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ORIGINAL ARTICLE

Clinical significance of the timing of early recurrence of atrial arrhythmia after pulmonary vein isolation: a two-institution clinical study

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Abstract

Early recurrence of atrial arrhythmia (ERAA) after ablation frequently occurs, but there is limited evidence about ERAA-timing. This study aimed to investigate the association between ERAA-timing and late recurrence. We retrospectively investigated 332 patients who underwent PVI for paroxysmal atrial fibrillation at Nagoya University Hospital and Komaki City Hospital. Seventy-six patients (23%) had ERAA. The cutoff value of the first ERAA for late recurrence was set as 3 days, with a specificity of 77% and sensitivity of 43%. On multivariate analysis, first ERAA beyond 3 days (hazard ratio, 2.477; 95% confidence interval, 1.168–5.25; $p = 0.018$) and large left atrial diameter (LAD) (hazard ratio, 1.101; 95% confidence interval, 1.024–1.184; $p = 0.009$) were independent predictors for late recurrence. Patients who had first ERAA within 3 days and no ERAA beyond 3 days showed a significantly higher recurrence–free rate than those who had first ERAA beyond 3 days and those who had ERAA both within 3 days and beyond 3 days (89% versus 39%, 44%; $p < 0.001$). Moreover, the patients with ERAA within 3 days and LAD ≤ 37.7 mm showed a significantly higher recurrence–free rate than those with ERAA beyond 3 days and LAD > 37.7 mm, and as compared with the other patients (100% versus 26% and 60%, respectively; $p < 0.001$). ERAA beyond 3 days after ablation was a predictor for late recurrence. Among patients with ERAA, those with ERAA within 3 days and smaller LAD showed favorable prognosis after ablation.

Keywords Paroxysmal atrial fibrillation · Catheter ablation · Early recurrence · Atrial arrhythmia recurrence · Left atrial diameter

Introduction

Pulmonary vein isolation (PVI) is an established therapy for drug-resistant paroxysmal atrial fibrillation (PAF) [1, 2], and the success rate and long-term efficacy of catheter ablation for PAF are widely accepted. After ablation, early recurrence of atrial arrhythmia (ERAA) is frequently observed [3]. However, not all the patients with ERAA experience late recurrence during the follow-up after ablation. Some studies reported that up to 60% of patients with ERAA became free from further arrhythmia recurrence [4, 5]. Therefore, recent consensus guideline statements recommend a "blanking period" of 3 months after AF ablation, during which the performance of repeat ablation in response to arrhythmia recurrence should be avoided [6]. Although this period is generally accepted in clinical practice, it is unclear whether the duration of the blanking period of 3 months is an appropriate length of time to distinguish between true and transient recurrences after ablation.

Recent studies have reported that recurrence of atrial arrhythmia during the blanking period after PVI was strongly associated with late recurrence beyond the blanking period [7, 8]. In contrast, on the basis of biological evidence, including inflammatory changes and myocardial injury considered as potential mechanisms of ERAA, these early transient changes did not continue for longer than a few days after ablation [9]. Furthermore, a previous clinical study

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has showed a shorter period of between 3 days and 1 month after the procedure for comparison of late recurrence during follow-up [10]. It is unclear which ERAA-timing is the appropriate timing without linking late clinical outcomes after ablation.

Thus, the present study aimed to investigate the association between the ERAA-timing and arrhythmia recurrence beyond the blanking period. Moreover, we evaluated which demographic characteristic could predict true late recurrence among the patients with ERAA occurrence.

Materials and methods

Study population

This study was a retrospective observational study from two clinical institutions. This ablation database was approved by each institutional ethics committee. A total of 398 consecutive patients with PAF who underwent radiofrequency catheter ablation of PVI for the first time between January 2012 and December 2015 at Nagoya University Hospital and Komaki City Hospital were enrolled. All patients were referred to undergo catheter ablation because of refractoriness to antiarrhythmic drugs. The indication of catheter ablation was in adherence with the guideline [11, 12]. The exclusion criteria were as follows: (1) left ventricular ejection fraction < 50% on echocardiography at baseline; (2) left atrium diameter > 50 mm; (3) renal dysfunction with estimated glomerular filtration rate < 45 mL/min/1.73 m^2; and/or (4) development of a major complication, such as cardiac tamponade, requiring continued hospitalization after catheter ablation. Informed consent was obtained from all patients before the procedure according to each institution's guidelines. This study was performed in accordance with the Declaration of Helsinki.

Preprocedural management

Patients were admitted to hospital the day before the procedure. A laboratory examination and echocardiography were performed at baseline. Antiarrhythmic drugs were discontinued five half-lives before ablation. To exclude the presence of atrial thrombus, all patients underwent transesophageal echocardiography or computed tomography before the procedure. Anticoagulant drugs, including novel anticoagulant agents, were continued during the procedure.

Ablation procedure

During the ablation procedure, after transseptal puncture using intracardiacechocardiography, two 8-French sheaths and one 8.5-French steerable sheath were introduced into the left atrium. PVI was performed with a 3.5-mm ablation catheter with an externally irrigated tip (Thermocool SF or Thermocool Smarttouch; Biosense-Webster, Diamond Bar, CA, USA) using the double-lasso technique under the guidance of a three-dimensional electroanatomical mapping system (CARTO3; Biosense-Webster). The radiofrequency energy output was titrated to 25–35 W at a flow rate of 17–30 mL/min, with a maximum temperature of 42 °C. During the procedure, the activated clotting time was maintained at ≥ 300 s. The endpoint of PVI was achievement of bi-directional complete electrical block between the PV and the left atrium. In addition, cavotricuspid isthmus ablation was performed if necessary. Finally, protamine was administered to reverse the effect of heparin.

Follow-up

Patients remained hospitalized under continuous rhythm monitoring for 3 days after the procedure. No antiarrhythmic drugs were prescribed after the ablation. If patients had atrial arrhythmia recurrence during hospitalization, class Ia or Ic antiarrhythmic drugs were administered. When atrial arrhythmia was not terminated, electrical cardioversion was performed. After discharge from the hospital, patients were scheduled for follow-up visits at 1, 3, 6, and 12 months post-procedure. At the time of each follow-up visit, each patient underwent 12-lead electrocardiography, and was asked about any symptoms related to the presence of arrhythmia. Twenty-four-hour Holter monitoring was performed 1 month after the ablation in all patients. If patients were suspected of having had an emergent arrhythmia, but had no evidence of the arrhythmia at the time of examination, additional Holter monitoring and short-duration follow-up were performed. In addition, if the patients noticed any rhythm disorder during the intervals between the follow-up visits, they were recommended to make a telephone call to arrange an early visit to the hospital and an electrocardiographic examination. If patients had severe symptoms by atrial arrhythmia recurrence at an outpatient clinic, antiarrhythmic drugs that were discontinued before procedure were re-administered. Electrical cardioversion was performed when recurrent arrhythmia did not terminate. If patients with re-administration of antiarrhythmic drugs did not have any arrhythmia recurrence, these drugs were discontinued at the end of the blanking period. Recurrence was defined as an atrial arrhythmia lasting longer than 30 s that was documented by any method of examination monitoring. The blanking period was defined as within 3 months after ablation.

Statistical analysis

Continuous variables are presented as means ± standard deviation values, whereas categorical variables are presented

as percentages. A chi-square test was used to compare categorical variables, and a Mann–Whitney *U* test was used to compare continuous variables. In this study, we adopted a method [points on curve closest to the (0, 1)] to determine the cutoff value of the receiver-operating characteristic (ROC) curve. This method is simply and widely used by calculating the distance between the point (0, 1) and each observed point on the ROC curve $\{d = \sqrt{[(1\text{-sensitivity})^2}$ and $(1\text{-specificity})^2]\}$, and locating the point where the distance is at a minimum. Univariate and multivariate analyzes using Cox proportional hazard models were performed to determine the independent predictors of AF recurrence. The factors shown to have a p value of < 0.05 in the univariate analysis were further assessed in the multivariate analysis. The event-free survival rate was estimated using the Kaplan–Meier method and compared by the log-rank test. Statistical analyzes were performed using SPSS version 24 (SPSS Inc., Chicago, IL, USA). A P value < 0.05 was considered to be statistically significant.

Results

Patient characteristics

A total of 398 consecutive patients who underwent PVI at the participating hospitals were enrolled and 43 patients were excluded based on the exclusion criteria. In total, 355 patients were eligible for the study and 23 patients were lost to follow-up. Therefore, 332 patients (248 patients from Nagoya University Hospital and 84 patients from Komaki City Hospital) were analyzed for this study. The baseline characteristics of patients are presented in Table 1. All patients were followed up for 12 months after ablation. Among them, 76 patients (23%) had ERAA within 3 months after ablation. A comparison of the baseline characteristics between the patients with ERAA and those without is shown in Table 1. There were significant differences in the prevalence of congestive heart failure and stroke, estimated glomerular filtration rate, brain natriuretic peptide levels, $CHADS_2$ score, and ablation procedure between the two groups. In the total population, late recurrence was observed in 56 patients during a mean follow-up period of 268 ± 12 days. We confirmed that patients with ERAA had a significantly greater prevalence of late recurrence than those without

Table 1 Patient characteristics between the patients with ERAA and those without in the study population

	All patients $n=332$	ERAA $n=76$	No ERAA $n=256$	*P* value
Age, years	64 ± 12	66 ± 11	63 ± 12	0.071
Male	205 (62%)	44 (58%)	161 (63%)	0.431
Hypertension	165 (50%)	39 (51%)	126 (49%)	0.748
Diabetes mellitus	46 (14%)	14 (18%)	32 (13%)	0.190
Congestive heart failure	10 (3%)	5 (7%)	5 (2%)	0.004
Stroke	26 (8%)	11 (15%)	15 (6%)	0.014
Recurrence beyond the blanking period	56 (17%)	28 (37%)	28(11%)	<0.001
BMI, kg/m^2	23.9 ± 4.0	24.2 ± 3.5	23.8 ± 4.2	0.24
Creatinine, mg/dL	0.81 ± 0.19	0.82 ± 0.20	0.80 ± 0.19	0.218
eGFR, ml/min/1.73 m^2	73.5 ± 17.8	70.3 ± 21.0	74.7 ± 16.2	0.005
CRP, mg/dL	0.12 ± 0.37	0.08 ± 0.09	0.13 ± 0.4	0.057
BNP, pg/mL	56.8 ± 76.8	92.0 ± 114.9	42.9 ± 48.8	<0.001
LVEF, %	64.9 ± 6.2	64.6 ± 6.5	65.0 ± 6.1	0.542
LAD, mm	37.1 ± 5.3	38.0 ± 5.4	36.7 ± 5.2	0.099
$CHADS_2$ score	0.85 ± 1.01	1.09 ± 1.2	0.75 ± 0.90	0.049
CHA_2DS_2-VASc score	1.55 ± 1.57	1.84 ± 1.77	1.43 ± 1.47	0.082
Procedure time, min	172 ± 43	169 ± 43	172 ± 44	0.633
Radiofrequency energy, wat	57,481 ± 42,664	55,811 ± 32,568	57,877 ± 44,777	0.981
Cavotricuspid isthmus conduction block	268 (81%)	55 (72%)	213 (83%)	0.302

Values are mean ±SD or number (percentage)

BMI body mass index, *BNP* brain natriuretic peptide, *CRP* C-reactive protein, *eGFR* estimated glomerular filtration rate, *ERAA* early recurrences of atrial arrhythmia, *LAD* left atrial diameter, *LVEF* left ventricular ejection fraction

ERAA (37% versus 17%, $p < 0.001$). In the patients with ERAA ($n = 76$), a comparison of the baseline characteristics and examination result between patients with late recurrence ($n = 28$) and those without ($n = 48$) is shown in Table 2. The left atrial diameter (LAD) was significantly larger in the recurrence group than in the non-recurrence group (40.1 ± 5.6 mm versus 36.9 ± 4.3 mm, $p = 0.024$), while other parameters did not show any significant difference between the two groups.

The cutoff value of first ERAA-timing and LAD

The ROC curve analysis was performed to evaluate the correlation between ERAA-timing and late recurrence beyond the blanking period after ablation, and we set the cutoff value of the first ERAA-timing as 3 days after PVI, with a specificity of 77% and sensitivity of 43% (Fig. 1a). In addition, the cutoff value of LAD for late recurrence based on the ROC curve was set as 37.7 mm, with a specificity of 71% and sensitivity of 68% (Fig. 1b).

The risk factors of late recurrence beyond the blanking period

Univariate and multivariate Cox proportional hazard analyzes for late recurrence after ablation beyond the blanking period are shown in Table 3. Univariate analysis showed that first ERAA beyond 3 days (hazard ratio [HR] 2.555; 95% confidence interval 1.206–5.411; $p = 0.014$) and large LAD (HR 1.102; 95% confidence interval 1.026–1.184; $p = 0.007$) were significantly associated with late recurrence. On multivariate analysis, first ERAA beyond 3 days (HR 2.477; 95% confidence interval 1.168–5.25; $p = 0.018$) and large LAD (HR 1.101; 95% confidence interval 1.024–1.184; $p = 0.009$) were independent predictors for late recurrence.

The association of ERAA-timing with late recurrence

Kaplan–Meier analysis was performed to evaluate recurrence–free rates of atrial arrhythmia after ablation in patients with ERAA for 12-month follow-up. The patients with first ERAA within 3 days showed significantly higher recurrence–free rates than those with first ERAA beyond 3 days

Table 2 Patient characteristics between the recurrence and no-recurrence groups beyond the blanking period for 12 months follow-up in the patients with ERAA

	Recurrence $n = 28$	No recurrence $n = 48$	*P* value
Age, years	66 ± 11	67 ± 9	0.763
Male	15 (54%)	29 (60%)	0.56
Hypertension	17 (61%)	22 (46%)	0.211
Diabetes mellitus	3 (11%)	11 (23%)	0.186
Congestive heart failure	2 (7%)	3 (6%)	0.88
Stroke	5 (18%)	6 (13%)	0.522
BMI, kg/m^2	23.8 ± 3.4	24.3 ± 3.7	0.582
Creatinine, mg/dL	0.84 ± 0.24	0.80 ± 0.19	0.454
eGFR, ml/min/1.73 m^2	70.2 ± 28.2	70.3 ± 16.4	0.346
CRP, mg/dL	0.08 ± 0.08	0.09 ± 0.1	0.871
Hs-CRP 3 days after ablation, mg/dL	1.85 ± 1.87	2.61 ± 3.31	0.275
BNP, pg/mL	105.3 ± 133.4	93.4 ± 110.9	0.979
LVEF, %	64.5 ± 6.5	65.1 ± 7.3	0.884
LAD, mm	40.1 ± 5.6	36.9 ± 4.3	0.024
$CHADS_2$ score	1.07 ± 1.09	1.06 ± 1.23	0.798
CHA_2DS_2-VASc score	1.75 ± 1.78	1.98 ± 1.66	0.458
Antiarrhythmic drugs using within blanking period	21 (75%)	41 (85%)	0.491
Class I	20 (71%)	38 (79%)	0.444
Class III	1 (4%)	3 (6%)	0.614
Electrical Cardioversion within blanking period	8 (29%)	7 (15%)	0.139
Procedure time, min	171 ± 43	169 ± 44	0.848
Radiofrequency energy, wat	58,195 ± 37,232	56,927 ± 32,207	0.65
Cavotricuspid isthmus conduction block	19 (68%)	36 (75%)	0.098

Values are mean ± SD or number (percentage)

BMI body mass index, *BNP* brain natriuretic peptide, *CRP* C-reactive protein, *eGFR* estimated glomerular filtration rate, *ERAA* early recurrences of atrial arrhythmia, *Hs-CRP* high-sensitivity C-reactive protein, *LAD* left atrial diameter, *LVEF* left ventricular ejection fraction

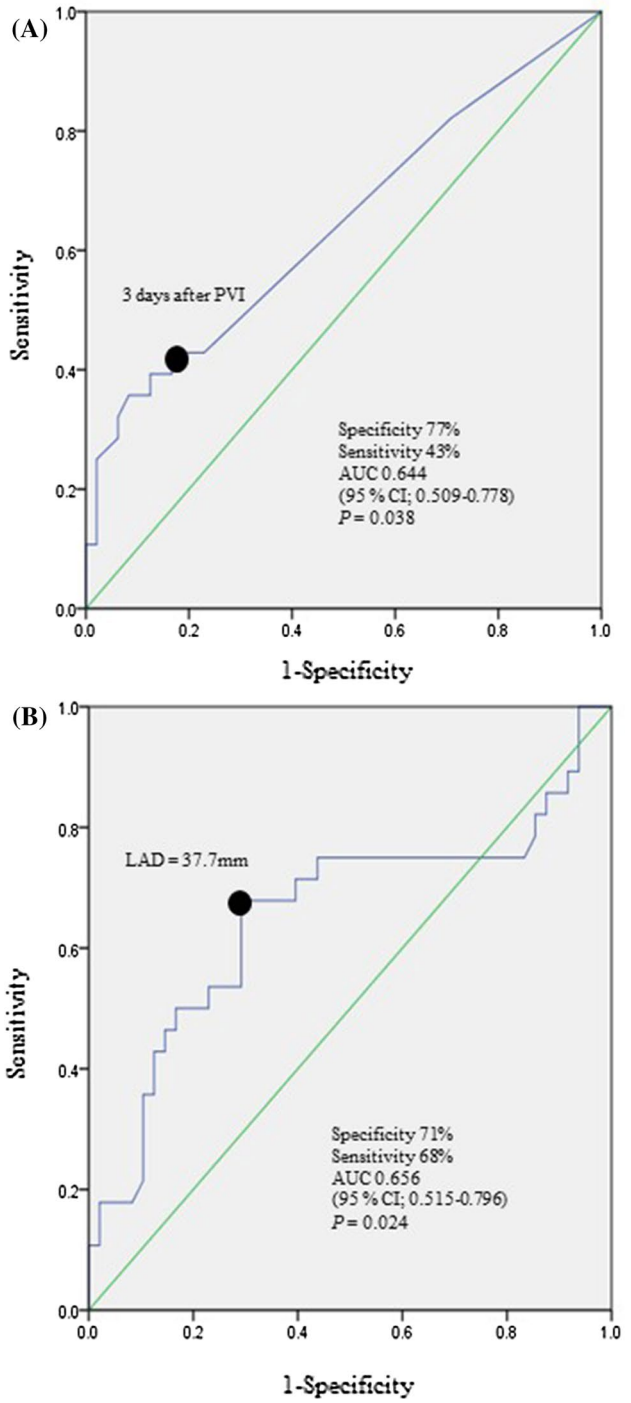

Fig. 1 **a** ROC curves of the first ERAA-timing after ablation for late recurrence beyond the blanking period (positive predictive value 52%, negative predictive value 70%), and **b** of LAD for late recurrence. *AUC* area under the curve, *CI* confidence interval, *ERAA* early recurrences of atrial arrhythmia, *LAD* left atrial diameter, *PVI* pulmonary vein isolation, *ROC* Receiver-operating characteristic

(71% versus 39%; $p = 0.011$) (Fig. 2a). The patients with ERAA were divided into three groups by ERAA-timing after PVI: first ERAA within 3 days and no ERAA beyond 3 days ($n = 34$), first ERAA beyond 3 days ($n = 20$), and ERAA both within 3 days and beyond 3 days ($n = 22$). The patients who had first ERAA within 3 days and no ERAA beyond 3 days showed significantly higher recurrence–free rates than those who had first ERAA beyond 3 days and those with ERAA both within 3 days and beyond 3 days (89% versus 39% and 44%, respectively; $p < 0.001$) (Fig. 2b). The number of patients who received antiarrhythmic drugs and electrical cardioversion within the blanking period was not significantly different among the three groups (Table 4). Moreover, high-sensitive C-reactive protein (hs-CRP) levels 3 days after ablation tended to be higher in the ERAA within 3-day group than in the ERAA beyond 3-day group (2.68 ± 2.46 mg/dL vs. 2.09 ± 3.20 mg/dL, $p = 0.107$).

In addition, we investigated the impact of ERAA-timing and LAD on late recurrence after ablation. The patients with ERAA were divided into four groups: ERAA within 3 days and LAD ≤ 37.7 mm ($n = 21$); ERAA beyond 3 days and LAD > 37.7 mm ($n = 21$); other patients (ERAA within 3 days and LAD > 37.7 mm; and ERAA beyond 3 days and LAD ≤ 37.7 mm, $n = 34$); and a no-ERAA group ($n = 256$). The patients with ERAA within 3 days and LAD ≤ 37.7 mm had no arrhythmia recurrence after follow-up and showed a significantly higher recurrence–free rate than those with ERAA beyond 3 days and LAD > 37.7 mm and those in the other patients group (100% versus 26% and 60%, respectively; $p < 0.001$) (Fig. 2c).

Discussion

This study assessed the significance of ERAA-timing after catheter ablation of PAF. ERAA beyond 3 days after ablation was significantly associated with late recurrence. Furthermore, patients who had ERAA within 3 days and LAD ≤ 37.7 mm showed no recurrence and a significantly lower recurrence rate than other patients with ERAA.

The 2012 HRS/EHRA/ECAS expert consensus statement recommends the use of a 3-month blanking period after ablation to avoid the performance of unnecessary repeat ablation [6]. Some reports revealed that ERAA is related to transient change, such as post-ablation inflammatory response [9, 13, 14]. Although ERAA due to PV reconnection or non-PV foci could occur naturally, these phenomena are clearly associated with late recurrence after ablation [15, 16]. It is possible that not all of the patients with ERAA have a favorable prognosis because of the mechanism of ERAA. In practice previous report revealed that ERAA frequently occurred after ablation and ERAA was strongly related to late recurrence [8]. However, the association of ERAA-timing with the mechanism of ERAA remains unclear.

The possible causes of ERAA include a transient stimulatory effect of acute inflammatory response following

Table 3 Univariate and multivariate Cox regression analyzes for late recurrence beyond the blanking period

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
First ERAA beyond 3 days	2.555 (1.206–5.411)	0.014	2.477 (1.168–5.25)	0.018
Age, years	0.993 (0.957–1.032)	0.729		
Male	0.79 (0.376–1.662)	0.535		
Hypertension	1.656 (0.775–3.537)	0.193		
Diabetes mellitus	0.457(0.138–1.515)	0.201		
Congestive heart failure	1.181 (0.28–4.977)	0.821		
Stroke	1.378 (0.654–2.902)	0.399		
BMI, kg/m2	0.96 (0.859–1.073)	0.473		
Creatinine, mg/dL	1.89 (0.343–10.431)	0.465		
eGFR, ml/min/1.73m^2	0.998 (0.98–1.016)	0.823		
CRP, mg/dL	0.236 (0.001–58.061)	0.608		
Hs-CRP 3 days after ablation, mg/dL	0.885 (0.694–1.129)	0.325		
BNP, pg/mL	1.001 (0.998–1.004)	0.603		
LVEF, %	0.99 (0.938–1.045)	0.71		
LAD, mm	1.102 (1.026–1.184)	0.007	1.101 (1.024–1.184)	0.009

BMI body mass index, *BNP* brain natriuretic peptide, *CI* confidence interval, *CRP* C-reactive protein, *eGFR* estimated glomerular filtration rate, *ERAA* early recurrences of atrial arrhythmia, *HR* Hazard ratio, *Hs-CRP* high-sensitivity C-reactive protein, *LAD* left atrial diameter, *LVEF* left ventricular ejection fraction

histopathologic tissue damage due to radiofrequency energy [9], a reconnection of electrical conduction between the LA and PVs [15], and non-PV foci triggering AF [16]. However, it is difficult to differentiate ERAA of post-ablation inflammation from PV reconnection in the early post-ablation period. Koyama et al. [14] showed that patients with paroxysmal AF whose first ERAA occurred within 3 days after ablation were more likely to be recurrence free at 6 months after ablation, as compared with those whose first ERAA occurred between days 4 and 30 post-ablation. They explained that acute inflammatory response after catheter ablation was responsible for early ERAA within 3 days, because those patients showed a higher body temperature and CRP levels. In addition, several groups [9, 13] investigated the role of inflammation during the acute phase post-ablation, and the results strongly supported the concept of inflammation playing a prominent role in the atrial arrhythmia recurrences that occurred within a few days after PVI. These results suggested that the clinical outcome would differ between patients with a first ERAA episode that occurred within a few days and patients with a first ERAA episode that occurred more than a few days after ablation. In the present study, the patients who had ERAA within 3 days showed a significantly higher recurrence–free rate than those who had ERAA beyond 3 days. We determined cutoff time of ERAA by statistical analysis, and our result was consistent with that of a former study showing an acute inflammatory response within 3 days after ablation, without any clinical outcomes [9, 14]. Indeed, our result demonstrated that the hs-CRP level 3 days after ablation was not found to be an independent predictor of late recurrence in patients with ERAA. In addition, the patients with ERAA within 3 days tended to show higher hs-CRP levels 3 days after ablation than the patients with ERAA beyond 3 days. Therefore, ERAA within 3 days after ablation might be associated with acute inflammatory response, and there is a possibility that the mechanism of ERAA within 3 days is different from that of ERAA beyond 3 days.

On the other hand, several reports showed the different timing of ERAA. Willems et al. [8] reported that the success rate of PVI was significantly higher in patients with a first ERAA within 1 month after ablation than those with a first ERAA beyond 1 month. Furthermore, Bertaglia et al. [17] revealed that the patients in whom atrial arrhythmia had recurrence within the 1 month after PVI expected long-term clinical success after ablation. However, the cutoff timing of ERAA in the former studies has been subjectively defined by the researchers, not based on the statistical results. In contrast, Alipour et al. [18] investigated ERAA-timing by similar statistical method and showed different ERAA-timing from this study. The possible explanation of the difference between two studies was that the regimen of antiarrhythmic drugs after ablation and the details of ablation procedure which was related to acute inflammatory response. Some patients with ERAA were expected to be delayed cure after the blanking period, but the timing of ERAA was inconsistent among papers.

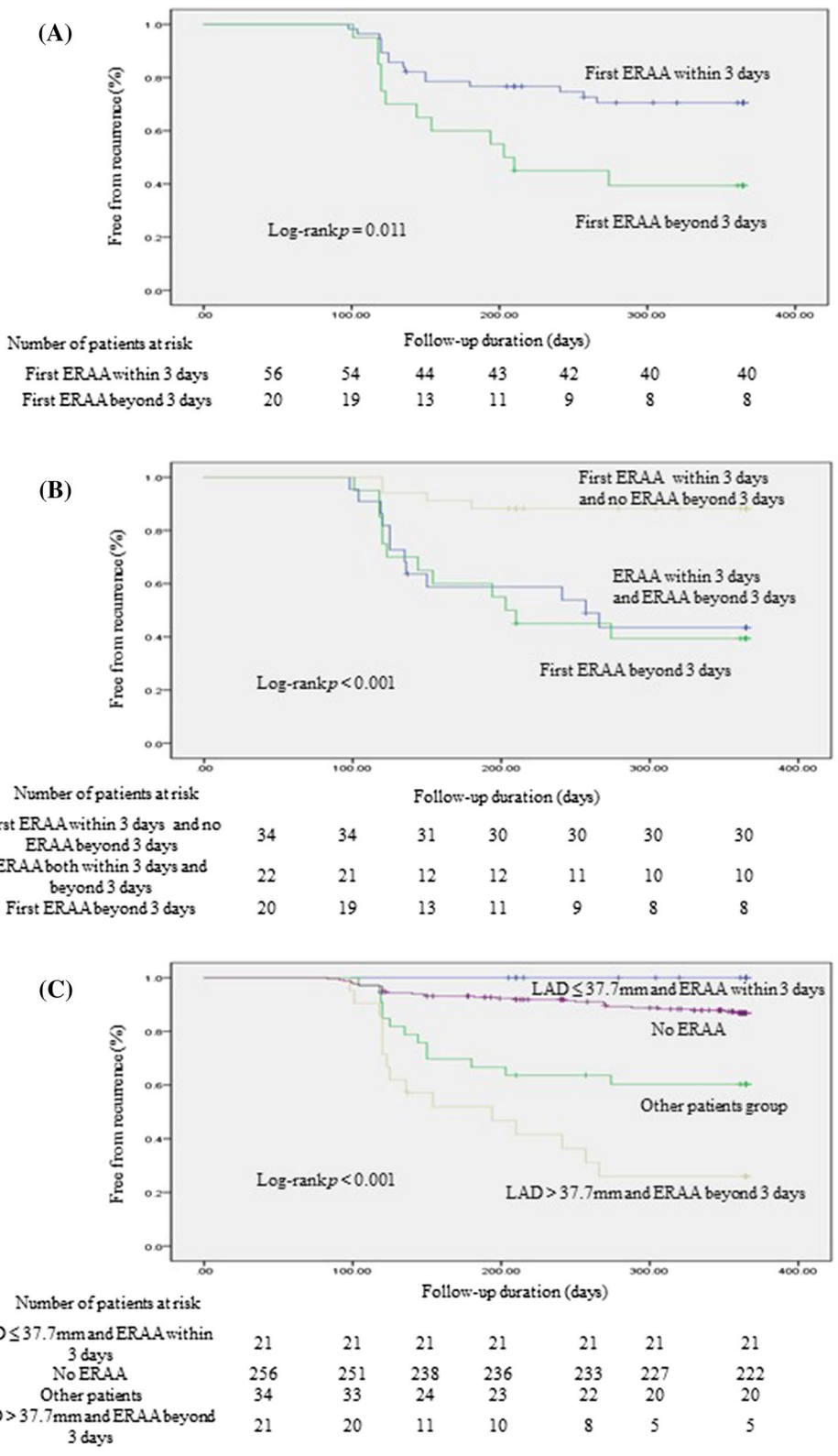

Fig. 2 **a** Kaplan–Meier curves of survival-free rate of late recurrence of atrial arrhythmia between the two ERAA groups; first ERAA episode within 3 days after PVI, first ERAA episode beyond 3 days after PVI. **b** Kaplan–Meier curves of a survival-free rate of late recurrence of atrial arrhythmia among the three ERAA groups; first ERAA episode within 3 days and no ERAA episode beyond 3 days after PVI, first ERAA episode beyond 3 days after PVI, and ERAA episode within 3 days and beyond 3 days after PVI. **c** Kaplan–Meier curves of survival-free rate of late recurrence of atrial arrhythmia among the patients with ERAA and LAD sub-groups; ERAA episode within 3 days and LAD ≤ 37.7 mm, ERAA episode beyond 3 days and LAD > 37.7 mm, and other patients (ERAA within 3 days and LAD > 37.7 mm, ERAA beyond 3 days and LAD ≤ 37.7 mm), no ERAA. ERAA, early recurrences of atrial arrhythmia; LAD, left atrial diameter. Other patients group: ERAA within 3 days and LAD > 37.7 mm, ERAA beyond 3 days and LAD ≤ 37.7 mm. *AUC* area under the curve, *CI* confidence interval, *ERAA* early recurrences of atrial arrhythmia, *LAD* left atrial diameter, *PVI* pulmonary vein isolation, *ROC* Receiver-operating characteristic

In this study, smaller LAD was also independently associated with a lower prevalence of arrhythmia recurrence after the blanking period in patients with ERAA. Miyazaki et al. [7] reported that LA size was strong predictor of a favorable long-term outcome after a single ablation procedure, because larger LAD was considered to represent advanced

Table 4 A comparison of treatment for ERAA within the blanking period among the three groups; first ERAA within 3 days and no ERAA beyond 3 days, first ERAA beyond 3 days, and ERAA both within 3 days and beyond 3 days

	All patients $n=76$	First ERAA within 3 days and no ERAA beyond 3 days $n=34$	First ERAA beyond 3 days $n=20$	ERAA both within 3 days and beyond 3 days $n=22$	*P* value
Antiarryhthmic drugs	62 (82%)	28 (82%)	14 (70%)	20 (91%)	0.215
Class I	58 (76%)	27 (79%)	12 (60%)	19 (86%)	0.113
Class III	4 (5%)	1 (3%)	2 (10%)	1 (5%)	0.525
Electrical Cardioversion	15 (20%)	3 (9%)	7 (35%)	5 (23%)	0.06

Values are number (percentage)

ERAA early recurrences of atrial arrhythmia

electrical and structural remodeling. In patients with AF recurrence, the arrhythmogenic substrate would stabilize multiple wavelet reentry circuits in the left atrium and fibrillatory wavelets could be more easily induced and maintained in a larger left atrium [8]. We hypothesize that the patients with larger LAD had the possibility of being associated with the presence of non-PV foci and had an increased risk of AF recurrence after PVI. Unfortunately, our study population included patients with paroxysmal AF who underwent the PVI procedure only, and we did not assess or apply an additional ablation for non-PV foci during the procedure. Further studies are required to evaluate the association of non-PV foci with larger LAD in patients with ERAA.

This study implies that patients with ERAA within 3 days are more likely to have acute inflammatory responses from radiofrequency energy, while ERAA beyond 3 days may be due to PV reconnection or non-PV foci. Furthermore, we found that patients who had ERAA within 3 days and LAD $\leq$37.7 mm had no recurrence. However, the patients who had ERAA beyond 3 days during the blanking period showed a significantly higher recurrence rate. Despite this, wecannot conclude whether patients with ERAA beyond 3 days should be treated with re-ablation, antiarrhythmic drugs or external electrical cardioversion proactively. The 2012 HRS/EHRA/ECAS expert consensus statement set the blanking period as 3 months to avoid unnecessary early re-ablation [8]. Thus, it is difficult to discuss the necessity of early re-ablation from the results in this study. However, the efficacy of the maintenance of sinus rhythm by the administration of antiarrhythmic drugs and external cardioversion during the blanking period remains unclear [11, 12]. Further studies are needed to assess the effectiveness of the treatment for ERAA, in particular for patients who had ERAA beyond 3 days during the blanking period.

There are some limitations in this study. This was a retrospective study, and the set follow-up duration of 12 months after ablation was relatively short. In addition, we did not use more intensive monitoring devices such as handheld symptom-driven rhythm monitor applications or auto-triggered external and implantable subcutaneous loop recorders to detect the recurrence after ablation. Thus, asymptomatic recurrences, in particular after discharge from the hospital, may have been not fully detected. Moreover, as mentioned above, this study did not assess the management techniques for patients who had ERAA during the blanking period. Finally, although the present study consisted patients from two clinical institutions, the number of patients included in this study was small. Therefore, further large-scale, multicenter, prospective studies are needed to confirm the optimal ERAA-timing associated with late recurrence after ablation.

Conclusion

This study demonstrated that patients with ERAA within 3 days and smaller LAD showed a favorable prognosis after ablation. If a patient with small LAD experiences ERAA within 3 days after PVI, but does not experience arrhythmia recurrence beyond 3 days during the blanking period, this patient could confidently be considered to have achieved ablation success.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

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