Comparison of the Efficacy of Cryoballoon Ablation for Paroxysmal and Persistent Atrial Fibrillation

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Background: Similar clinical outcomes have been demonstrated following pulmonary vein (PV) isolation (I) by radiofrequency catheter and cryoballoon ablation (CBA) in patients with paroxysmal atrial fibrillation (PAF). However, no comparison of the clinical outcome in patients with PAF and persistent AF (PerAF) by CBA has been reported to date. The purpose of this study was to compare the efficacy of PVI in patients with PAF and PerAF.

Methods: CBA based PVI using a second-generation 28-mm balloon was performed in 58 patients with PAF and 32 with PerAF. Follow-up (FU) was based on outpatient clinic visits at 1, 3, 6, and 12 months, which included Holter electrocardiograms and ambulatory event electrocardiograms.

Results: The freedom from atrial tachyarrhythmia recurrences following a single cryoballoon ablation in patients with PAF and PerAF did not differ significantly between the PAF and PerAF patients over a relatively shorter follow-up period, as estimated by the Kaplan-Meir method.

Conclusion: CB-based PVI had similar efficacy for both PAF and PerAF.

Key words: cryoballoon ablation, paroxysmal atrial fibrillation, persistent atrial fibrillation

Original Article

Introduction

Catheter ablation is now the well-established interventional approach for treating symptomatic drug-refractory, paroxysmal atrial fibrillation (AF), with a Class 1 level A recommendation in the ESC and ACC/AHA guidelines. Electrical isolation achieved by creating contiguous and transmural lesions between the pulmonary veins (PVs) and atrium by radiofrequency (RF) ablation has become the cornerstone ablation strategy for paroxysmal AF. More recently, cryoenergy has been introduced to overcome the procedural difficulties arising from the time consuming and technically challenging ‘point-by-point’ RF ablation (RFA). Recent multicenter trials comparing the efficacy and safety of the PV isolation of PAF by cryoballoon ablation (CBA) and RFA have demonstrated that CBA is noninferior to RFA with respect to the efficacy and safety. Furthermore, the CBA had significantly fewer repeat ablations. A recent meta-analysis on CBA vs. RFA of PAF also demonstrated a comparable efficacy and safety. A meta-analysis study showed that the PVI alone single procedure arrhythmia-free survival for PerAF was 66.7%. Several studies on the efficacy of CBA for persistent AF (PerAF) have been demonstrated and the 1–2 year freedom from atrial tachyarrhythmias was 56–69%. However, to the best of our knowledge, a comparison of the efficacy of CBA between PAF and PerAF in the same study is lacking. The purpose of this study was to compare the efficacy of CBA between PAF and PerAF in a single center.

Methods

Study patients

This study consisted of 90 patients (mean age, 63.0 ± 10.0 y/o; male: 63) scheduled for their first catheter ablation of AF who underwent a CBA of PAF (AF lasting less than 7 days, n = 58) and PerAF (AF lasting more than 7 days, n = 32) between September 2016 and May 2017. Adequate oral anticoagulation therapy was given for at least 1 month before the ablation procedure, and all antiarrhythmic drugs were discontinued for at least 5 half-lives before the procedure. The study was approved by the Institutional Review Board of Nihon University Itabashi Hospital (May 25, 2016; RK-160614-10) and all patients provided written informed consent for their participation.

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The study was supported by departmental resources only, and the authors have no conflict of interest to declare.
Electrophysiologic study and voltage map

An electrophysiologic study was performed under conscious sedation achieved with dexmedetomidine, propofol, and fentanyl. After vascular access was obtained, a single transseptal puncture was performed, and intravenous heparin was administered to maintain an activated clotting time of > 300 seconds. The three-dimensional (3D) geometry of the LA and 4 PVs was reconstructed followed by high-density PV-LA bipolar voltage mapping during SR before and after completion of the cryoenergy applications at each PV by means of an EnSite NavX mapping system (St. Jude Medical, Inc., Minneapolis, MN). Bipolar signals, high-pass filtered at 30 Hz and low-pass filtered at 300 Hz, were acquired with a 20-pole circular mapping catheter (Inquiry AFocus II, St. Jude Medical; interelectrode spacing 4 mm). If the patient was in an AF rhythm, the voltage map was created after SR was restored by internal low energy electrical cardioversion (10–20 joules).

Cryoablation

A 28-mm cryoballoon (ARC-Adv-CB, Arctic Front Advance; Medtronic Inc., Minneapolis, MN) 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 an optimal PV occlusion, assessed by a contrast injection, was achieved, cryothermal energy was applied to each target PV, first for 180 seconds, then for 120 seconds. A decapolar catheter was advanced into the superior vena cava and the phrenic nerve (PN) was paced continuously during the cryothermal energy applications to the right superior (RS) PV and the right inferior (RI) PV at a cycle length of 1000 ms, current of 25 mA, and pulse width of 2 ms. In addition to palpation of the diaphragmatic excursions, the diaphragmatic compound motor action potentials (CMAPs) were assessed for PN injury (PNI) monitoring. The details of the CMAP recordings were reported previously. The cryothermal energy applications were discontinued when either the diaphragmatic excursions decreased on palpation or a > 30% reduction in the CMAP amplitude occurred.

Acute PV reconnections

Thirty minutes after the last CBA, 30 mg of adenosine triphosphate (ATP) was administered for a reassessment of PV entrance block, and exit block was confirmed by sequential pacing from the A Focus II catheter. If an acute PV reconnection, defined as a spontaneous PV reconnection or dormant conduction provoked by ATP, was observed, additional touch-up radiofrequency ablation was performed with a 4-mm-tip catheter (FlexAbility, St. Jude Medical). RF energy was delivered point by point at a maximum power output of 25–30 W (25 W for the posterior aspects and 30 W for the anterior aspects of PVs), and the upper temperature limit was set to 43°C at a saline irrigation rate of 10–20 mL/minute (Cool Point, St. Jude Medical).

Follow up

Follow-up was based on outpatient clinic visits at 1, 3, 6, and 12 months, and every 6 months thereafter by 12-lead electrocardiograms, 24-hour Holter electrocardiograms and ambulatory event electrocardiograms if necessary. We continued or added bepridil in paroxysmal and persistent atrial fibrillation patients after PVI in whom AF was induced by rapid atrial pacing, and continued for more than 5 minute after PVI.

Statistical analysis

The continuous variables are expressed as the mean ± SD values or as median values with interquartile ranges, as appropriate. The differences in the variables were analyzed by a Mann-Whitney U test, depending on whether the values were normally distributed. The event-free survival was estimated by the Kaplan-Meier method and compared by a log-rank test. All statistical analyses were performed with JMP 9 software (SAS Institute, Cary, NC), and a P < 0.05 was considered significant.

Results

Patient characteristics

The patient characteristics and echocardiographic features are shown in Table 1. The body mass index, prevalence of heart failure, left atrial dimension, and left atrial volume were higher in PerAF patients.

Comparison of each PV diameter and the nadir balloon temperature between paroxysmal and persistent atrial fibrillation

Each PV ostial dimension and nadir balloon temperature are shown in Fig. 1. The LSPV and LIPV diameters were marginally larger in PerAF patients and the RSPV and RIPV diameters were significantly larger in the PerAF patients. However, the nadir balloon temperature did not differ between the PAF and PerAF patients. Residual PV potentials were observed in 16 (27.6%) PAF patients and 19 (59.4%) PerAF patients (P = 0.0031). Dormant PV conduction was observed in 12 (20.7%) PAF patients and 6 (18.8%) PerAF patients (P = 0.2116). All residual and dormant PV conduction was successfully ablated by additional touch-up radiofrequency ablation applications.

Ablation outcome

After the ablation procedure, 9 (16%) PAF patients and 4 (13%) PerAF patients were treated with class I antiarrhythmic drugs (P = 0.697) and 14 (24%) PAF patients and 23 (72%) PerAF patients were treated with bepridil (P
Cryoballoon ablation for paroxysmal and persistent atrial fibrillation

The median follow-up period was significantly shorter in the PerAF patients than the PAF patients (12.3 vs. 6.9 months, \( P = 0.012 \)) (Table 2). Freedom from atrial tachyarrhythmia recurrences following a single CBA for patients with PAF and PerAF, excluding the blanking period, did not differ significantly when estimated by the Kaplan-Meir method (Fig. 2).

**Discussion**

The main findings of this clinical study showed a similar freedom from atrial tachyarrhythmia recurrences following a single CBA in patients with PAF and PerAF. Previous studies demonstrated a similar clinical outcome after the PVI by a ‘point-by-point’ RFA and ‘single shot’ CBA with sinus rhythm maintenance at 1 year follow-up (CBA: 60% vs. RFA 56%), and atrial tachyarrhythmias recurrence rate at 15.6 months follow-up (CBA: 40.7% vs. RFA: 45.8%)\(^{13,18}\). A recent clinical trial showed that catheter ablation was superior to medical therapy for the maintenance of sinus rhythm in patients with PerAF during a 12-month follow-up\(^{21}\). However, recent clinical trials also have demonstrated that no reduction in the rate of recurrent AF when either linear ablation, ablation of fractionated atrial electrograms, or a stepwise approach (full defragmentation) was performed in addition to the
Previous studies showed freedom from atrial tachyarrhythmia recurrences in PerAF patients after the PVI by a CBA and/or RFA. In the present study, freedom from atrial tachyarrhythmia recurrences after the CBA was compared between PAF and PerAF in a single center, and the freedom from atrial tachyarrhythmia recurrences did not differ significantly between the PAF and PerAF patients. A possible explanation for the better outcome with the CBA is that unexcitable ablated tissue around the PVs was significantly wider with the CBA than RFA, and therefore, a more durable PVI could be achieved with the CBA.

Study limitations

Our study limitations should be considered. The study involved a relatively smaller number of patients with PerAF. The follow-up duration was significantly shorter in the PerAF patients. Therefore, our results should be applied up to 12 months after PVI. The use of the class III antiarrhythmic drug, bepridil, was significantly higher in the PAF patients than PAF patients (23 [72%] vs. 14 [24%], P < 0.0001). Previous studies showed that the restoration of sinus rhythm by the use of the class III antiarrhythmic drug, bepridil or amiodarone before the ablation of PerAF predicted a favorable outcome after ablation in PerAF patients, and also in patients free of AF at the end of 3 months of post-ablation blanking period, continued use of previously ineffective antiarrhythmic drug therapy significantly reduces the recurrence of atrial tachyarrhythmia in the 1st year after PVI. Therefore, the higher freedom from atrial tachyarrhythmia recurrences in PerAF patients in the present study, in spite of excluding the blanking period, may in part, be related to the use of bepridil even when used after ablation. Therefore, a longer follow-up with an off antiarrhythmic drug study is warranted in a larger number of patients.

Conclusions

The CB-based PVI might be an effective strategy for PerAF, with a short-term AF recurrence free rate similar to PAF.

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