Tokyo Rinkai Hospital, Edogawa-ku, Tokyo 134-0086, Japan

Background: Cryoballoon ablation for pulmonary vein isolation (PVI) is efficacious for the treatment of paroxysmal atrial fibrillation (PAF). However, the effectiveness of cryoballoon-based PVI on the left atrial (LA) ganglionated plexi (GPs) has not been reported. Therefore, we conducted a retrospective study in which we compared vagal responses during cryoballoon ablation (CBA) or radiofrequency ablation (RFA) for PVI.

Methods: The study included 49 patients with AF (23 women and 26 men, 62.7 ± 10.9 years of age) who were symptomatic, despite treatment with 1 or more antiarrhythmic drugs, and thus underwent PVI by means of CBA or RCA. High-frequency stimulation (20 Hz, 25 mA, 10 ms) was performed at 5 major LA GP sites before and after PVI in 18 patients treated by RFA and in 31 patients treated by CBA, and vagal responses and treatment outcomes were compared between the 2 patient groups.

Results: Elimination of the vagal responses was similar between the 2 groups. At a median follow-up of 7 (3–9) months, AF recurred in 1 of the 31 (3.2%) patients treated with CBA and in 2 of the 18 (11.1%) patients treated with RFA (p = 0.3017).

Conclusion: The efficacy of CBA for AF may be due in part to ablation of the LA GPs that occurs during PVI.

Key words: atrial fibrillation, left atrial ganglionated plexi, radiofrequency ablation, cryoballoon ablation


1. Introduction

According to the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guideline, symptomatic drug-refractory paroxysmal atrial fibrillation (PAF) is a class I level A indication for catheter ablation. The cornerstone of ablation therapy for PAF is pulmonary vein isolation (PVI). When performed by the conventional radiofrequency (RF) ablation method, PVI is achieved by heating the tissue for creation of contiguous, transmural point-by-point lesions. However, RF-based PVI is time-consuming, and cryoballoon ablation (CBA) was developed to shorten and simplify the procedure. With CBA, transmural lesions are created by freezing the tissue, and a recent clinical trial showed the safety and efficacy of CBA for PAF to be equal to that of RF ablation (RFA). A previous study showed the posterior left atrial (LA) wall area isolated by CBA to be wide and antral, and the resulting debulking of this area, in addition to discrete PVI, was thought to explain, at least in part, the efficacy of CBA. However, a more recent study showed the PV antral area isolated by CBA to be significantly smaller than the circumferential PV area isolated by RFA. The intrinsic cardiac autonomic nervous system (i.e., the ganglionated plexi [GPs]) has been thought to contribute to the AF substrate and specifically to the initiation and persistence of AF. The LA GPs are located within the epicardial fat pads at the LA/PV junction and adjacent LA antrum, and therefore, RF-based circumferential PVI also ablates the LA GPs. In the retrospective study described herein, we compared the effects of CBA and RFA on the LA GPs.

2. Materials and methods

2.1 Study patients

Included in the study were 49 consecutive patients (34 men, 15 women; age 62.8 ± 10.7 years) who underwent extensive encircling PVI (EEPVI) by RFA or by CBA with a second-generation cryoballoon catheter for PAF (AF lasting ≤ 7 days; n = 33) or persistent AF (AF lasting > 7 days, n = 16) at Nihon University Itabashi Hospital between September 2014 and February 2016. None had undergone a previous ablation procedure or had significant valvular heart disease, a left ventricular (LV) contraction abnormality, marked LV hypertrophy, or thyroid disease. All patients had been on adequate oral anticoagulant therapy.
lant therapy for at least 1 month before ablation, and all antiarrhythmic drugs had been discontinued for at least 5 half-lives before ablation. Upon admission, transesophageal and transthoracic echocardiograms were obtained. The study was approved by the Nihon University Hospital Institutional Review Board (May 25, 2016; RK-160614-10). All patients provided written informed consent for the electrophysiologic study and ablation.

2.2 Electrophysiologic study
Electrophysiologic study was performed with patients under conscious sedation achieved with dexmedetomidine, propofol, and fentanyl. After vascular access was obtained, single transseptal puncture was performed, and intravenous heparin was administered for maintenance of an activated clotting time of > 300 seconds.

2.3 RFA
Eighteen of the 49 patients were treated by RFA. Two decapolar Lasso catheters (Biosense-Webster, Diamond Bar, CA, USA) and a THERMOCOOL SMARTTOUCH catheter (Biosense-Webster) were placed in the left atrium. The 3-dimensional (3D) geometry of the left atrium and the 4 PVs was reconstructed with a CARTO 3 mapping system (Biosense-Webster) from data obtained from a decapolar Lasso catheter. EEPVI was performed by the double-lasso technique, with delivery of RF energy at a target contact force of 10–20 g and power setting of 30 W for 30 seconds along the anterior wall and 25 W for 30 seconds along the posterior wall, as previously described.[13, 14]

2.4 CBA
Thirty-one of the 49 patients were treated by CBA. The 3D geometry of the left atrium and the 4 PVs was reconstructed with an Ensite NavX velocity mapping system (St. Jude Medical, Minneapolis, MN, USA) from data obtained with an Inquiry AFocus II 20-pole circular mapping catheter (St. Jude Medical). Thereafter, a 28-mm cryoballoon (ARC-Adv-CB, Arctic Front Advance, Medtronic PLC, Minneapolis, MN, USA) used in conjunction with an inner lumen mapping catheter (Achieve, Medtronic) was inflated and advanced to each PV orifice through a steerable 15Fr sheath (FlexCath advance, Medtronic). Once optimal PV occlusion, as assessed by contrast injection, was achieved, cryothermal energy was applied to each target PV, first for 180 seconds, then for 120 seconds, as described previously.[15]

2.5 GP stimulation
High-frequency stimulation of the LA GPs was performed before and after RFA or CBA. The LA GP stimulation was performed as previously described.[16] In brief, a THERMOCOOL SMARTTOUCH ablation catheter or EPstar Snake decapolar catheter (Japan Lifeline Co, Tokyo, Japan) was placed at each of the presumed anatomic areas of the 5 major GPs in the LA, i.e., the superior left GP (SLGP), inferior left GP (ILGP), Marshall tract GP, anterior right GP (ARGP), and inferior right GP (IRGP).[17] High-frequency stimulation (20 Hz, 10 ms, 25 mA) was applied for 5 seconds at 3 different endocardial sites within each of the areas, and the GP response was assessed. A positive GP response was defined as a vagal response identified as an increase of 50% or more in the RR interval.[18]

2.6 Between-group comparisons
For assessment of CBA in relation to RFA, characteristics of patients in the 2 groups, the resulting GP ablations, and the ablation outcomes in terms of AF recurrence within a follow-up period of 7 (3–9) months were compared.

2.7 Statistical analysis
Continuous variables are expressed as mean ± SD or median and interquartile ranges. Differences between the RFA group and CBA group were analyzed by Mann-Whitney U test. Categorical variables are expressed as percentages, and differences were analyzed by chi-square test. All statistical analyses were performed with JMP software program (version 11; SAS Institute, Inc., Cary, NC, USA), and p < 0.05 was considered significant.

3. Results

3.1 Patients’ clinical characteristics
Clinical characteristics of the study patients are shown per group in Table 1. PAF was more prevalent in the CBA group than in the RFA group, but the difference was not significant (p = 0.0634). Diabetes mellitus was significantly more prevalent in the CBA group (p = 0.0377).

3.2 GP responses before and after ablation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RFA group (n = 18)</th>
<th>CBA group (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.1 ± 11.7</td>
<td>63.8 ± 10.1</td>
<td>0.4152</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>14 (78%)</td>
<td>20 (65%)</td>
<td>0.5313</td>
</tr>
<tr>
<td>PAF</td>
<td>9 (50%)</td>
<td>24 (77%)</td>
<td>0.0634</td>
</tr>
<tr>
<td>Duration of AF (months)</td>
<td>36 (6–60)</td>
<td>14 (5–96)</td>
<td>0.7482</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.8 ± 4.1</td>
<td>24.3 ± 4.3</td>
<td>0.8719</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>68.1 ± 8.9</td>
<td>66.5 ± 6.0</td>
<td>0.5209</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>11 (61%)</td>
<td>13 (42%)</td>
<td>0.2436</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>0</td>
<td>7 (23%)</td>
<td>0.0377</td>
</tr>
</tbody>
</table>

Values are shown as mean ± SD or n (%), unless otherwise indicated. *Per Mann-Whitney U test or chi-square test.
RFA: radiofrequency catheter ablation; CBA: cryoballoon catheter ablation; PAF: paroxysmal atrial fibrillation; LAD: left atrial dimension; LVEF, left ventricular ejection fraction.
GP responses before and after RFA and CBA are shown in Table 2. The percentages of GPs for which a negative response was achieved by RFA or by CBA are shown in Fig. 1. Ninety-three to 100% of Marshall tract GP and SLGP responses were eliminated by both CBA and RFA. Elimination of ILGP, ARGP, and IRGP responses ranged from 63% to 77% in the CBA group and did not differ significantly from that (44% to 88%) in the RFA group. Overall elimination of the GP responses, whether by CBA or by RFA, was similar (79 ± 22% vs. 73 ± 22%; \( p = 0.3554 \)). Locations of response-positive GPs before and after CBA and RFA are shown on the 3D voltage maps in Fig. 2. As seen on the map, the Marshall tract GP and SLGP were included within the ablation areas, but some of the inferior GPs were located outside the ablation areas.

3.3 Outcomes

Freedom from AF during the median follow-up period of 7 (3–9) months was 30/31 (97%) in the CBA group and 16/18 (89%) in the RFA group (\( p = 0.3017 \))

4. Discussion

4.1 Main findings

Our main study finding was that the total overall elimination of GP responses did not differ significantly between treatment by CBA and treatment by RFA. All or almost all Marshall tract GPs and SLGPs were ablated in both patient groups. ARGP ablation was similar between the 2 groups. However, ILGP and IRGP ablation were less frequent in the RFA group than in the CBA group.

4.2 GP ablation

We found in our study that many LA GPs were included within the ablation area. Extensively ablation of the left atrium including GP areas (identified as fat pads on the LA surface) along with PV antrum isolation has been reported to enhance denervation of the autonomic nervous system and improve treatment outcomes in patients with AF\(^{17} \). Nakagawa et al. showed that 3LA GPs were located

Table 2 Vagal responses at sites of the 5 major atrial ganglionated plexi before and after PVI performed by CBA or RFA.

<table>
<thead>
<tr>
<th></th>
<th>Marshall tract</th>
<th>Superior left</th>
<th>Inferior left</th>
<th>Anterior right</th>
<th>Inferior right</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBA Before</td>
<td>28/31 (90%)</td>
<td>24/31 (77%)</td>
<td>30/31 (97%)</td>
<td>30/31 (97%)</td>
<td>30/31 (97%)</td>
</tr>
<tr>
<td>After</td>
<td>0/31 (0%)</td>
<td>0/31 (0%)</td>
<td>10/31 (32%)</td>
<td>7/31 (23%)</td>
<td>11/31 (35%)</td>
</tr>
<tr>
<td>RFA Before</td>
<td>14/18 (78%)</td>
<td>12/18 (67%)</td>
<td>15/18 (83%)</td>
<td>16/18 (89%)</td>
<td>18/18 (100%)</td>
</tr>
<tr>
<td>After</td>
<td>1/18 (6%)</td>
<td>0/18 (0%)</td>
<td>8/18 (44%)</td>
<td>2/18 (11%)</td>
<td>10/18 (56%)</td>
</tr>
</tbody>
</table>

The ratio (number of positive responses against the number of patients) and percentage of positive responses are shown.

CBA: cryoballoon ablation; RFA: radiofrequency ablation.

![Fig. 1 Prevalence of vagal response elimination by cryoballoon ablation (CBA) and radiofrequency ablation (RFA). SLGP: superior left ganglionated plexus; ILGP: inferior left ganglionated plexus; ARGP: anterior right ganglionated plexus; IRGP: inferior right ganglionated plexus.](image-url)
at adjacent to the LA antra, but LI and RI GPs were located to more lower LA sites. Pappone et al. were the first to report that complete vagal denervation, i.e., elimination of the vagal response (manifested as sinus bradycardia, asystole, atrioventricular block, or hypotension during RF application and reduced heart rate variability during follow-up) decreased the incidence of AF recurrence in patients with PAF treated by circumferential PVI. Quin et al. also reported that a positive RFA-induced vagal response was associated with reduced AF recurrence in patients with lone PAF. Yorgun et al. reported that vagal reactions (bradycardia, hypotension) during CBA were associated with decreased AF recurrence in a subgroup of patients with PAF and PerAF. Results of our study are in keeping with these various reports. Recent report showed that GP ablation in addition to PVI by endoscopic surgery did not affect one-year freedom from AF rate, but addition of GP ablation increased the incidence of more major adverse events.

4.3 Limitations

Our findings should be considered in light of our study limitations. The study, which was conducted at a single-center, included a relatively small number of patients who were not randomized to treatment, and shorter follow-up period. In addition, autonomic activity was not assessed in our patients on the basis of mean heart rate and heart rate variability before and after the ablation procedure. Neural pathways between LA GPs and the atrioventricular node travel via the IRGP and the neural pathway connecting the left atrium to the sinus node travel via the ARGP. Therefore, ARGP and IRGP ablation by RFA or CBA may blunt the vagal response elicited by the SLGP and ILGP after ablation even if these GPs remained intact. Furthermore, Miyazaki et al. showed that CBA area was smaller than CPVI by RFA. However, their CPVI area was not an actual data, but they estimated from their conventional experience. In our experience, LA antrum ablated area (especially RPV antrum) was larger than RFA area. Therefore, the influence of the ablated area between CBA and RFA on the LA GP response after ablation needs further evaluation. Higher incidence of DM in the CBA group may affect the autonomic activity and influence the results. However, LA GP response before ablation was not different between CBA and RFA groups. Therefore, in the present study, the influence of DM on the results might be small.

5. Conclusions

We found elimination of the high-frequency stimulation-evoked LA GP-based vagal response to be similar between CBA and RFA performed in patients with AF.
This effect may explain, in part, the similar success of CBA and RFA.

**Source of funding**

This study was supported by departmental resources only.

**Conflict of interest**

The authors declare no conflict of interest related to this study.

**References**


