Background: Although pulmonary vein (PV) antrum isolation is an established therapy for drug-resistant paroxysmal atrial fibrillation (PAF), long-term (>5 years) follow-up data are limited. This study investigated long-term clinical outcome of catheter ablation.

Methods and Results: From September 2003 to August 2006, 161 patients (mean age, 60±9 years; 119 male) with symptomatic drug-refractory PAF who underwent extensive encircling PV isolation (EEPVI) with a double Lasso technique were included. Right-sided and left-sided circular lesions encircling the ipsilateral PVs were created. The procedure endpoint was electrical isolation of the PV antrum. Patients with recurrent atrial tachyarrhythmia (ATa) had their previous lesions assessed and consolidated. Trigger ablation was added if necessary. EEPVI was successfully performed at the initial procedure. During a median follow-up of 6.4 years (25th–75th percentile, 5.8–7.1 years), 86 patients (53.4%) had recurrent ATa. Among 78, 15 and 4 patients undergoing 2nd, 3rd and 4th procedures, PV reconnections were observed in 68, 10 and 2, respectively. During a median follow-up of 6.0 years (25th–75th percentile, 5.2–6.9 years) after a mean of 1.6±0.7 procedures per patient, 144 patients (89.4%) were free from ATa. No progression toward persistent AF was observed in any patients.

Conclusions: The vast majority of drug-resistant PAF could be controlled by EEPVI without an additional atrial substrate modification. No progression toward persistent AF was observed during a median follow-up of 6 years. (Circ J 2013; 77: 2722–2727)

Key Words: Atrial fibrillation; Catheter ablation; Long-term follow-up; Pulmonary vein isolation

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and paroxysmal AF naturally progresses to persistent AF with the risk of thromboembolic events.1–3 Since the seminal paper by Haïssaguerre et al, pulmonary veins (PVs) have been recognized as the most important source of triggers that initiate AF in patients with paroxysmal AF.4 This key observation led to the development of segmental ostial isolation of each individual PV.5 This technique subsequently evolved to include the whole PV antrum to avoid PV stenosis, and several studies confirmed that PV antrum isolation resulted in a better clinical outcome than segmental PV isolation.6–8 Nowadays, catheter ablation has become an acceptable option for the treatment of drug-resistant paroxysmal AF.9–11 It has only been a decade, however, since the original observation of PV triggering AF was described, and, coupled with the evolving understanding and techniques, this has meant that there are few long-term (>5 years) studies of the effectiveness of AF ablation.12–14 Moreover, recent data have highlighted the very late recurrence after the ablation procedure, which has enhanced the importance of long-term follow-up. The purpose of the present study was to evaluate the long-term efficacy and feasibility of catheter ablation of paroxysmal AF.

Methods

Subjects
Among 225 consecutive patients with drug-refractory symptomatic paroxysmal AF who underwent extensive encircling PV isolation (EEPVI)15 at Tsuchiura Kyodo Hospital from September 2003 to August 2006, 161 patients (mean age, 60±9 years; 119 male) for whom the follow-up data could be updated on October 2011 were included in this study. AF was classified as paroxysmal if episodes terminated spontaneously in <7 days according to the HRS/EHRA/ECAS 2012 Consensus Statement on Catheter and Surgical Ablation of AF.16 All patients gave written informed consent.

Mapping and Ablation Protocol
All anti-arrhythmic drugs were discontinued for at least 5 half-lives prior to the procedure. Patients were effectively antico-
agulated for >1 month, and trans-esophageal echocardiography was performed to exclude any atrial thrombi. Enhanced cardiac computed tomography (CT) was performed for the evaluation of the relevant cardiac anatomy before the procedure. Surface electrocardiogram (ECG) and bipolar intracardiac electrograms were continuously monitored and stored on a computer-based digital recording system (LabSystem PRO, Bard Electrophysiology, Lowell, MA, USA). Bipolar electrograms were filtered from 30 to 500 Hz. A 7-Fr 20-pole or 14-pole 2-site mapping catheter (Irvine Biomedical, Irvine, CA, USA) was inserted through the right jugular vein and positioned in the coronary sinus (CS) for pacing, recording and internal cardioversion. Electrophysiological examination was performed under sedation with pentazocine and hydroxyzine pamoate.

Catheter Ablation

The details of the ablation strategy have been described previously,19,20 but in brief, after 1 transseptal puncture, a long sheath (SR0, AF Division, St. Jude Medical, Minneapolis, MN, USA) and Mullins transseptal sheath (Medtronic, Minneapolis, MN, USA) were introduced into the left superior pulmonary vein (LSPV) and left inferior pulmonary vein (LIPV), respectively. Left pulmonary venography and contrast esophagography were performed to obtain the anatomical relationship of the PV ostia relative to the esophagus. Subsequently, right pulmonary venography was undertaken. A 5000-U dose of heparin was given following the transseptal puncture, with a continuous infusion of 1000–2000 IU/h.

Before the radiofrequency (RF) applications, the AF trigger was identified using multiple mapping catheters with an isoproterenol infusion (2 μg/min) or cardioversion of spontaneous persistent AF and/or induced AF by pacing. Two circular mapping catheters (Lasso; Biosense Webster, Diamond Bar, CA, USA) were placed in the superior and inferior PVs, and the left- and right-sided ipsilateral PVs were circumferentially and extensively ablated under fluoroscopic and electrophysiologic guidance. The left atrium (LA) posterior wall, at a distance of 1–3 cm from the left- or right-sided ostia of the PVs, was anatomically ablated and the distal edges of the anterior aspect of the PVs with early PV potentials or continuous PV and LA potentials were targeted for ablation. Isolation of the left-sided PVs was performed during distal CS pacing and isolation of the right-sided PVs during distal CS pacing or sinus rhythm. RF current delivery was applied with a 4-mm-tip ablation catheter (Japan Lifeline, Tokyo, Japan) in the temperature control mode, with a target temperature of 50°C and maximum power of 35 W. RF energy delivery was applied for 25–35 s per point. The endpoint was the elimination of all PV potentials.

If a cavotricuspid isthmus (CTI)-dependent atrial flutter was observed or suspected on 12-lead ECG before or during the procedure, a CTI line was created with an endpoint of bidirectional conduction block following the EEPVI.17,18 When the superior vena cava (SVC) triggering AF and/or premature atrial contractions originating from the SVC were identified during the procedure, electrical SVC isolation was performed.19,20

During a repeat ablation procedure for recurrent atrial tachyarrhythmia (ATa), first the prior ablation lesions were evaluated. In the presence of recovery of conduction, re-ablation was performed with the same ablation strategy as in the initial procedure. In patients without recovered PV conduction, the initial mapping and ablation strategy targeted non-PV triggers. If non-PV triggers were absent, ablation of complex fractionated atrial electrograms was performed during either spontaneous or induced AF.21

Follow-up

The patients underwent continuous ECG monitoring as inpatients for 3 days after the procedure. The first outpatient clinic visit was 3 weeks after the procedure. The follow-up visits consisted of a clinical interview, ECG, and 24-h Holter monitoring 3, 6, 9, and 12 months at the cardiology clinic in addition to a later routine follow-up by the referring physician or at the hospital including Holter monitoring in the event of symptoms. This study did not adhere to a predefined blanking period. Anti-arrhythmic drugs were not prescribed after the procedure, but were allowed for patients with symptomatic premature atrial contractions and/or recurrent ATa. If any symptoms suggestive of arrhythmia occurred, the patients were asked to come to the emergency department, and a 12-lead ECG or 24-h Holter monitoring and/or 1-month-event recording were performed in order to define the cause of the symptoms. All patients were personally contacted for an updated follow-up in October 2011. Warfarin was discontinued 3 months after the procedure if no recurrent ATa were observed. Success was defined with and without anti-arrhythmic drugs as the absence of all documented arrhythmias lasting ≥30 s or symptoms suggestive of an arrhythmia recurrence. Repeat procedure was strongly recommended for patients with documented recurrent ATa. Cardiac CT was done ≥3 months after the initial procedure for the evaluation of PV stenosis.

Statistical Analysis

Continuous data are expressed as mean±SD for normally distributed variables or as median (25th–75th percentile) for non-normally distributed variables, and compared using Student’s t-test or Mann-Whitney U-test, respectively. Categorical variables were compared using the chi-squared test. P<0.05 indicated statistical significance. Kaplan-Meier analysis was used to determine the percentage of patients free from ATa after the initial and last ablation procedure. Multiple logistic regression analysis was used to determine arrhythmia recurrence after the initial procedure. Variables with P<0.2 on univariate analysis were included in multivariate analysis. The following patient variables were evaluated in association with age, sex, hypertension, diabetes mellitus, AF duration, LA diameter, left ventricular ejection fraction, CHADS: score, and CHA2DS2-VASc score.

Procedural Data

Patient clinical characteristics are listed in Table 1. Left common PV was identified in 15 patients (9.3%). Arrhythmogenic PVs were identified during the procedure in 99 patients (61.5%; LSPV in 30, LIPV in 30, left common PV in 1, right superior PV in 24, right inferior PV in 5, and non-PV in 15 patients).

Successful EEPVI was achieved in all patients at the initial procedure. SVC isolation was added in 13 patients (8.1%), and bidirectional CTI block was created in 51 patients (31.7%). During a median follow-up period of 6.4 years (25th–75th percentile, 5.8–7.1 years), 86 patients (53.4%) had recurrent ATa (Figure 1A). The time of the ATa recurrences is shown in Figure 2. Recurrent ATa were most frequently observed within 3 months after the initial procedure. The recurrent ATa were AF, AT, and common atrial flutter in 77 patients (89.5%), 7 patients (8.1%), and 2 patients (2.3%), respectively. There was no statistically significant pre-procedural parameter that could predict recurrent ATa after the initial procedure (Table 2).

In 78 patients (48.4%), a repeat procedure was performed at a median of 3.4 months (25th–75th percentile, 1.9–13.0 months)
after the initial procedure. Recovered PV conduction was found in 68 patients (87.2%); conduction gaps were located along the right-sided PVs in 58 patients (74.4%) and the left-sided PVs in 50 patients (64.1%). All conduction gaps were successfully closed with RF current application. SVC isolation was added in 15 patients (19.2%), and bidirectional CTI block was created in 20 patients (25.6%). After the second procedure, recurrent ATa were observed in 22 patients (28.2%) during a median follow-up period of 5.7 years (25th–75th percentile, 4.8–6.5 years). The recurrent ATa were observed within and after 3 months in 18 and 4 patients, respectively. The type of recurrent ATa was AF and common atrial flutter in 21 and 1 patient, respectively.

A third ablation procedure was performed in 15 patients (9.3%) at a median of 29.0 months (25th–75th percentile, 18.5–39.3 months) after the second procedure. In 10 patients (66.7%), recovered PV conduction was found. Conduction gaps were located along the right-sided PVs in 6 patients (40%) and along the left-sided PVs in the other 9 (60%). SVC isolation was added in 5 patients (33.3%). After the third ablation procedure, 11 pa-

Table 1. Patient Clinical Characteristics

|                           | n=161 |
|---------------------------|-------|
| Age (years)               | 60.0±9.0 |
| Male                      | 119 (74) |
| PAF duration (months)     | 31 (13–74) |
| Hypertension              | 58 (36) |
| Diabetes mellitus         | 9 (6) |
| LA diameter (mm)          | 41.4±6.4 |
| LVDd (mm)                 | 48.5±5.2 |
| LVEF (%)                  | 67.8±11.1 |
| CHADS2 score              | 0.48±0.67 |
| CHA2DS2-VASc score        | 1.0±1.07 |

Data given as n (%), mean±SD or median (25th–75th percentile). LA, left atrium/atrial; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation.

Figure 1. Kaplan-Meier analysis of freedom from recurrent atrial tachyarrhythmia (ATa) after (A) the initial procedure and (B) the last ablation procedure.
Long-Term Follow-up of PAF Ablation

Patients were free of ATa during a median follow-up of 3.0 years (25th–75th percentile, 2.2–4.2 years). Paroxysmal AF recurred within and after 3 months in 3 and 1 patient, respectively.

A fourth ablation procedure was performed in 4 patients at a median of 31.4 months (25th–75th percentile, 20.2–37.3 months) after the third procedure. In 2 patients (50%), recovered PV conduction was found. Conduction gaps were located along the right-sided PVS in 2 patients (50%) and along the left-sided PVS in the other 1 patient (25%). An SVC isolation was added in 2 patients (50%). After the fourth ablation procedure, 2 patients were free of ATa, and AF recurred in 2 patients during a median follow-up of 1.9 years (25th–75th percentile, 1.7–2.2 years).

Clinical Outcome
Clinical outcome is summarized in Figure 3. In total, SVC isolation was performed in 40 patients (24.8%), and bidirectional CTI linear block was created in 66 patients (41.0%). In 152 of 161 patients (94.4%), only EEPVI was performed. In 2 of 161 patients (1.2%), additional linear lesions were placed for the treatment of macronreentrant atrial tachycardia. In 7 of 161 patients (4.3%), additional ablation of complex fractionated atrial electrograms was performed. During a median follow-up of 6.0 years (25th–75th percentile, 5.2–6.9 years) from the last procedure and after a mean of 1.6±0.7 procedures per patient, 144 patients (89.4%) were free from ATa (Figure 1B). Among the 144 patients, anti-arrhythmic drugs were prescribed in 41 patients. On univariate analysis, AF duration was significantly longer in the patients with recurrent ATa than in those without after the last procedure (P=0.01; Table 2).

No progression toward persistent AF after EEPVI was observed in any patients. Warfarin, dabigatran and aspirin were prescribed in 22 patients (13.7%), 5 (3.1%) and 26 (16.1%) at the time of the last follow-up, respectively. A cerebral infarction was observed in 2 patients during the follow-up period. In 1 patient, it occurred following an AF recurrence during acute

![Figure 2.](image)

**Figure 2.** Time to the first episode of atrial tachyarrhythmia after the initial atrial fibrillation ablation.

**Table 2. Predictors of Arrhythmia Recurrence**

|                | Single procedure | Last procedure |
|----------------|-----------------|---------------|
|                | Univariate P-value | Multivariate P-value | Univariate P-value |
| Age (years)    | 0.78            | 0.42          | 0.42            |
| Sex            | 0.19            | 0.60          | 0.09            |
| Hypertension   | 0.21            | 0.82          | 0.82            |
| Diabetes mellitus | 0.41         | 0.96          | 0.96            |
| AF duration (months) | 0.77         | 0.01          | 0.01            |
| LA diameter (mm) | 0.23           | 0.30          | 0.30            |
| LVEF (%)       | 0.92            | 0.28          | 0.28            |
| CHADS2         | 0.54            | 0.77          | 0.77            |
| CHA2DS2-VASc   | 0.10            | 0.26          | 0.94            |

AF, atrial fibrillation. Other abbreviations as in Table 1.
complications. It suggests that additional substrate modification, which potentially leads to iatrogenic atrial arrhythmias, is not necessary in the vast majority of patients with paroxysmal AF in order to maintain sinus rhythm. It is well known that PV reconnections are associated with recurrent ATa in the vast majority of patients with an ATa recurrence. The high incidence of PV reconnections in the repeat procedures in the present study seems to be associated with recurrent ATa. The rate of recurrence was highest during the first 3 months, followed by a low but steady rate of recurrence throughout the 6-year follow-up period. The present 6-year follow-up period was longer than in prior reports, and the present data extend the results of those papers. The results clearly emphasize the importance of careful long-term follow-up after catheter ablation to identify very late ATa recurrence. The present study also highlights the importance of additional ablation after PV antrum isolation, such as SVC isolation or CTI linear ablation. These arrhythmias frequently coexist with AF, and their elimination is essential for the maintenance of sinus rhythm in the long term.

Although all ablation procedures were undertaken without a 3-D mapping system or irrigation tip catheter, such new technologies, which are now available as standard practice, might improve the present clinical outcome and reduce the procedure complications.

As the present study has shown, the vast majority of AF could be controlled by creating a durable electrical PV antrum isolation and eliminating the non-PV triggers that were provoked. Even after multiple procedures, however, freedom from arrhythmias was not obtained in some of the patients. In a subset of the patients, it was difficult to identify the AF trigger using various provocation maneuvers or to eliminate all of the multiple AF triggers during the procedure. The development of a further new technology might be necessary to improve clinical outcome in these patients.

Figure 3. Flowchart detailing clinical outcome after each ablation procedure. AF, atrial fibrillation; AT, atrial tachycardia; SR, sinus rhythm.
Progression to Persistent AF and Thromboembolic Events

Usually AF occurs first as paroxysmal AF, then develops into persistent AF. Kato et al reported a rate of progression of paroxysmal AF toward persistent AF of 77% (5.5% of patients per year) under conventional anti-arrhythmic therapy during a 14-year follow-up in Japanese patients. The present data showing that no patients developed persistent AF after catheter ablation during a median of 6 years is notable. This suggests that the PVs and PV antrum might contribute to the progression of AF. Although a prospective randomized trial is required to prove this, it is likely that catheter ablation might retard the process of AF progression.

AF is also an important cardiogenic cause of thromboembolisms, and their prevention is a major goal for the management of patients with AF. It is well known that not only persistent AF but also paroxysmal AF can be the cause of thromboembolic events. The present data extend the prior data, which have shown a low incidence of thromboembolic events after catheter ablation during a mean follow-up of 28 months.

Study Limitations

First, the subject group was not a consecutive patient series, which could lead to entry bias, but the other studies also had a similar limitation. Second, AF recurrence may have been underestimated because the patients were not constantly monitored. This study, however, included only highly symptomatic patients, who were able to identify their frequent AF episodes. Third, we could not obtain follow-up data for some of the patients undergoing AF ablation during the data collection period, but the other studies also had a similar limitation. Fourth, all ablation procedures were performed using non-irrigated tip catheters because irrigated tip catheters were not approved. Second, AF recurrence may have been underestimated because the patients were not constantly monitored. This study, however, included only highly symptomatic patients, who were able to identify their frequent AF episodes. Third, we could not obtain follow-up data for some of the patients undergoing AF ablation during the data collection period, but the other studies also had a similar limitation. Fourth, all ablation procedures were performed using non-irrigated tip catheters because irrigated tip catheters were not approved.

Conclusions

The vast majority of drug-resistant symptomatic paroxysmal AF could be controlled by catheter ablation over the long-term follow-up period. No progression to persistent AF was observed during a median follow-up of 6 years after catheter ablation.

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Disclosures

Conflict of interest: there are no conflicts of interest to report. Financial support: none.

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