INTRODUCTION

Catheter ablation is a well-established interventional approach to symptomatic drug-refractory paroxysmal atrial fibrillation (AF), having been assigned a Class 1 level A recommendation according to the ESC and ACC/AHA guidelines. Electrical isolation achieved by creation of contiguous and transmural radiofrequency (RF) lesions between the pulmonary veins (PVs) and atrium has become the cornerstone ablation strategy for paroxysmal AF (PAF). PV isolation (PVI) by means of contact force-sensing RF ablation alone as a single procedure for PAF has been reported to result in a 12-month arrhythmia-free survival rate of 81.9%. For persistent atrial fibrillation (PerAF), however, PVI alone has been reported to result in comparatively lower 12- and 18-month arrhythmia-free survival rates of 63.9% after 12 months and 59% after 18 months. Nonetheless, catheter ablation is superior to medical therapy for 1-year maintenance of sinus rhythm (SR) in patients with PerAF (60.2% of patients who underwent ablation group vs. 29.2% of patients who underwent antiarrhythmic drug therapy).

The presence of SR before or early during the ablation procedure has been shown to be a predictor of a favorable outcome in patients with PerAF. Therefore, we investigated whether a relation exists between the presence of SR before catheter placement or maintenance of SR before the ablation procedure by internal direct current (DC) cardioversion and clinical efficacy of ablation for PerAF.

METHODS

Study patients

Our study involved 46 patients (39 men and 7 women aged 60.8 ± 10.1 years) scheduled for their first catheter ablation of PerAF (AF lasting more than 7 days) between September 2016 and May 2017. Oral anticoagulants were administered 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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Electrophysiologic study

Electrophysiologic study was performed under conscious sedation achieved with dexmedetomidine, propofol and fentanyl. After vascular access was obtained, a single transeptal puncture was performed, and intravenous heparin was administered to maintain an activated clotting time of > 300 seconds. A sixteen-pole catheter with electrodes 4 mm in length and interelectrode spacing of 2 mm between electrodes 1–2,...7–8, of 70 mm between electrodes 8–9, and of 2-mm between electrodes 9–10,...15–16 (BeeAT, Japan Lifeline Co., Tokyo, Japan) was introduced into the coronary sinus via the right internal jugular vein. If the patient was in AF rhythm before PVI, biphasic internal atrial cardioversion shocks were delivered between the distal 8 electrodes and the proximal 8 electrodes of the BeeAT catheter with the use of a SHOCK AT defibrillator (Japan Lifeline Co.) at an energy setting of 10–25 Joules. If the AF recurred immediately after 2 shocks, RF ablation or cryoablation was performed during AF.

Radiofrequency ablation

After 3 long sheaths (2 SR0 sheaths and 1 SL1 sheath; St. Jude Medical, St. Paul, MN, USA) were inserted into the left atrium (LA) via transseptal puncture, 2 decapolar circular mapping catheters (Lasso; Biosense Webster, Diamond Bar, CA, USA) and an irrigated 3.5-mm-tip mapping and ablation catheter (ThermoCool SmartTouch Catheter; Biosense Webster) were advanced into the LA. Extended encircling ipsilateral PVI was performed, guided by 2 20-pole circular mapping catheters placed at the ipsilateral PVs and a 3-dimensional electroanatomical mapping system (CARTO 3; Biosense Webster). Targeting the ipsilateral PVs in pairs, we placed the RF catheter ablation lesions at least 1 cm outside the PV ostia. An exception was made for the left superior PV. There, the lesions were placed within 1 cm of the ostium because of the narrow ridge of tissue between its anterior aspect and the left atrial appendage. RF energy was delivered at a power of 20–35 W, contact force of 10–20 g, and irrigation flow rate of 17–30 mL/min. The temperature was set to a maximum of 41°C. For the posterior wall in particular, the RF power was set to 25 W, and the flow rate was set to 17 mL/min. For patients in AF at the end of the procedure, cardioversion was performed to restore SR, and all PVs were then mapped to confirm PVI. Additional ablation was performed if residual LA-PV conduction was noted during SR.

Cryoablation

A 28-mm cryoballoon (ARC-Adv-CB, Arctic Front Advance; Medtronic Inc., Minneapolis, MN, USA) with an inner lumen mapping catheter (Achieve, Medtronic) was inflated and advanced to each PV orifice through a steerable 15 Fr 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. A decapolar catheter was then advanced into the superior vena cava, and the phrenic nerve was paced continuously during cryothermal energy application to the right superior PV and the right inferior 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 excursion, diaphragmatic compound motor action potentials (CMAPs) were assessed for detection of any phrenic nerve injury. The CMAP recording technique was as reported previously. Cryothermal energy application was discontinued when either the diaphragmatic excursions decreased on palpation or a > 30% reduction in CMAP amplitude occurred. For patients in AF at the end of the procedure, cardioversion was performed to restore SR, and all PVs were then mapped to confirm PVI. Additional ablation was performed if residual LA-PV conduction was noted during SR.

ATP-induced dormant conduction

After PVI was confirmed, provocation testing with 30 mg of intravenous ATP was performed to unmask dormant conduction. ATP was administered during atrioventricular sequential pacing with an atrial-ventricular delay of 200 ms at a cycle length of 600 ms. The sites of dormant conduction, which were identified by the reappearance of PV activity recorded for 1 or more beats on 2 circular catheters appropriately positioned at the ipsilateral PVs, were tagged on the electroanatomic map. Additional RF ablation was performed to abolish dormant conduction. The procedure endpoint was confirmation of bidirectional block in all PVs despite repeat ATP provocation. Left atrial linear ablation and ablation of complex fractionated atrial electrograms and/or left atrial ganglionic plexi were performed, at the operator’s discretion, after complete PVI.

Follow up

Electrocardiographic monitoring was continued during the hospitalization period. Patients were followed up through outpatient clinic visits at 2 weeks, 1, 3, 6, and 12 months and every 6 months thereafter, and 12-lead electrocardiograms, 24-hour Holter recordings, and/or ambulatory event electrocardiograms were obtained if necessary. AF lasting more than 30 sec was considered as recurrence of AF. An initial Three months after the procedure were considered as a blanking period.

Statistical analysis

For comparison, patients were divided into 3 groups: patients in whom SR was present before placement of the
catheter (SR group, n = 10), patients in whom SR was maintained after internal cardioversion (DC group, n = 28), and patients in whom ablation was performed during AF but AF recurred immediately after internal cardioversion (n = 8). Continuous variables are expressed as mean ± SD or median (interquartile range) values. Differences in variables were analyzed by Mann-Whitney U test or post hoc test. AF-free survival was estimated by the Kaplan-Meier method and analyzed by log-rank test. All statistical analyses were performed with JMP 9 software (SAS Institute, Cary, NC, USA), and P < 0.05 was considered significant.

RESULTS

Patient characteristics

AF duration in the total patient group was 13.0 (5.0–48.0) months. Left atrial diameter and left ventricular ejection fraction measured by transthoracic echocardiography were 41.9 ± 5.6 mm and 65.0 ± 8.6% respectively.

Patient characteristics and echocardiographic variables are shown per group in Table 1. AF duration was longer in the AF group than in the other 2 groups. There were no significant between-group differences in ablation strategies, as shown in Table 2.

Ablation outcomes

Post-ablation recurrence of AF was classified according to the time of recurrence: very early recurrence, i.e., recurrence within 3 days after ablation; early recurrence, i.e., recurrence of between 4 days and 3 months after ablation; and late recurrence, i.e., recurrence after 3 months. The incidences of very early recurrence and early recurrence were lowest in the SR group than DC and AF groups, but the differences were not statistically significant (Figs. 1, 2). No incidence of late recurrence was observed in the SR group, but no significant difference was found between the DC and AF groups (Fig. 3). Length of the follow-up period and the use of class 1 antiarrhythmic drugs and/or bepridil did not differ significantly between the 3 groups, but the freedom from arrhythmia rate was significantly higher in the SR group after the 3-month blanking period (Table 3). Kaplan-Meier recurrence-free survival rates after initial 3 months blanking period are shown for the SR group, DC group, and AF group in Fig. 4. As shown in Figure 1, 2, 3, incidence of very early and early recurrence of AF did not differ significantly among SR, DC, and AF groups but incidence of late recurrence was significantly lower in SR group.

Overall, the rate of freedom from AF after the single procedure was significantly higher in the SR group than that in the DC and AF groups (100%, 46% and 50%, respectively, P = 0.0110) during median follow-up periods of 15.5, 19.4, and 28.2 months.

DISCUSSION

The main findings of this clinical study were that AF-free survival rates after catheter ablation in patients with PerAF were significantly higher after the 3-month blanking period in patients in whom SR had been restored
spontaneously before ablation than in patients in whom it had not. Rivard et al.\textsuperscript{12}) showed that when SR was restored prior to catheter ablation for PerAF, the extent of ablation could be reduced without decreasing clinical efficacy. Kochhäuser et al.\textsuperscript{9}), in a the substrate and trigger ablation for reduction of atrial fibrillation trial part II (STAR AF II) trial substudy, showed that acute termination of AF during ablation did not consistently predict long-term outcomes, that prolongation of the intra-procedural AF cycle length did not predict long-term outcomes and that the presence of SR early during the procedure (either because AF rhythm was not present or because of early cardioversion) was a strong predictor of AF-free survival. They speculated that the presence of SR before or early during the ablation procedure characterizes a subgroup of patients with only minimally or moderately advanced disease or that SR itself may facilitate PVI\textsuperscript{12}). Among our patients, the outcome was similar between those in whom SR was maintained after cardioversion before PVI and those in whom AF recurred immediately after internal cardioversion. The difference in the results between our study and the STAR AF II substudy may be related to the method used for cardioversion. External cardioversion was used in the STAR AF II patients, whereas internal cardioversion was used in our patients. Therefore, patients with AF refractory to external cardioversion may have been included in our group of patients in whom internal cardioversion was successful. Previous studies have shown that pharmacological cardioversion before ablation for PerAF predicts a favorable outcome\textsuperscript{13, 14}). The antiarrhythmic drugs used before ablation in our study patients were stopped for at least 5 half-lives before the procedure. Post-ablation administration of antiarrhythmic drugs, mainly bepridil, began on the day after ablation and continued for at least 6 months or until recurrence of AF. A previous study showed that the short-term use of an antiarrhythmic drug for 90 days following AF ablation reduced the incidence of recurrent atrial tachyarrhythmia during the treatment period, but it did not lead to im-

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Table 3 Clinical outcomes after 3-month blanking period

|                      | SR group (n = 10) | DC group (n = 28) | AF group (n = 8) | P value |
|----------------------|-------------------|-------------------|------------------|---------|
| Follow-up period     |                   |                   |                  |         |
| (months)             | 15.1 (14–17)      | 19.6 (12–27)      | 28.2 (16–36)     | 0.1311  |
| Class I AAD          | 0 (0%)            | 6 (21%)           | 1 (13%)          | 0.2451  |
| Bepridil             | 7 (70%)           | 23 (82%)          | 8 (100%)         | 0.2151  |
| No AF recurrence     | 10 (100%)         | 13 (46%)          | 4 (50%)          | 0.0110  |

Number (and percentage) of patients are shown. SR: sinus rhythm, DC: direct Cardioversion, AF: atrial fibrillation, AAD: antiarrhythmic drug.
Sinus rhythm before ablation in persistent atrial fibrillation on outcome

proved outcomes in the later phase\(^{(5)}\). Long-term use of bepridil after AF ablation might be related to the higher AF-free survival rate observed in our SR group.

Study limitations

Our findings should be interpreted in light of the study limitations. The study was retrospective; therefore, the ablation strategy, the type and use of antiarrhythmic drugs, and the duration of antiarrhythmic drug administration after ablation varied. In addition, our patient groups were small, and the follow-up times were somewhat longer in the DC and AF groups than that in the SR group. Secondary, number of SR group was only 10 patients; therefore, we did not perform univariate and multivariate analysis for presence of sinus rhythm before ablation for the midterm predictor of sinus rhythm after ablation.

Conclusion

According to our study, presence of spontaneous SR before ablation for PerAF appears to be related to AF-free survival.

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