Early Recurrence after Longstanding Persistent Atrial Fibrillation Ablation

Time Course, Optimization of the Blanking Period, and Clinical Outcome

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Summary

Early recurrence (ER) of atrial fibrillation (AF) is common after ablation of longstanding persistent AF. However, optimal timing for repeat ablation has yet to be established.

Two-hundred-four patients (mean age 62 ± 9 years) with longstanding persistent AF underwent catheter ablation including pulmonary vein (PV) isolation and substrate modification. ER defined as AF recurrence within 60 days, occurred in 115 patients (56.4%) 9 ± 1 days after the procedure. Analysis showed optimal blanking period to be 15 days. At 426 ± 224 days of follow-up, 30 of 50 (60.0%) patients with ER during the first 15 days ($ER \leq 15$) and 13 of 65 (20.0%) patients with ER from the 16th to the 60th day (ER_{16-60}) were free from protocol-defined treatment failure (PDTF) ($P < 0.0001$). In multivariate analysis, AF duration and LA diameter were independent predictors of ER_{16-60} . Peak first ER was in the first 5 days, with a small maximum in the day 15~20 bin. The mean time to the first ER was longer in patients found to have PV reconnection during the repeat ablation than in those without (13 ± 14 versus 6 ± 7 days, $P = 0.002$).

When adopting a blanking period of 15 days, fewer patients with an $ER \leq 15$ had PDTF than those with an ER_{16-60} . AF duration and LA diameter were predictive of an ER_{16-60} .

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Key words: Early Recurrence, Catheter ablation

Catheter ablation, especially pulmonary vein (PV) isolation, has become an established procedure for treatment of atrial fibrillation (AF), although its so-called success rate is poorer in persistent AF.¹⁾ Therefore, in cases of longstanding persistent AF (LPAF), substrate modification is commonly performed in addition to PV isolation, and it has been shown to improve the long-term maintenance of SR after LPAF ablation.²⁻⁵⁾ Nevertheless, recurrence of AF is common, and repeat ablations are often necessary. One problem, however, with repeat ablations is that it is known that AF that recurs within the first 2 to 3 months of the procedure (early recurrence, ER), may terminate spontaneously and permanently.⁵⁻¹⁰⁾ Repeat ablations performed too early may have been unnecessary. Accordingly, arrhythmias that occur within the first few months after the initial procedure known as “the blanking period” are not considered as recurrences, and the consensus is that repeat ablation procedures should be deferred until the blanking period is over. However, there is currently no agreement on the duration of the blanking period nor are there guidelines for optimal timing for performing repeat ablation procedures. PV reconnection is one cause of AF recurrence. The relation-

ship between ER and PV reconnection is also largely unknown.

In the present study, the three clinically relevant questions that we wanted to address in the performance of catheter ablation of LPAF were (1) what is the clinical outcome and time course of ER, (2) what is the appropriate duration of the blanking period, and (3) who are the candidates for a repeat ablation procedure.

Methods

This is a retrospective single-center analysis. The study protocol was approved by the Ethics Committee of Tokyo Medical and Dental University.

Patients: This study enrolled 204 out of 254 consecutive patients with LPAF who underwent PV isolation and substrate modification procedures for the first time at Tsuchiura Kyodo Hospital between August 2006 and February 2010. We excluded a total of 50 patients, 38 of whom had received repeat ablation procedures within the first 60 days and 12 patients whose follow-up period was less than 60 days. ER was defined as documented episodes of AF or atrial tachycardia (AT) occurring within 60 days of

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Table I. Characteristics of the Patients with No Early Recurrence, Early Recurrence during the First 15 Days, and Early Recurrence between the 16th and 60th Day

	Total (n = 204)	No ER (n = 89)	ER ≤ 15 (n = 50)	16 < ER < 60 (n = 65)	P
Age, years*	62 ± 9	62 ± 10	63 ± 9	62 ± 9	0.76
Male	169 (83%)	74 (83%)	39 (74%)	56 (89%)	0.51
AF duration, months*	74 ± 84	61 ± 78	73 ± 80	92 ± 92	0.04
EF, %*	62 ± 9	62 ± 9	63 ± 7	61 ± 9	0.61
LA diameter, mm*	47.2 ± 5.5	46.3 ± 5.7	46.5 ± 4.5	48.9 ± 5.6	0.01
Structural heart disease	46 (23%)	23 (26%)	10 (20%)	13 (20%)	0.61
Hypertension	127 (62%)	62 (70%)	27 (54%)	38 (58%)	0.14
Hyperlipidemia	52 (25%)	25 (27%)	11 (22%)	16 (25%)	0.71
Diabetes mellitus	22 (11%)	10 (11%)	4 (8%)	8 (12%)	0.75

Categorical data are given as number (percentage) and * continuous data as mean ± SD. AF indicates atrial fibrillation; EF, ejection fraction; ER, early recurrence; and LA, left atrium.

the initial procedure; anything later was defined as protocol-defined treatment failure (PDTF). LPAF was defined as AF that had been present for more than 1 year without detected intervening spontaneous periods of sinus rhythm (SR).

After determining optimal blanking period duration based on data from this study, ER were categorized by whether the first episode of the ER occurred within the blanking period, or later. One-hundred one of 254 patients underwent a repeat ablation procedure for recurrences. At the time of the repeat ablation, we noted whether or not the PVs had electrically reconnected (PVR). The clinical characteristics of the 204 study patients and the three subgroups, No ER, ER within blanking period, and ER post blanking period, are described in Table I.

Determination of the blanking period in this study:

Receiver operating characteristic analysis was utilized to determine optimal blanking period from the first day to the 60th day. Optimal blanking period was the period that produced the highest sensitivity and specificity for PDTF prediction.

Catheter ablation of LPAF: All patients provided written informed consent for the procedure and had agreed to use their de-identified data for future research purposes. They received effective anticoagulation therapy (target international normalized ratio of 1.6 to 2.5) for at least 1 month before the procedure. All antiarrhythmic drugs except amiodarone were discontinued 5 half-lives before the procedure. Transthoracic echocardiography was performed to assess the left ventricular ejection fraction and the left atrial (LA) diameter, and transesophageal echocardiography was performed to exclude the presence of cardiac thrombi in all patients. Quantitative measures on all echocardiography were performed according to the American Society of Echocardiography recommendation by dedicated analysts at our laboratory who were blinded to clinical information.⁽¹⁾ A surface electrocardiogram and bipolar endocardial electrograms were continuously monitored and recorded on a computer-based digital amplifier system (Bard Electrophysiology, Lowell MA, USA). Following the trans-septal puncture, systemic anticoagulation was achieved with intravenous heparin titrated to maintain activated clotting time at 300 to 350 s. Intra-PV electrograms were monitored with double decapolar catheters

with a distal ring configuration (Lasso Catheter, Biosense Webster, Diamond Bar, CA, USA) positioned in both ipsilateral superior and inferior PVs.

Encircling continuous radiofrequency lesions surrounding both ipsilateral PV antrums were created until the local electrogram inside the encircled area disappeared or was dissociated. Complete PV isolation was confirmed by lack of conduction to the LA after pacing at several sites within the PV antrum. Radiofrequency energy of 20 to 35 W was delivered with a 4 mm open irrigated tip catheter at a maximum temperature of 50 for 25 to 35 s at each site.

Following PV isolation, linear ablation and electrogram-based ablation were performed at sites in the LA showing complex electrogram features: fractionated continuous electric activity or repetitive rapid activity with a cycle length < 120 msec or shorter than the cycle length in the coronary sinus (CS). Radiofrequency energy of 20-30 W was applied by a 4 mm open irrigated tip catheter with the endpoint of transformation of all identified complex fractionated atrial electrograms into discrete electrograms and slowing of the local cycle length compared with the CS cycle length. AT was subsequently mapped with entrainment maneuvers and ablated without the routine use of three-dimensional tools. If AF terminated to SR, we did not perform AF induction. When SR was not restored during ablation, patients underwent electrical cardioversion. Following restoration of SR, supplemental ablation was performed if necessary to complete the PV isolation. A cavotricuspid isthmus ablation was performed with an 8-mm-tip conventional catheter in a temperature-controlled fashion in all patients with the endpoint of bidirectional conduction block.

Post-ablation follow-up: All patients were hospitalized for at least 3 days following the procedure. After being discharged, the patients underwent follow-up consisting of a clinical interview, electrocardiogram, and 24 hours ambulatory monitoring every 1 to 2 months at our cardiology clinic. If they experienced any symptoms suggestive of arrhythmias, an electrocardiogram, 24 hours ambulatory monitoring, and/or cardiac event recording with a recording duration of 1 month were performed. Oral anticoagulation treatment was restarted 1 day after the procedure and continued for at least 3 months. All antiarrhythmic

Figure 1. Kaplan-Meier analysis of the long-term freedom from recurrent atrial arrhythmias in patients with and without an ER. ER indicates early recurrence.

drugs were discontinued within 1 month after the ablation. SR was restored by electrical cardioversion in all patients who experienced recurrences of AF or AT. A repeat ablation procedure was offered to all patients with recurrent arrhythmias regardless of whether they were symptomatic or not.

Clinical outcome of longstanding persistent AF ablation: Therapeutic success was defined as maintenance of SR with or without antiarrhythmic drug treatment for more than 60 days after the final procedure. Failure was defined as documented recurrence of AF or AT lasting more than 3 minutes.

Statistical analysis: Continuous variables are expressed as the mean $\pm$ 1 SD and were compared using Student's *t* test or analysis of variance (ANOVA). Categorical variables were compared by the chi-square test or Fisher's exact test. Significant predictors presenting a $P < 0.1$ in the univariate analysis were included in a forward, stepwise multiple logistic-regression model to identify the most important risk factors for a recurrence. Kaplan-Meier analysis was used to determine the percentage of patients free from AF after the initial procedure and the difference in the arrhythmia-free survival rates was evaluated using the log-rank test. All tests were two-tailed, and a P value of < 0.05 was considered statistically significant.

Results

Patient characteristics: A total of 204 study patients (age 62 ± 9 years, 83% male) were followed for a mean of 426 ± 224 days after their first LPAF ablation procedure. At the time of the procedure, patients had had AF for 74 ± 84 months and the mean LA diameter was 47.2 ± 5.5 mm. One-hundred sixty out of 204 (78%) patients took an average of 1.5 ± 0.9 antiarrhythmic drugs, and among them, 39 (19% of 204) patients took amiodarone within 3 months before the procedure.

Clinical outcome after the LPAF ablation and time

course of the first episode of ER: In the 60 days after the initial ablation procedure, 115 (56%) patients had at least one ER. Of these 115, only 43 (37%) were free from PDTF, in contrast to the 89 patients with no ER, of whom 65 (73%) were free from PDTF ($P < 0.0001$, Figure 1). In total, 108 out of 204 (53%) patients were free from PDTF at the time of the last follow-up visit.

The mean time to the first recurrence was 9 ± 1 days. Figure 2 shows the timing of the first occurrence of AF after the procedure in bins of 5 days for the 115 patients who had ER. As shown in the figure, 72 (63%) had ER within the first 5 days. Within those 5 days, nearly half (31), had their ER within the first 24 hours post-ablation. After 5 days, the first occurrence of AF dropped and tapered toward zero over the next 55 days. A small maximum was observed on the day 15–20 bin.

Optimization of the blanking period and clinical outcome after the LPAF ablation: On the basis of receiver operator characteristic analysis, the duration of the blanking period was determined to be 15 days with a specificity of 88% and sensitivity of 54% in predicting a PDTF (Figure 3). The 60 day ER period was divided into the 15 day blanking period (ER ≤ 15) and later (ER16–60). Using this cutoff value resulted in 50 patients belonging to ER ≤ 15 and 65 patients belonging to ER16–60. ANOVA found AF duration and LA diameter to be statistically significant parameters (Table I). According to post hoc analysis, the patients with an ER16–60 had a longer AF duration history (92 ± 92 versus 61 ± 78 months, $P < 0.05$) and larger LA diameter (48.9 ± 5.6 versus 46.3 ± 5.7 mm, $P = 0.01$) than those with no ER.

Kaplan-Meier analysis revealed that the patients with an ER ≤ 15 and with no ER had a significantly better clinical outcome than those with an ER16–60 ($P < 0.0001$, Figure 4). There was no significant difference in the long-term outcome between the first two patient groups, patients with an ER ≤ 15 and those with no ER ($P = 0.055$, Figure 4). In multivariate analysis, AF duration and LA

Figure 2. Cumulative percent of the patients with an ER and time to the first recurrence of an ER after the catheter ablation in 115 patients. The abbreviations are as in Figure 1.

Figure 3. Diagnostic accuracy of a recurrence after the blanking period in predicting an LR calculated for each blanking period from the first day to the 60th day after the initial procedure. The arrows indicate the threshold point for the sensitivity and specificity. LR indicates late recurrence.

diameter were independent predictors of ER16-60 ($P < 0.05$, Table II).

Findings during the repeat ablation: One-hundred one out of 204 (49%) patients underwent a repeat ablation for AF recurrence. At the time of repeat ablation, electrical conduction between the PV and LA was identified in at least one of the PVs in 74 of the 101 (73%) patients, with a mean number of 2.4 ± 1.0 PVRs per patient. There was no significant difference in the incidence of ER between the 74 patients with and 27 patients without a PVR (Table III). The mean time to the first recurrence was longer in the patients with a PVR than in those without a PVR (13 ± 14 versus 6 ± 9 days, $P = 0.002$, Table III). Nearly 80%

of the ER in patients without PVR occurred within the first 10 days, and another 15% in the next 10 days, whereas ER in patients with PVR were distributed more evenly over the first 60 days, with approximately half occurring over days 11-60 (Figure 5). There was no significant difference in the long-term freedom from PDTF after the repeat ablation regardless of whether the patients had a PVR or not (Table III).

Discussion

Major findings: This study demonstrated three key observations about recurrent arrhythmias that present early after initial LPAF ablation. First, our results suggested that the optimal duration of the blanking period was 15 days after the initial ablation procedure, although this needs confirmation by further studies. Second, the patients with an ER during the first 15 days had a significantly better clinical outcome with respect to freedom from AF than those with an ER from the 16th day to the 60th day. Finally, the time to the first ER was longer in the patients found to have PVR at the time of the repeat ablation.

Time course of the first episode of ER after the LPAF ablation: The majority of atrial arrhythmia recurrences are known to occur within several weeks after catheter ablation of LPAF.^{6,12)} Because variable substrate modification strategies can be limitations to describing long-term outcome after LPAF ablation,^{5,13,14)} we studied a homogeneous population and applied a uniform ablation strategy to all patients in this study. All patients had LPAF longer than 1 year and underwent PV isolation followed by substrate modification including a linear ablation and electrogram-based ablation.

For the time course of the first episode of ER, our study found peak incidence to be within the bin of the first 5 days and a small maximum at the day 15-20 bin. The timing of the initial peak coincided with previously reported “very early recurrence” that had good clinical outcome.¹⁵⁻¹⁷⁾ Recent studies have provided important evidence^{18,19)} that LA enhancement by magnetic resonance

Figure 4. Kaplan-Meier analysis of the long-term freedom from recurrent atrial arrhythmias in the patients with no ER versus the patients with an ER ≤ 15 versus the patients with an ER16-60. ER ≤ 15 indicates early recurrence during the first 15 days; ER16-60, early recurrence between the 16th and 60th day after ablation; the other abbreviations are as in Figure 1.

Figure 5. Time to the first episode of an atrial arrhythmia in the longstanding persistent AF patients who had early recurrence of AF after catheter ablation. Patients with and without pulmonary vein (PV) reconnection at the time of the repeat ablation procedure are shown separately.

Table II. Multivariate Analysis of the Predictors of Early Recurrences between the 15th Day and 60th Day after the Ablation

	<i>P</i>	Hazard ratio	95% Confidence interval
AF duration, months	0.046	1.004	1.0001-1.0071
LA diameter, mm	0.0035	1.091	1.029-1.16
Hypertension	0.19	0.65	0.34-1.23

The abbreviations are as in Table I.

imaging^{20,21)} or an increase in the C-reactive protein level during the first several days after ablation^{16,22)} appear to be associated with a transient inflammatory response. Accordingly, we regard ER that comprised the first peak as a temporary recurrence that is less likely to influence the long-term success of the LPAF ablation. In contrast, when patients with and without PVR (assessed at time of repeat ablation) were compared, the latter had first ER occurrence that tapered quickly with time after ablation, almost

Table III. Characteristics of the Patients with No PV Reconnection versus PV Reconnection in the Repeat Ablation

	No PVR (n = 27)	PVR (n = 74)	P
Age, years*	62 ± 11	61 ± 10	0.49
Male	23 (85%)	63 (85%)	0.76
AF duration, months*	109 ± 94	80 ± 85	0.76
EF, %*	65 ± 9	63 ± 8	0.45
LA diameter, mm*	47 ± 6	48 ± 6	0.42
Early Recurrence	23 (85%)	63 (85%)	0.10
Time to first recurrence, days*	6 ± 9	13 ± 14	0.002

Data are given as number (percentage) or as * mean ± SD. PVR indicates pulmonary vein reconnection; the other abbreviations are as in Table I.

to zero after 20 days, whereas in the former, half of the first ER occurrences were after day 11. Therefore, we speculate that the small maximum of the ER at the days 15–20 bin and indeed, any recurrence after the 15 day blanking period suggest a high likelihood of PVR and the necessity of repeat ablation.²³⁾ These results also support previous reports that a durable PV isolation is essential for improving the efficacy of LPAF ablation.^{24–26)}

Optimization of the blanking period after the LPAF ablation: Current guidelines from the HRS/EHRA/ECAS define ER of AF as a recurrence of AF within 3 months of the ablation procedure.²⁷⁾ However, various shorter duration blanking periods have been employed with respect to LPAF because of a higher incidence of ER and greater patient burden when arrhythmias recur.^{13,28)} We focused on how often patients with an ER after the blanking period went on to display PDTF. To the best of our knowledge, this is the first report to statistically define the appropriate duration of the blanking period. Our observations suggested that a blanking period of 15 days discriminated best, long-term clinical outcome.

Candidates for a repeat ablation procedure after the initial LPAF ablation: The majority of the patients with LPAF require at least two procedures to treat the arrhythmia recurrences, whereas early repeat ablation procedure within the first month increases the total number of the procedures.^{13,25)} According to our observations, an ER during the first 15 days had a relatively low risk of a further recurrence. Furthermore, the AF duration and LA diameter were predictive of an ER16–60. Consequently, to enhance the efficacy and decrease the risk of unnecessary LPAF ablation, a repeat ablation procedure should target patients whose recurrence occurs after the 15 day blanking period and who have a long preceding AF duration and large LA diameter.

Study limitations: This was a single-center and retrospective study. It was possible that asymptomatic episodes of AF may have been unrecognized after discharge from the hospital. We must have underestimated the incidence of recurrent AF because AF may be asymptomatic in some patients. Finally, the blanking period was optimized for the current study population. The duration may differ by a few days in different study populations, and needs to be confirmed.

Conclusions

When adopting a blanking period of 15 days, freedom from PDTF was significantly better in patients with an ER ≤ 15 than in those with an ER16–60. Longer AF duration and larger LA diameter were predictive of an ER 16–60.

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Disclosures

Conflicts of interest: None to disclose.

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