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The proportion of asymptomatic recurrence after catheter ablation of atrial fibrillation in patients with a pacemaker for sick sinus syndrome



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ABSTRACT

Background: Catheter ablation (CA) of paroxysmal atrial fibrillation (PAF) is an effective treatment. However, the frequency of asymptomatic AF recurrence after CA in patients with PAF and sick sinus syndrome (SSS) is not clear. The aim of this study was to elucidate the real AF recurrence after CA in patients with PAF and a pacemaker for SSS.

Methods and results: Fifty-one consecutive patients (mean age 66.6 ± 7.0 years, male 34) with PAF and SSS and pacemakers underwent CA. All patients were followed at 1, 3, 6, 9, and 12 months after the CA using a 12-lead ECG, Holter-ECG, and 1-month event recorder as a conventional follow-up. In addition, the pacemakers were interrogated every 12 months. During a 5-year follow-up after the final CA procedure, AF recurrences were observed in 7 patients (13.7%) with a conventional follow-up, including 1 (2.0%) asymptomatic patient. Pacemaker-interrogation revealed another 10 patients (19.6%) with asymptomatic AF recurrences. Ultimately, the conventional follow-up plus pacemaker-interrogation provided a higher incidence of AF recurrences ($P = 0.009$). Multiple CA procedures contributed to a significant increase in the AF-free survival rate at 5 years: 58.6% after a single CA and 86.0% after multiple CA procedures with a conventional follow-up, but which decreased to 40.6% and 60.9% with a conventional follow-up plus a pacemaker interrogation, respectively.

Conclusions: One-third of PAF patients with SSS and pacemakers recurred after multiple CA sessions. However, 65% of them were asymptomatic and difficult to be identified with conventional follow-up. Pacemaker interrogation significantly increased the detection rate of AF-recurrence.

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1. Introduction

Catheter ablation (CA) of paroxysmal atrial fibrillation (PAF) is an effective treatment [1]. A rhythm follow-up after CA is mainly assessed by a 12-lead electrocardiogram (ECG), Holter-ECG, and event recorder [2,3] based on the patient's symptoms. However, several studies using a 7-day Holter [4] or tele-ECG [5] follow-up revealed a significant number of asymptomatic recurrences. Current pacing systems can automatically detect and record

asymptomatic atrial tachyarrhythmias. Implanted dual-chamber devices are assumed to have a high appropriate detection rate of atrial high frequency episodes [6]. Little data were available in asymptomatic AF recurrences after CA in PAF patients who had received a pacemaker for the treatment of coexistent sick sinus syndrome (SSS) [7–9]. Thus, the aim of this study was to elucidate the real AF burden after CA in patients with PAF and a pacemaker for SSS.

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2. Methods

2.1. Study population

Among consecutive drug-refractory PAF patients who underwent catheter ablation, 51 patients (mean age 66.6 ± 7.0 years, male 34) with a pacemaker implantation for the treatment of SSS were included in this study. AF was defined as paroxysmal when it terminated spontaneously within 7 days [10]. All patients provided written, informed consent and our institutional review board approved the protocol.

2.2. Electrophysiological study

Antiarrhythmic drugs (AADs) were discontinued for >7 days (amiodarone was discontinued for >1 month) before the ablation; all patients were also effectively anticoagulated for >1 month. A 7-Fr, 20- or 14-pole, two-site mapping catheter (Irvine Biomedical, Irvine, CA, USA) was inserted through the right jugular vein and positioned in the coronary sinus for pacing, recording, and internal cardioversion.

2.3. CA technique

The strategy of an extensive pulmonary vein isolation (EPVI) has been previously described [11]. Briefly, after a transseptal puncture, pulmonary venography and contrast esophagography were performed to determine the anatomical relationships of the PV ostia, left atrium (LA), and esophagus. An activated clotting time of 250–350 s was maintained with a continuous infusion of heparin during the procedure. Two circular mapping catheters were placed in the superior and inferior pulmonary veins (PVs), and the left and right ipsilateral PVs were circumferentially and extensively ablated under fluoroscopic and electrophysiological guidance. Radio-frequency current applications were delivered with an 8-mm tip ablation catheter (Japan Lifeline, Tokyo, Japan) in the temperature control mode, with a target temperature of 55°C (maximum power, 35 W on the LA posterior wall; 40 W at the anterior aspect of the PVs), and the esophageal temperature was measured during the application [11]. The endpoint was the elimination or any dissociation of the PV potentials. After completing the EPVI, adenosine triphosphate (20–40 mg) was injected to unmask any dormant conduction, and that was disconnected [12]. Thereafter, a cavotricuspid isthmus (CTI) line was created with a bidirectional conduction block endpoint [13]. Isoproterenol ($5\text{--}20\ \mu\text{g}/\text{min}$) was intravenously injected before completing the procedure. If sustained or non-sustained AF was reproducibly initiated from non-PV foci, they were focally ablated [14]. When non-PV foci were located in the superior vena cava (SVC), the SVC was electrically isolated [15,16]. If spontaneous AF did not occur, rapid atrial pacing was performed to induce AF. After an episode of pacing-induced AF was sustained, internal cardioversion was attempted to convert the AF to sinus rhythm (SR). If post pacing spontaneous AF was seen, then the source of the initiation was ablated. Linear ablation (left atrial roof and/or bottom and/or mitral isthmus lines) was performed only when AF from an undetermined origin or macroreentrant atrial tachycardia spontaneously occurred, with an endpoint of a bidirectional conduction block [17,18]. In case atrioventricular nodal reentrant tachycardia or atrioventricular reentrant tachycardia was induced, they were also treated. On completion of the procedure, the endpoints of the EPVI, SVC isolation, and linear ablation were re-confirmed. In the re-do session, PVs were re-isolated when they were reconnected. Isoproterenol ($5\text{--}20\ \mu\text{g}/\text{min}$) was intravenously injected and non-PV foci were targeted. Linear ablation lines were added with an endpoint of bidirectional

conduction block only when AF from an undetermined origin or macroreentrant atrial tachycardia occurred.

2.4. Follow-up

AADs were not prescribed after the procedure. All patients were followed up at 1, 3, 6, 9, and 12 months after the CA conventionally using a 12-lead ECG, Holter-ECG, and 1-month event recorder (in patients with symptoms). Atrial tachyarrhythmias lasting longer than 30s after the blanking period of 2 months were defined as an AF recurrence (Conventional follow-up). After the procedure, the patients' devices were programmed to their original settings with one exception: in all patients, mode switching was programmed to occur at an atrial sensed rate of >170 bpm, and the pacemaker was interrogated every 12 months unless they did not have any symptomatic episodes. A Sudden increase in the heart rate of >170 bpm lasting longer than 30s detected by the device was generally determined as a recurrence. We excluded any inappropriate high rate episodes by manual interpretation of the documented electrocardiograms.

2.5. Statistical analysis

The data were expressed as means \pm standard deviations (continuous variables) or frequencies and percentages (categorical variables). To compare the 2 groups, a Chi-square analysis or Fisher's exact test were used for categorical variables. A Cox-proportional hazard model was used to assess the association of the baseline variables with the endpoint of AF recurrence. Survival curves were calculated using the Kaplan-Meier method. *P*-values of <0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics and clinical outcomes

The baseline characteristics of the 51 patients are shown in Table 1. The patients were predominantly male ($n = 34$, 66.7%) with an age of 66.6 ± 7.0 years. The mean duration of an AF history was 82.4 ± 63.9 months. Forty (78.4%) patients were highly symptomatic on the baseline evaluation. Acute success was achieved in all patients without any complications. Immediately after the ablation, all permanent pacemakers (PPMs) were interrogated and the integrity and function of the leads were checked. The PPM was determined to have a normal function in all patients post-ablation. No device-related complications occurred in the patients as a result

Table 1
Baseline characteristics (N = 51).

Patient age, years	66.6 \pm 7.0
Gender, male (%)	34 (66.7)
Duration of an AF history, months	82.4 \pm 63.9
SHD, n (%)	5 (9.8)
Symptomatic (%)	40 (78.4)
Hypertension, n (%)	25 (49.0)
Diabetes, n (%)	14 (27.4)
CHF, n (%)	7 (13.7)
Stroke, n (%)	4 (7.8)
CHADS ₂ score	1.1 \pm 1.0
Echocardiography	
LAD, mm	39.7 \pm 5.4
LVEF, %	63.6 \pm 8.7

Data are presented as the n (%) or mean \pm SD.
AF; atrial fibrillation, CHF; congestive heart failure, LAD; left atrial dimension at end-systole, LVEF; left ventricular ejection fraction, SHD; structural heart disease.

of ablation: e.g., lead dislodgement, resetting of the PPM generator, etc. After a single CA procedure, AF recurrences were observed in 28 patients (54.9%). Among these patients, the conventional follow-up successfully detected AF recurrences in 20 of 28 patients (71.4%) during a mean follow-up period of 32.2 ± 35.1 months. However, pacemaker interrogations added another 8 patients with AF recurrences, none of whom had any symptoms (Fig. 1A). After the final CA procedure, AF recurrences were observed in 17 patients (33.3%) during a mean follow-up period of 45.6 ± 33.9 months. Among these patients, the conventional follow-up successfully detected AF recurrences in 7 of 17 patients (41.2%). However, the pacemaker interrogations added another 10 patients with AF recurrences, none of whom had any symptoms (Fig. 1B). In total, 11/17 patients (64.7%) recurred without symptoms.

Multiple CAs contributed to a significant increase in the AF-free survival rate at 5 years: 58.6% after a single CA vs. 86.0% after multiple CAs with a conventional follow-up (Fig. 2). However, the AF-free survival rate at 5 years was 40.6% after a single CA and 60.9% after multiple CA procedures with a conventional follow-up plus a pacemaker interrogation (Fig. 2). Ultimately, the conventional follow-up plus a pacemaker interrogation provided a significantly higher incidence of AF recurrences after multiple CA procedures ($p = 0.01$). There was no significant parameter to predict real AF-recurrences after the initial CA in this patient population.

3.2. Asymptomatic AF recurrence

The clinical characteristics of the recurrent patients with or without symptoms are compared in Tables 2 and 3. A female prevalence tended to be higher in the symptomatic recurrence group than in the asymptomatic recurrence group after a single CA (Table 2). No significant differences were shown in the patient characteristics between the 2 groups after the multiple CAs (Table 3). By a multivariate analysis, there were no significant factors that were associated with the symptoms after both a single and multiple CAs.

3.3. Duration of the recurrent AF episodes and incidence of thromboembolisms

The maximum duration of the AF episodes after the final CA in each of the 17 patients was 26.0 ± 40.2 h (median 6 h, from 0.02 to 120 h) as shown in Fig. 3. Asymptomatic recurrences were observed in 11 (64.7%) patients. The mean maximum duration of the recurrent AF was 21.1 ± 38.8 h (median 1 h, from 0.02 to 120 h) in the asymptomatic patients, and 35.0 ± 44.8 h (median 15 h, from 6 to 120 h) in the symptomatic patients. The duration of the recurrent AF tended to be shorter in the asymptomatic patients but did not reach significance. ($P = 0.27$).

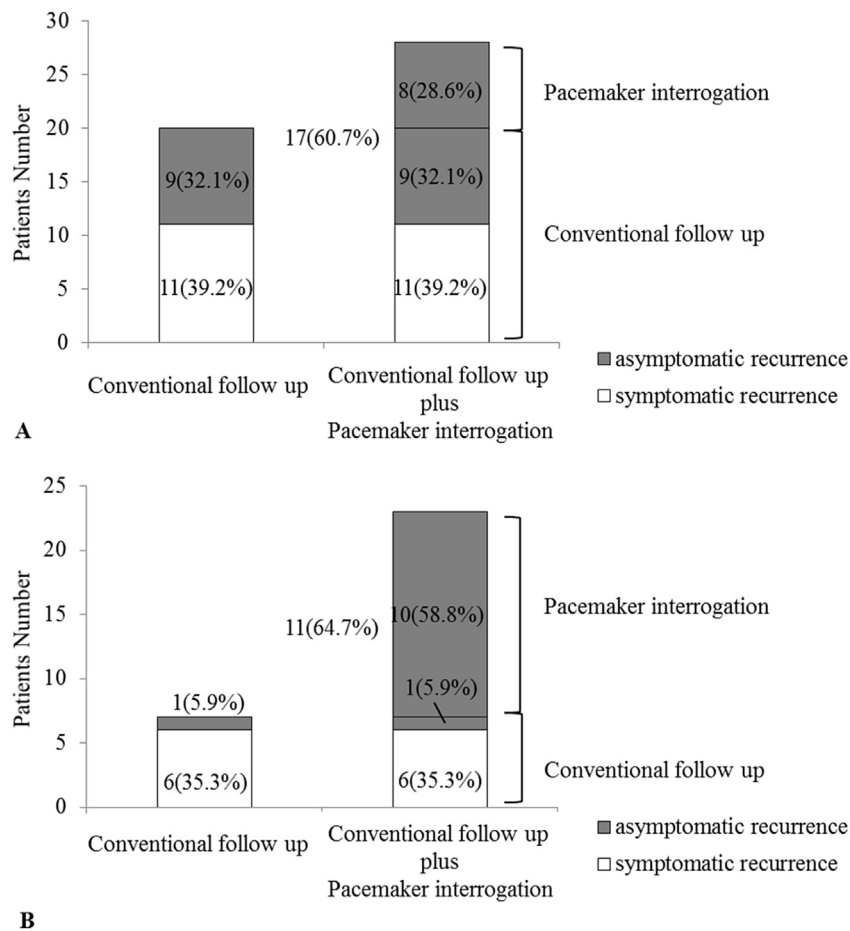


Fig. 1. A: The number of patients who had a recurrence after a single CA session during the mean follow-up period of 32.2 ± 35.1 months. AF recurrences were observed in 28 patients. 8 (28.6%) of them were not detected by a conventional follow-up. In total, 17 (60.7%) had no symptoms (gray bar). B: The number of patients who had a recurrence after the final CA session during the mean follow-up period of 45.6 ± 33.9 months. AF recurrences were observed in 17 patients. 10 (58.8%) of them were not detected by a conventional follow-up. In total, 11 (64.7%) had no symptoms (gray bar).

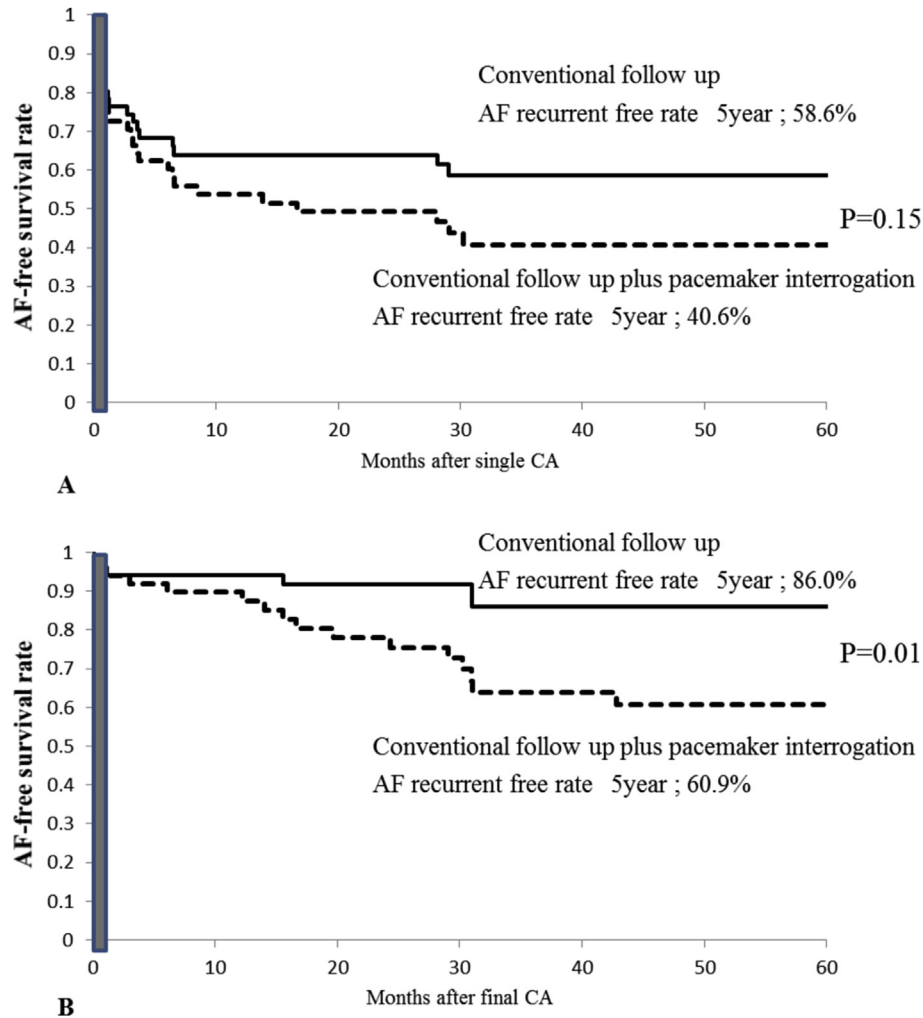


Fig. 2. A: The AF-recurrence free survival rate after a single CA. The AF-recurrence free rate was similar between the conventional follow-up vs. that plus a pacemaker-interrogation (58.6% vs. 40.6%, $p = 0.15$). The gray bar is a blanking period of 2 months. B: The AF-recurrence free survival rate after the final CA. The AF-recurrence free rate was significantly higher in the conventional follow-up compared with that plus a pacemaker-interrogation (86.0% vs. 60.9%, $p = 0.01$). The gray bar is a blanking period of 2 months.

Table 2

Characteristics in symptomatic versus asymptomatic recurrence patients after the initial CA session.

	Symptomatic recurrence (N = 11)	Asymptomatic recurrence (N = 17)	p-values
Patient age, year	67.6 ± 6.5	68.1 ± 7.6	0.43
gender, female	7 (63.6%)	4 (23.5%)	0.03
Duration of an AF history, months	92.4 ± 52.8	79.6 ± 77.8	0.30
SHD	1 (9.0%)	1 (5.8%)	0.33
Hypertension	7 (63.6%)	9 (52.9%)	0.57
Diabetes	2 (18.2%)	6 (35.3%)	0.32
CHF	2 (18.2%)	1 (5.9%)	0.30
Stroke	0 (0.0%)	2 (11.8%)	0.23
CHADS ₂ score	1.09 ± 0.53	1.35 ± 1.22	0.19
Symptomatic at baseline	9 (81.8%)	9 (52.9%)	0.12
AFL and/or AT	0 (0.0%)	2 (11.8%)	0.23
Echocardiography			
LAD, mm	39.1 ± 6.24	40.1 ± 5.80	0.38
LVEF, %	66.8 ± 9.74	63.6 ± 7.2	0.19

Data are presented as the n (%) or mean ± SD.

AF; atrial fibrillation, CHF; congestive heart failure, LAD; left atrial dimension at end-systole, AFL; Atrial flutter, AT; Atrial tachycardia, LVEF; left ventricular ejection fraction, SHD; structural heart disease.

CI, confidence interval; OR, Odds ratio.

No significant predictors remained by a multivariate analysis.

Table 3

Characteristics in symptomatic versus asymptomatic recurrence patients after the final CA session.

	Symptomatic recurrence (N = 6)	Asymptomatic recurrence (N = 11)	p-values
Patient age, year	69.8 ± 3.1	69.9 ± 3.1	0.25
gender, female	4 (66.7%)	4 (36.4%)	0.85
Duration of an AF history, months	110 ± 93.5	68 ± 71.0	0.12
SHD	1 (16.7%)	0 (0.0%)	0.16
Hypertension	3 (50.0%)	8 (72.7%)	0.23
Diabetes	0 (0.0%)	4 (36.4%)	0.09
CHF	2 (33.3%)	1 (9.1%)	0.21
Stroke	1 (16.7%)	1 (9.1%)	0.64
CHADS ₂ score	1.33 ± 1.33	1.64 ± 1.12	0.39
Symptomatic at baseline	5 (83.3%)	5 (45.5%)	0.62
AFL and/or AT	3 (50.0%)	1 (9.1%)	0.05
Echocardiography			
LAD, mm	39.0 ± 3.91	39.7 ± 6.08	0.31
LVEF, %	67.2 ± 9.81	62.7 ± 7.11	0.21

Data are presented as the n (%) or mean ± SD.

AF; atrial fibrillation, CHF; congestive heart failure, LAD; left atrial dimension at end-systole, AFL; Atrial flutter, AT; Atrial tachycardia, LVEF; left ventricular ejection fraction, SHD; structural heart disease.

CI, confidence interval; OR, Odds ratio.

No significant predictors remained by a multivariate analysis.

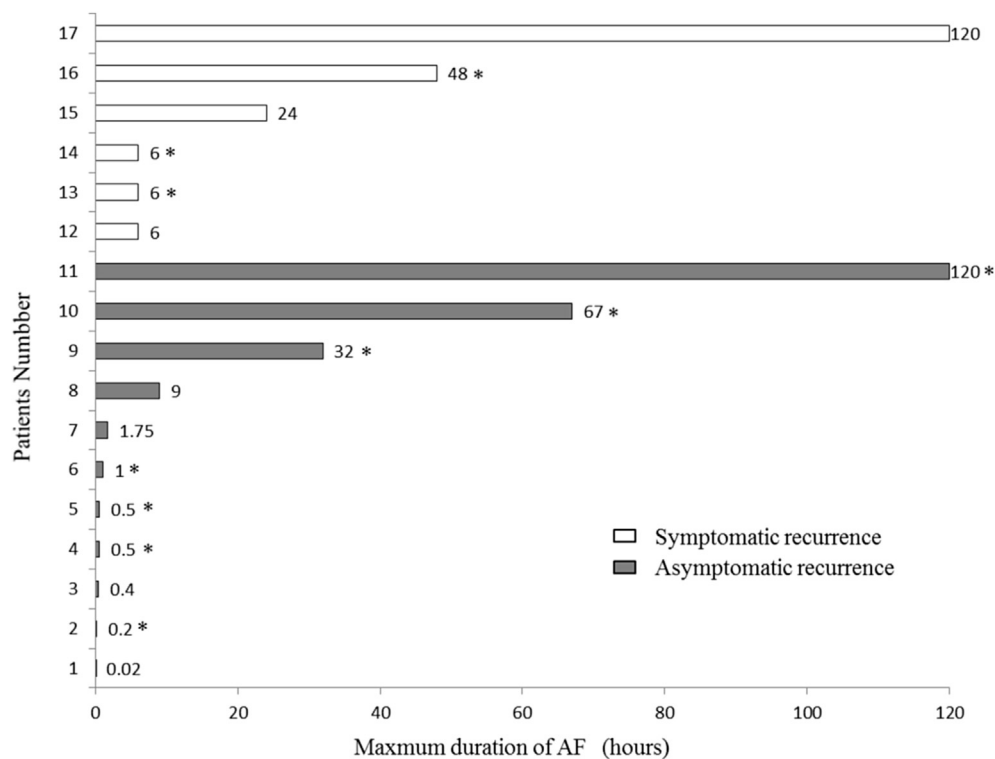


Fig. 3. The maximum duration of AF recurrences after the final CA session. Asymptomatic recurrences were observed in 11 patients (gray bar). Symptomatic recurrences were observed in 6 patients (white bar). Eleven patients were on anticoagulation treatment (*). Patient No.17 had an ischemic stroke. The maximum AF duration in that patient was 120 h (5 days).

During the follow-up period, 1 of 51 (2.0%) patients developed an ischemic stroke (Patient 17). In that patient, although AF episodes of <30 min were observed twice within 6 months after the final catheter ablation, no episodes were detected thereafter. In addition, the CHADS₂ score at the time of the procedure was 0, so the oral anticoagulation therapy was discontinued. However, this patient had a symptomatic AF recurrence 3 years after the final CA procedure, and finally developed an ischemic stroke 5 days after that AF episode despite the resumption of the anticoagulation.

4. Discussion

In the present study, we demonstrated that the conventional follow-up underestimated the AF recurrence episodes in patients with SSS and pacemaker. In addition, the incidence of asymptomatic AF recurrences in these patients might have been relatively high, and it may be difficult to predict.

4.1. The real AF recurrences

We clarified the real incidence of AF recurrences in AF patients who had received a pacemaker implantation for the treatment of coexistent SSS. Under the conventional follow-up, the AF-free survival rates at 5 years after the initial CA and final CA were 58.6% and 86.0%, respectively. However, when a pacemaker interrogation was added to the analysis, those rates decreased to 40.6% and 60.9%, respectively. Although the difference did not reach a significance after the initial CA ($P = 0.15$), the tendency became remarkable ($P = 0.01$) after the final CA procedure. This result suggested that the conventional follow-up underestimated the real incidence of AF-recurrences in AF patients with a pacemaker for SSS. A similar study with a short-term follow-up was performed by Verma et al. They examined 86 AF patients with pacemakers, 95% had SSS as a primary heart disease. That study demonstrated that mode switching episodes occurred in 40 patients (47%) at 9 months after the CA [9], which coincided with the results of the present study shown in Fig. 2A. In addition, Tondo C et al., studied 143 consecutive AF patients who were implanted with a continuous cardiac monitor (RevealXT, Medtronic Inc., Minneapolis, MN, USA) following their first pulmonary vein ablation procedure and found that at a mean follow-up of 14 ± 6 months, 98/143 (69%) patients had at least one AF recurrence [19]. In the present study, a distinct difference in the long-term outcome was demonstrated between the conventional follow-up and that plus pacemaker interrogations, and the real AF recurrence free-rate at 5 years was 86.0% and 60.9%, respectively. Although, comparing our result to the previous reports is somehow difficult because of the different patient populations, catheter ablation strategies, and the follow-up method and period, these data strongly supported the fact that the conventional follow-up underestimated the AF recurrence episodes.

4.2. The incidence of asymptomatic AF recurrences

In patients with PAF and SSS with a pacemaker, approximately 60% of the patients with AF recurrences did not have any symptoms both after the initial and final CA procedures. In the study using a continuous cardiac monitor (RevealXT, Medtronic Inc., Minneapolis, MN, USA) after the first CA, 69% of the patients had at least one AF recurrence, and among those patients 46% were asymptomatic [19]. The study using pacemaker interrogation demonstrated that detection of atrial tachyarrhythmias after the CA occurred in 47%, and half of them did not have any symptoms [9].

We found that even though 78% of the patients were symptomatic on the baseline evaluation, 65% of the patients with AF recurrences after the final CA had no symptoms. Based on these findings, a symptom based standard follow up is probably not sufficient to detect the real AF recurrences after CA in these patients. Atrial flutter (AFL) and atrial tachyarrhythmias (ATs) seemed to be symptomatic as rate control was difficult [20]. However, 2 patients with episodes of AFL or ATs after the initial CA had no symptoms. Out of 4 patients with episodes of AFL and ATs after the final CA, one had an asymptomatic recurrence. Although, after the final CA, AFL and ATs tended to be higher in the patients with symptomatic recurrences than those with asymptomatic recurrences, there were no significant differences in the clinical characteristics between the AF recurrent patients with or without symptoms. This finding suggested that it seems to be difficult to predict asymptomatic recurrent patients. A pacemaker may help detect and record events of asymptomatic AF recurrences, so that we could select the appropriate timing of the re-initiation of anti-coagulant therapy.

4.3. Duration of recurrent AF episodes detected by a pacemaker interrogation

A previous study using a pacemaker interrogation or external loop recorder demonstrated that the duration of asymptomatic atrial high frequency episodes after PVI were significantly shorter than the duration of the symptomatic ones [8,9,19,21]. These atrial high frequency episodes were short in duration (<60 s) and largely waned after 3 months [9]. Another study reported that shorter episodes (lasting more than 6 min and less than 1 h) are often undetected by the patient (50% asymptomatic), whereas longer episodes (lasting more than 24 h) are significantly associated with a higher subjective perception (only 29% asymptomatic) [19]. In our study, asymptomatic AF recurrences tended to have shorter episodes. However, some asymptomatic patients also developed longer episodes, and there seemed to be a large overlap.

A recent study suggested that an AF burden of ≥ 1 h was associated with ischemic strokes [22]. Another study reported that atrial tachyarrhythmia episodes lasting longer than 6 min in patients with pacemakers were independently associated with an increased risk of ischemic strokes or systemic embolisms [23]. Although, both of these data exhibited a relatively large discrepancy and did not include patients after AF ablation, careful follow-up should be recommended and an appropriate timing of restarting anticoagulation therapy should be selected after the CA in patients with a pacemaker for SSS.

4.4. Limitations

First, this study was a small retrospective study with a limited number of patients. Second, since a pacemaker interrogation only once a year may be insufficient to detect asymptomatic AF recurrences and restart properly the anticoagulation if required, the appropriate frequency of a pacemaker interrogation should be further examined. Additionally, although irrigated ablation catheters with contact force sensors may have improved the success rate of CA, 8-mm-tip non-irrigated catheters were used because of the availability in Japan during the study period. The use of 3D-mapping system would also improve the outcome. Finally, the results of this study may not be generalized to all patients with AF after CA.

5. Conclusions

One-third of PAF patients with SSS and pacemakers recurred after multiple CA sessions. In addition, 65% of them were asymptomatic and difficult to be identified with conventional follow-up. No significant factor was associated with asymptomatic recurrences.

Disclosures

None.

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