Early recurrence during the blanking period and left atrial reverse remodeling after catheter ablation for non-paroxysmal atrial fibrillation

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ABSTRACT

Background: Early recurrence of atrial tachyarrhythmia (ERAT) during a 90-day blanking period (BP) often occurs after atrial fibrillation (AF) ablation. Left atrial reverse remodeling (LARR), which is the reduction in LA volume (LAV), also occurs during the BP. Both ERAT and LARR are associated with late recurrence (LR, greater than 90 days after ablation). We investigated the association between ERAT and LARR following non-paroxysmal AF (NPAF) ablation.
Methods: We retrospectively reviewed 330 consecutive patients undergoing initial NPAF ablation (median follow-up: 4.0 years). Based on the timing of the final ERAT, we divided the patients into No-ERAT (N = 154, without ERAT), Early (N = 39, 0–7 days after ablation), Intermediate (N = 67, 8–30), and Late-ERAT (N = 70, 31–90) groups. We assessed the extent of LARR, defined as the percentage of decrease in LAV (%ΔLAV). The %ΔLAV cutoff value was determined by receiver operating characteristic analysis, and incorporated into a multivariate analysis to assess the association between ERAT and LARR.
Results: Late-ERAT was associated with LR (hazard ratio: 6.31, 95% confidence interval (CI): 4.21–9.47, *p* = 0.0001). The %ΔLAV in the Late-ERAT group was significantly smaller than the other groups (*p* < 0.0001). The predictive power of %ΔLAV for LR was slight (AUC, 0.604; best cutoff, 18.8% decrease; *p* = 0.0011). In the multivariate logistic regression analysis, Late-ERAT was associated with poor LARR (%ΔLAV < 18.8% decrease) (odds ratio, 0.13; 95%CI, 0.06–0.27; *p* < 0.001), whereas Early- and Intermediate-ERAT did not show any correlation.
Conclusions: Late-ERAT was strongly associated with poor LARR after NPAF ablation. Both Late-ERAT and poor LARR might reflect a residual arrhythmogenic substrate causing LR.

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1. Introduction

Early recurrence of atrial tachyarrhythmia (ERAT) within 90 days after atrial fibrillation (AF) ablation is frequently observed in the clinical setting [1]. A consensus statement [2] noted that ERAT was not strongly associated with late recurrence (recurrence beyond 90 days after ablation) and termed the period of 90 days after ablation as the blanking period (BP). However, several recent studies [3,4] have shown an association between ERAT and LR.

Maintenance of sinus rhythm (SR) by AF ablation leads to a reduction in left atrial volume (LAV), which is referred to as left atrial reverse remodeling (LARR) [5,6]. LARR and ERAT have two common characteristics: they occur during the 90-day BP [7,8] and are associated with LR [7,9–11]. However, the association between ERAT and LARR has not been fully elucidated. We hypothesized that ERAT and LARR are closely associated.

In this study, patients undergoing non-paroxysmal AF (NPAF) ablation were stratified into four groups based on the timing of the final ERAT episodes [no-ERAT (without ERAT) and ERAT at early (7 days after ablation), intermediate (8–30 days), and late phases (31–90 days)] to investigate the association between ERAT and LARR using 256-slice multi-detector computed tomography (MDCT).

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2. Methods

2.1. Study protocol

We retrospectively reviewed the data of 374 consecutive patients who underwent initial radiofrequency catheter ablation (RFCA) for NPAF at the Sakurabashi Watanabe Hospital from June 2010 to December 2013. Before and at 3 months after RFCA, we performed 256-slice MDCT to assess LARR. Forty-four patients were excluded because of the lack of an MDCT dataset. We analyzed the remaining 330 patients. Based on the timing of the final ERAT event, we divided patients into the following four groups: No-ERAT (N = 154, patients who did not experience ERAT), Early-ERAT (N = 39, final ERAT 0–7 days after ablation), Intermediate-ERAT (N = 67, 8–30 days), and Late-ERAT (N = 70, 31–90 days). If the patient had multiple episodes during the BP, we defined the last one as the final ERAT event. Ten patients undergoing redo procedures during the BP were categorized into the Late-ERAT group. The percentage decrease in the maximum LAV (%ΔLAV) was used as a representative of LARR, which was calculated as follows: %ΔLAV = {[(pre-ablation LAV_{max}) – (post-ablation LAV_{max})]/(pre-ablation LAV_{max})} $\times$ 100. First, we assessed the association between the timing of the final ERAT and LR after a single procedure. The LR was defined as AF/atrial tachycardia (AT) beyond 90 days after the initial procedure. Next, we assessed the association between ERAT and LARR. A receiver operating characteristics (ROC) analysis was performed to obtain the cutoff value of the %ΔLAV that can predict LR after a single procedure. After dividing patients into good and poor LARR groups according to the optimal cutoff value of %ΔLAV, we assessed the association between ERAT and LARR through multivariate logistic regression analysis. The study protocol was approved by the institutional review board at the Sakurabashi Watanabe Hospital, and all patients gave informed consent for the use of their data.

2.2. Electrophysiological study and ablation protocol

For the electrophysiological study and RFCA [12,13], a 6-French (Fr) decapolar catheter was placed in the coronary sinus, and a 7-Fr decapolar catheter was placed in the superior vena cava (SVC) and right atrium (RA). Two long sheaths were introduced into the LA, and circumferential pulmonary vein isolation (PVI), defined as the abolition or dissociation of PV potentials, was performed under either fluoroscopic or three-dimensional (3D) mapping guidance. We used an irrigated ablation catheter with a 3.5-mm tip (Navistar Thermocool; Biosense Webster, Diamond Bar, CA). RF energy was delivered for 20–30 s at each point, at up to 35 W with a temperature limit of 43 °C. After PVI, we induced non-PV premature atrial contractions (PACs) with 0.1 μg/kg/min of isoproterenol and atrial flutter (AFL)/AT by atrial burst pacing. We attempted to ablate non-PV PACs that triggered AF (non-PV foci) and targeted AFL/AT coexisting with AF. When maintenance of SR was difficult, SVC isolation, cavotricuspid isthmus linear ablation, LA linear ablation (e.g., of the LA roof, floor, and mitral valve isthmus), and/or complex fractionated atrial electrography were empirically performed at the discretion of the operator.

2.3. Echocardiographic study

Pre-procedural echocardiographic data were obtained no more than 1 month before RFCA. Left ventricular ejection fraction (LVEF) was quantified from LV end-diastolic and systolic dimensions (LVDd and LVDs). All data were obtained by trained observers.

2.4. Multi-detector computed tomography

MDCT was performed within 1 month prior to the RFCA and 3 months after RFCA [13]. A 256-slice MDCT scanner (Brilliance iCT; Philips Medical Systems, Cleveland, OH) was used with the following parameters: collimation, 128 mm $\times$ 0.625 mm; gantry rotation time, 270 ms; effective tube current, 320–840 mA (with higher values in obese patients); and tube voltage, 120 kV. The iterative reconstruction technique (iDose[4] level6; Philips Medical Systems) was utilized to reduce image noise. The scanning technique was determined by the attending physician in charge. A bolus of nonionic iodinated contrast (Iopamirone 370, 1 mL/kg; Bayer, Osaka, Japan) was injected according to the bolus-tracking method (6 s after the threshold of 100 Hounsfield units in the LA). Cardiac images were acquired 20-mm above the bifurcation of the pulmonary artery to the apex of the heart during a single breath-hold. Using the Comprehensive Cardiac Analysis software on the Extended Brilliance Workspace (version 4.5.5.5; 1035 Philips Medical Systems), LAV_{max} and LAV_{min} were measured over one cardiac cycle using a volumetric segmentation method, with contour detection visually checked and manually corrected if necessary.

2.5. Follow-up protocol

A 90-day BP after RFCA was employed. After RFCA, all patients were hospitalized with continuous rhythm monitoring for 3 days. Prescription of anti-arrhythmic drugs (AADs) at discharge and in the outpatient clinic was determined by the patient's attending physician as necessary. Discontinuation of AADs was encouraged at 3 months after the procedure. We directed patients to check their pulse rate and rhythm three times a day and to visit the outpatient clinic if they experienced a relapse of AF/AT. All patients were scheduled for visits to the outpatient clinic at 1, 3, 6, 9, and 12 months after ablation, and every 6 months thereafter. A 12-lead electrocardiogram (ECG) was obtained at each visit. Holter ECGs were performed 6 months after RFCA. Recurrence of AF/AT was defined as recurrent symptoms and/or documented AF/AT on ECG and Holter ECG.

2.6. Statistical analysis

In the univariate analysis for covariates of interest, independent continuous variables were analyzed using the independent-sample Student's t-test or the Mann-Whitney U test for comparisons among the two groups. One-way analysis of variance or the Kruskal-Wallis test was performed for comparisons among the four groups. Categorical variables were analyzed using the chi-squared test. To assess the impact of ERAT on LR, we performed multivariate Cox regression analysis after adjustment for age, sex, body mass index (BMI), long-standing persistent AF, hypertension, congestive heart failure (CHF), pre-ablation indexed LAV_{max} ($LAVI_{max}$), LVDd, and AADs during BP. ROC analyses were subsequently performed to obtain the optimal cutoff value of %ΔLAV. Based on the cutoff value, we divided patients into good and poor LARR groups and performed multivariate logistic regression analysis to assess the association between ERAT and LARR. All data are expressed as the mean ± standard deviation or median (interquartile range, IQR). All reported p-values are 2-sided with a pre-specified significance of p < 0.05. Analyses were performed using MedCalc software version 16.8.4 (MedCalc Software bvba, Ostend, Belgium).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the study population are summarized in Table 1. The mean age was 60 ± 10 years, and 16% of patients were female. The BMI was 24.7 ± 3.8 kg/m². Twenty-four percent of patients had long-standing persistent AF. About 90% of patients were in AF at the start of ablation. The CHADS$_2$ score was 1.09 ± 0.99. During the BP, 69% of patients were receiving AADs (groups I and III) and 40% were receiving a beta-blocker. LVEF was 61.4 ± 10.9% and the LA diameter was 4.00 ± 0.52 cm. With regard to the MDCT parameters, preoperative LAVI$_{max}$ was 66.4 ± 18.8 mL/m².

3.2. Association between the timing of the final ERAT and LR

The AF/AT-free survival rate after a single procedure was 43.6% (median follow-up duration: 4.0 years [IQR 3.4, 4.0]). Details of the ablation procedures are shown in Table 1. Fig. 1A shows that the AF/AT-free survival differed among the four groups (64% vs. 31% vs. 37% vs. 11%, No-ERAT vs. Early-ERAT vs. Intermediate-ERAT vs. Late-ERAT, p < 0.0001). After adjustment for age, sex, BMI, long-standing persistent AF, administration of AADs and beta-blockers during BP, hypertension, CHF, LVDd, and preoperative LAVI$_{max}$, Late-ERAT showed a strong association with LR, with No-ERAT being the reference group (hazard ratio [HR], 6.31; 95%

confidence interval [95%CI], 4.21–9.47; p = 0.0001) (Fig. 1B). Early- and Intermediate-ERAT showed a slight association with LR (Early: HR 2.24, 95%CI 1.40–3.59, p = 0.0008; Intermediate: HR 2.22, 95%CI 1.49–3.30, p = 0.0001). Of the 186 patients with recurrence after a single procedure, 124 (67%) underwent redo procedures (No-ERAT, 28; Early, 15; Intermediate, 30; Late, 51). Among 496 PVs, the PV reconnection rate did not differ among the 4 groups (63% vs. 60% vs. 65%, 67%, No-ERAT vs. Early vs. Intermediate vs. Late, p = 0.39). The prevalence of non-PV foci and/or AFL/AT (except common AFL) was high in the Late-ERAT group (21% vs. 13% vs. 20% vs. 45%, p = 0.019).

3.3. Association between the timing of the final ERAT and LARR

As shown in Table 1, the pre-ablation LAVI$_{max}$ was significantly higher in the Late-ERAT group (63.6 ± 16.6 mL/m² vs. 64.1 ± 18.2 vs. 66.5 ± 18.7 vs. 74.0 ± 22.0, No-ERAT vs. Early vs. Intermediate vs. Late, p = 0.001). We compared the extent of LARR among the four groups. As shown in Fig. 2A and Table 1, although all four groups exhibited a decrease in LAV, the Late-ERAT group showed the smallest decrease (23.5% decrease vs. 22.2% vs. 27.3 vs. 10.9%, p < 0.0001 for both). In the ROC analysis for the prediction of LR (Fig. 2B), the %ΔLAV showed minor predictive accuracy for LR (AUC: 0.604, p = 0.001) at an optimal cutoff of 18.8%. Patients were subsequently divided into good (N = 187, %ΔLAV decrease ≥ 18.8%) and poor LARR groups (N = 143, %ΔLAV decrease < 18.8%) and compared. Supplementary File 1 shows the results of the univariate

Table 1
Baseline characteristics of the groups stratified based on the timing of ERAT.

Group	Total	No-ERAT	Early ERAT	Intermediate ERAT	Late ERAT	
Final timing of ERAT (post-ablation day)		None	0–7 days	8–30 days	31–90 days	
Number of patients	n = 330	n = 154	n = 39	n = 67	n = 70	P-value
Female (%)	54 (16%)	22 (14%)	11 (28%)	13 (19%)	8 (11%)	0.10
Age, years.	60 ± 10	60 ± 10	60 ± 10	59 ± 11	62 ± 10	0.64
Body mass index, kg/m²	24.7 ± 3.8	25.0 ± 4.0	24.7 ± 4.4	24.5 ± 3.8	24.0 ± 2.8	0.28
Long-standing persistent AF	80 (24%)	25 (16%)	13 (33%)	16 (24%)	26 (37%)	0.002
AF duration, months	5 (3, 12)	4 (2, 9)	9 (3, 12)	6 (3, 12)	6 (3, 24)	0.004
Comorbidity						
Congestive heart failure	20 (6%)	23 (7%)	2 (5%)	13 (19%)	9 (13%)	0.044
Hypertension	165 (50%)	80 (52%)	18 (46%)	31 (46%)	36 (51%)	0.75
Diabetes	65 (20%)	35 (23%)	7 (18%)	13 (19%)	10 (14%)	0.16
Thromboembolism	28 (8%)	11 (7%)	3 (8%)	4 (6%)	10 (14%)	0.17
CHADS$_2$ score	1.09 ± 0.99	1.18 ± 1.13	0.92 ± 1.06	0.97 ± 0.92	1.10 ± 1.12	0.44
Prior myocardial infarction	4 (1%)	1 (1%)	1 (3%)	1 (1%)	1 (1%)	0.78
Cardiomyopathy	28 (8%)	16 (10%)	1 (3%)	5 (7%)	6 (9%)	0.46
Medications during the blanking period						
Beta-blocker	131 (40%)	56 (36%)	18 (46%)	27 (40%)	30 (43%)	0.64
Anti-arrhythmic drug (groups I and III)	229(69%)	81(53%)	32 (82%)	55(82%)	61(87%)	<0.001
Biomarkers						
BNP*, pg/mL	115.7 (65.5, 195.7)	111.8 (61.8, 191.4)	113.0 (74.4, 213.7)	110.8 (67.0, 182.7)	132.2 (71.4, 201.9)	0.85
Creatinine clearance, mL/min/1.73 m²	70.8 (61.4, 77.7)	69.5 (60.7, 76.7)	69.0 (61.0, 76.9)	74.8 (62.6, 83.8)	70.3 (60.5, 77.2)	0.16
C-reactive protein, mg/dL	0.07 (0.03, 0.15)	0.07 (0.03, 0.15)	0.11 (0.05, 0.26)	0.05 (0.03, 0.13)	0.07 (0.03, 0.13)	0.10
Echocardiography						
LV end-diastolic diameter, cm	4.70 ± 0.54	4.72 ± 0.58	4.50 ± 0.50	4.76 ± 0.51	4.76 ± 0.50	0.078
LV end-systolic diameter, cm	3.14 ± 0.63	3.17 ± 0.70	2.96 ± 0.45	3.21 ± 0.55	3.12 ± 0.59	0.21
LV ejection fraction, %	61.4 ± 10.9	60.5 ± 12.8	62.7 ± 8.0	61.0 ± 9.0	63.2 ± 9.3	0.32
LA diameter, cm	4.00 ± 0.52	3.96 ± 0.54	3.95 ± 0.39	4.10 ± 0.47	4.15 ± 0.55	0.045
Multi-detector computed tomography						
LAVI$^{‡}_{max}$, mL/m²	66.4 ± 18.8	63.6 ± 16.6	64.1 ± 18.2	66.5 ± 18.7	74.0 ± 22.0	0.001
LAEF‡, %	16.6 ± 9.0	17.5 ± 10.6	16.6 ± 8.4	16.6 ± 7.6	14.5 ± 6.6	0.16
Left atrial reverse remodeling						
Decrease in LAV$_{max}$ (%ΔLAV$_{max}$)	−21.4(−32.0, −10.3)	−23.5(−32.6, −16.3)	−22.2 (−31.5, −8.5)	−27.3(−34.7, −14.3)	−10.9 (−19.3, −0.4)	<0.001
Ablation procedures						
Pulmonary vein isolation	330 (100%)	154 (100%)	39 (100%)	67 (100%)	70 (100%)	
Cavo-tricuspid isthmus linear ablation	145 (44%)	71 (46%)	14 (36%)	29 (43%)	31 (44%)	0.720
LA linear ablation	24 (7%)	8 (5%)	6 (15%)	4 (6%)	6 (9%)	0.160
Superior vena cava isolation	10 (3%)	2 (1%)	2 (5%)	3 (4%)	3 (4%)	0.390
Non-PV foci ablation	20 (6%)	6 (4%)	5 (13%)	4 (6%)	5 (7%)	0.210
CFAE§ ablation	18 (5%)	7 (5%)	3 (8%)	2 (3%)	6 (9%)	0.430

*BNP: brain natriuretic peptide, †LAVI$_{max}$: maximum indexed LA volume, ‡LAEF: LA emptying fraction, §CFAE: complex fractionated atrial electrogram.
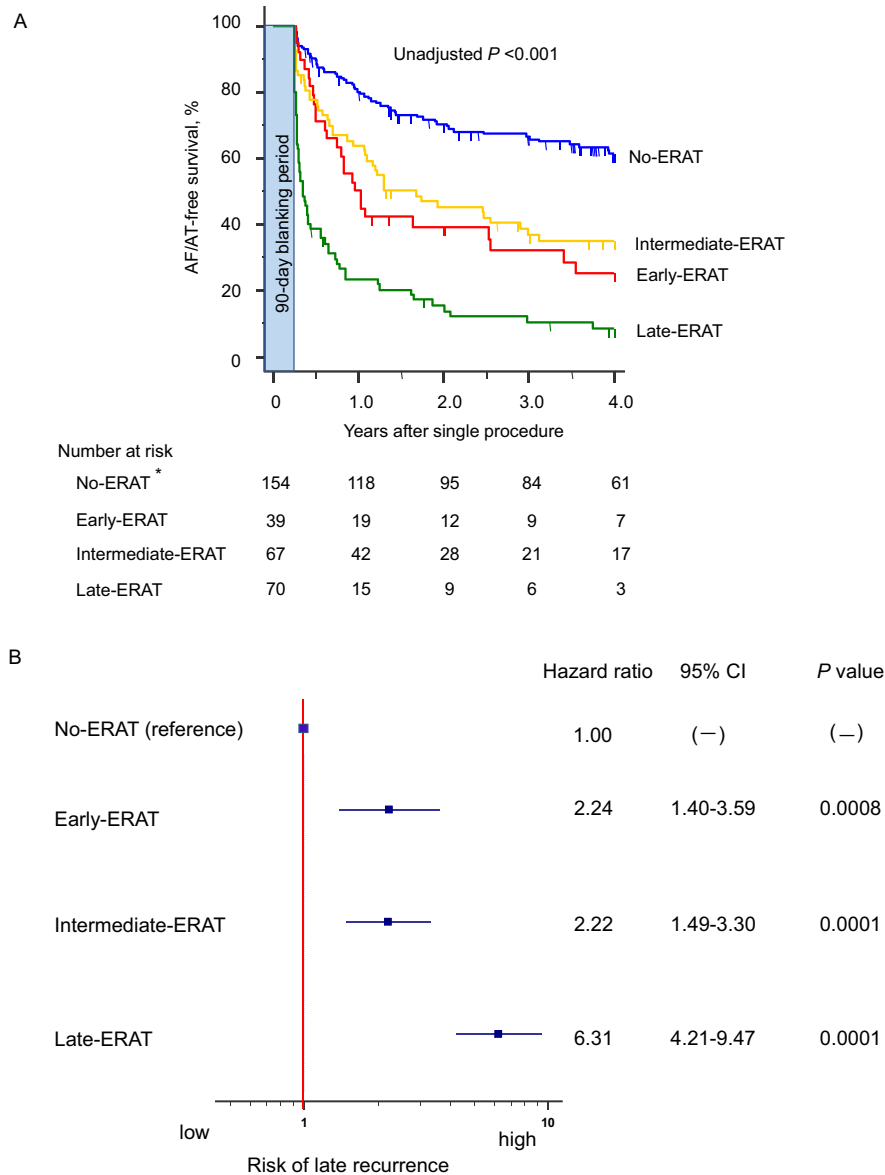
Fig. 1. The association between ERAT and late recurrence. (A) Long-term AF/AT-free survival after the initial NPAF ablation among the four groups stratified by the timing of the final ERAT episode. (B) Risk of late recurrence after the initial NPAF ablation among the groups stratified by the timing of the final ERAT episodes by multivariate Cox regression analysis. *ERAT: early recurrence of atrial tachyarrhythmia.

analysis. In the multivariate logistic regression analysis adjusted for ERAT, among the covariates found to be significant at the pre-specified p < 0.10 in the univariate analysis and patient demographic data (Fig. 2C), Late-ERAT was strongly associated with poor LARR (Odds ratio: 0.13, 95% CI: 0.06–0.27, p = 0.0001). Early- and Intermediate-ERAT did not show any association with LARR.

3.4. Association between LARR and LR

We assessed the association between LARR and LR. Patients with recurrence showed a smaller %ΔLAV decrease (18.3% vs. 24.2% decrease, with vs. without recurrence, p = 0.0015) (Fig. 3A). In the Kaplan-Meier analysis (Fig. 3B), AF/AT-free survival was significantly longer in the good LARR group than in the poor LARR group (55% vs. 29%, p < 0.0001). As shown in Fig. 3C, we divided the patients into 4 groups based on the presence of Late-ERAT and poor LARR. AF/AT-free differed significantly among the

4 groups (59% vs. 40% vs. 21% vs. 8%, Good LARR/ Late-ERAT(-) vs. Poor LARR/Late-ERAT (-), Good LARR/Late-ERAT(+) vs. Poor LARR/Late-ERAT(+), p < 0.0001).

4. Discussion

4.1. Major findings

We investigated the associations between the timing of the final ERAT episode and LARR after the initial NPAF ablation and noted the following: i) Late-ERAT (31–90 days during the BP) was associated with poor LARR and increased risk of LR; and ii) neither Early- (within 7 days) nor Intermediate-ERAT (8–30 days) was associated with poor LARR, but both were associated with the intermediate risk of LR compared with No-ERAT. Both Late-ERAT and poor LARR might reflect the presence of a residual arrhythmogenic substrate, causing a recurrence.
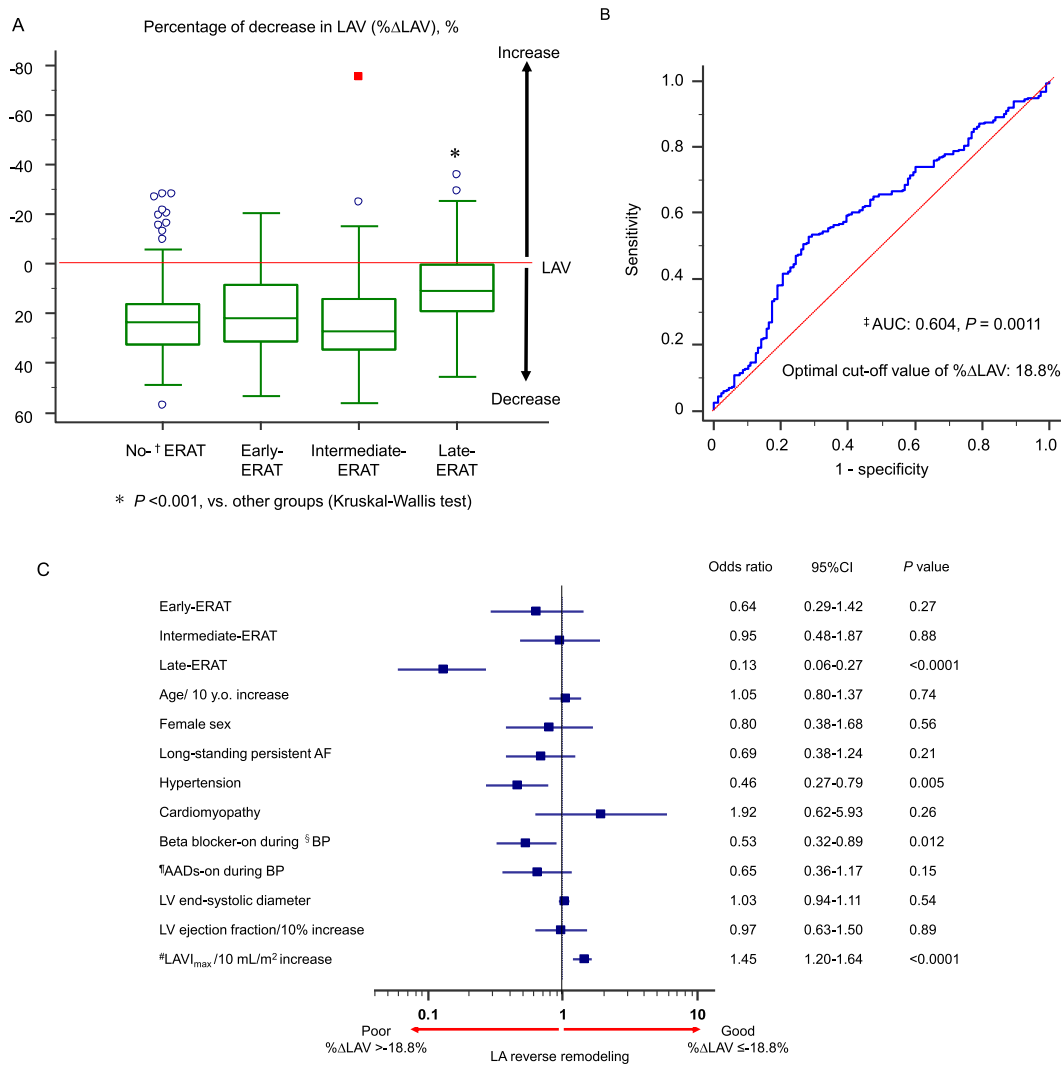
Fig. 2. The association between the extent of LA reverse remodeling and ERAT. (A) The extent of LA reverse remodeling among the four groups stratified by the timing of the final ERAT episode after the initial NPAF ablation. (B) The area under the curve of %ΔLAV for the prediction of late recurrence after NPAF ablation. (C) The association between LARR and ERAT by multivariate logistic regression analysis. †ERAT: early recurrence of atrial tachyarrhythmia, ‡AUC: area under the ROC curve, §BP: blanking period, ¶AADs: anti-arrhythmic drugs, #LAVI$_{max}$: indexed maximum left atrial volume.

4.2. Association between ERAT and ablation outcome

ERAT was defined as an AF/AT episode in the period immediately after the AF ablation. The consensus statement released by the Heart Rhythm Society, European Heart Rhythm Association, and European Cardiac Arrhythmia Society has defined BP as the period within 90 days after ablation [2]. ERAT episodes during the 90-day BP are considered transient phenomena and were not classified as treatment failures. The frequency of ERAT has been reported to range from 16% to 67% [1,14–20] with a pooled estimate of 37.8%. In the current study, the frequency of overall ERAT after NPAF ablation was 53%, which was comparable with that of the previous studies, although asymptomatic AF might have been underestimated. Then, we validated the association between the timing of ERAT and LR after NPAF ablation, as several recent studies have demonstrated that ERAT was associated with LR and the timing of ERAT had a clear gradient of effect on LR [3,4]. We divided the 90-day BP into early (0–7 days after ablation), intermediate (8–30 days), and late periods (31–90 days) based on the pathophysiological stage after ablation. The early period is considered

the acute phase after ablation, during which the transient factors (inflammation, autonomic imbalance) are at their peak [21]. The intermediate period is the lesion maturation period after the acute phase. Das et al. reported that post-ablation LA electroanatomical changes are also complete at 4 to 8 weeks after ablation [22]. The late period is the post-inflammation period after completion of lesion maturation. In the univariate analysis, the No-ERAT group had lower administration of AADs than the other groups, because AADs might often be started after the patients experienced ERAT, and at the discretion of their physician. In the multivariate analysis, the Late-ERAT group was at a higher risk of LR after NPAF ablation, consistent with the previous studies [3,4]. The Late-ERAT group possibly had a residual arrhythmogenic substrate associated with LR. Furthermore, the HR for LR in the Early- and Intermediate-ERAT groups was lower than that in the Late-ERAT group, but it was higher than that of the No-ERAT group. Some patients in the Early- and Intermediate-ERAT groups might have had a concealed arrhythmogenic substrate. Mugnai et al. reported that late ERAT occurring 1.5 months post-ablation predicted PAF cryo-balloon ablation outcome [23]. Our results, which focused on NPAF
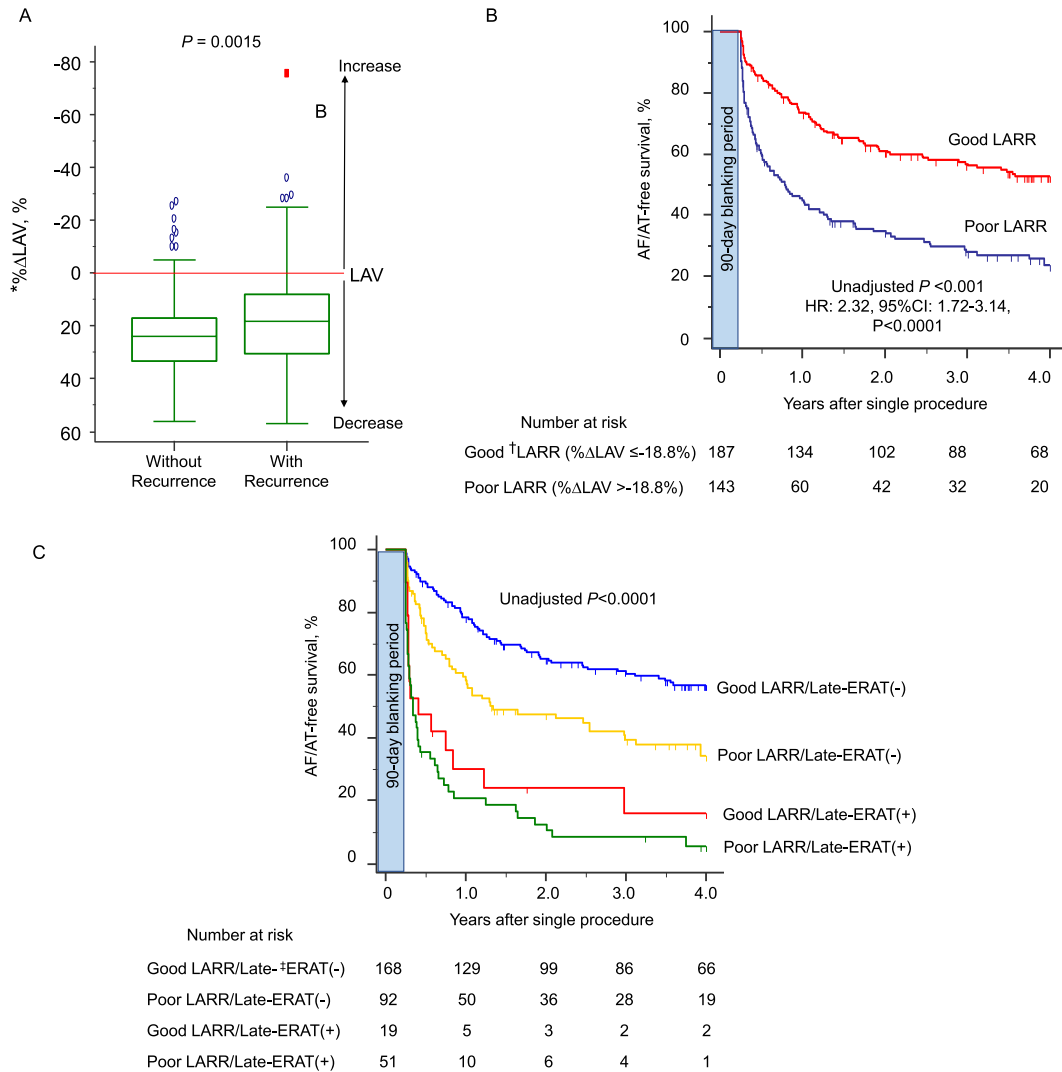
Fig. 3. The association between LA reverse remodeling and late recurrence. (A) Reduction in LA volume in patients with and without late recurrence. (B) AF/AT-free survival in the good LARR and poor LARR groups. (C) AF/AT-free survival in the four groups divided on the basis of the presence of Late-ERAT and Poor LARR. *%ΔLAV: decrease in LAV_{max}, [†]LARR: left atrial reverse remodeling, [‡]ERAT: early recurrence of atrial tachyarrhythmia.

patients, were consistent with previous findings showing that late ERAT confers a high risk of LR. Late ERAT after PAF and NPAF ablation both might reflect a residual arrhythmogenic substrate.

4.3. Association between LARR and ablation outcome

AF promotes LA remodeling through the development of atrial fibrosis, increase in LA pressure, and changes in ionic fluxes [6,24]. The clinical phenotype of LA remodeling is characterized by the enlargement of the LA chamber and impairment of LA function. LA remodeling is partially reversible. LARR is induced after maintenance of SR through a successful AF ablation [5]. LAV reduction has been often used as a representative of LARR. Reant et al. analyzed the time course of post-ablation changes in LA chamber size using echocardiography and showed that LAV reduction was completed at 3 months post-ablation [8]. Some small-scale studies have reported that LAV reduction was positively associated with ablation outcomes during a short-term follow-up period [7,9–11]. Therefore, we validated the association between LARR and NPAF ablation outcomes over a longer follow-up period of 4 years. In our analyses, $LAVI_{max}$ was 66.4 ± 18.8 mL/m², suggesting that our NPAF patients had notable enlargement of the LA at baseline.

Patients with recurrence showed poorer LARR than those without recurrence. Furthermore, the extent of LAV reduction was slightly correlated with LR in the ROC analysis. Patients with good LARR showed a higher AF/AT-free survival rate than those with poor LARR. LAV reduction after NPAF ablation might indicate a reduction in arrhythmogenic substrates relating to LR.

4.4. Association between ERAT and LARR

We focused on the association between ERAT and LARR since they share two characteristics: i) both may occur during the same 90-day BP post ablation period, and ii) both showed an association with LR [7,9–11]. Therefore, we hypothesized that ERAT and LARR are closely associated. In the univariate analysis, only patients in the Late-ERAT group showed poor LARR compared with the other groups. The presence of ERAT and prescription of AADs were higher in poor LARR groups. As AADs are frequently started after patients experience an ERAT, their higher usage might be the result of the higher percentage of ERAT in poor LARR groups. We speculated that the AADs were not the cause of poor LARR. In the multivariate analysis, Late-ERAT was strongly associated with poor LARR, whereas Early- and Intermediate-ERAT did not show any

association. As shown in Fig. 3C, more than 90% of patients with Late-ERAT and poor LARR experienced recurrence over 4 years of follow-up, while only 40% of patients without ERAT and with good LARR experienced recurrence. Thus, evaluation of ERAT and LARR at the end of the BP allows us to stratify the risk of recurrence after NPAF ablation.

We speculated that two mechanisms may possibly explain the association between Late-ERAT and poor LARR. First, that Late-ERAT itself inhibits LARR. It is natural to assume that LARR occurs during SR after NPAF ablation. Given that LARR occurs during the absence of ERAT, suppression of ERAT could promote LARR, leading to the success of the ablation. Kaitani et al. investigated whether the short-term use of AADs during the BP was effective in improving ablation outcomes in the Efficacy of Antiarrhythmic drugs Short-term use after catheter ablation for Atrial Fibrillation (EAST-AF) trial [25]. They found that the administration of AADs during the 90-day BP reduced the incidence of ERAT by 16% but it did not reduce the incidence of LR. Although no data regarding LARR was reported by EAST-AF, the suppression of ERAT by AADs could not induce sufficient LARR to reduce LR. The direct effect of ERAT on LARR might appear to be limited and additional factors should be considered to explain the association between ERAT and LARR. The second hypothesis is that Late-ERAT and poor LARR may be caused by a common underlying mechanism, which is the presence of a residual arrhythmogenic substrate. The mechanisms of ERAT generally involve two factors: i) transient factors occurring after the ablation procedure (post-procedural inflammation, autonomic imbalances, and lesion maturation time); and ii) residual arrhythmogenic factors, such as PV reconnection and non-PV substrates (non-PV foci triggering AF and residual AT/AFL substrates) [16,21]. The weight of these factors might depend on the timing of ERAT after ablation [22]. The main cause of Late-ERAT is considered to be residual arrhythmogenic substrates, such as extensive myocardial injury and irreversible atrial fibrosis. In our analyses, the PV reconnection rate in redo procedures was not statistically different among the 4 groups, but the prevalence of non-PV substrates was high in Late-ERAT. Thus, Late-ERAT might be caused by a non-PV substrate rather than by PV reconnection. Furthermore, LARR could be inhibited by the irreversible arrhythmogenic substrate. In the current study, pre-ablation $LAVI_{max}$ was higher in the Late-ERAT group, suggesting that patients in the Late-ERAT group had more advanced baseline LA remodeling. Thus, both Late-ERAT and poor LARR might reflect the presence of a residual arrhythmogenic substrate. Patients with Early- and Intermediate-ERAT have an intermediate risk of developing LR and experiencing normal LARR. In contrast to Late-ERAT, acute responses were considered a predominant cause of Early- and Intermediate-ERAT. The partial involvement of irreversible arrhythmogenic substrates could explain the normal LARR and intermediate risk of LR in patients with Early and Intermediate-ERAT. Taken together, the presence of a residual arrhythmogenic substrate could reasonably explain the association between ERAT and LARR, rather than the direct effect of ERAT on LARR.

4.5. Clinical implications

Late-ERAT and poor LARR strongly reflect the presence of a residual arrhythmogenic substrate leading to LR. Evaluation of ERAT and LARR at the end of the BP might allow us to stratify the risk for recurrence after NPAF ablation in clinical practice.

4.6. Study limitations

This study should be interpreted in light of its methodological limitations. First, our study was designed as a single-center retrospective study. Second, we should emphasize that the methods used to detect recurrent arrhythmias were limited, and that we might have missed asymptomatic AFs or underestimated the recurrence rate. Furthermore, this registry enrolled patients in Japan from 2010 to 2013; therefore, the follow-up approaches used may be out of date. Third, contact-force guided ablation, and cryoballoon ablation were not available when our registry data were collected. Thus, the recurrence rate observed might be higher than that in the era of contact-force guided ablation. Forth, patients without MDCT data were excluded since LARR evaluation would not have been possible in these patients. This issue might have lead to selection bias.

5. Conclusions

The ERAT beyond 1 month was strongly associated with poor LARR, possibly causing an increased risk of LR. The ERAT within 1 month was not associated with poor LARR, but it was associated with an intermediate risk of LR compared with the absence of ERAT. Both Late-ERAT and poor LARR might reflect a residual arrhythmogenic substrate causing LR.

CRediT authorship contribution statement

Takafumi Oka: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Yasushi Koyama:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Koji Tanaka:** Data curation, Methodology, Writing - review & editing. **Yuko Hirao:** Data curation, Methodology, Writing - review & editing. **Nobuaki Tanaka:** Data curation, Methodology, Writing - review & editing. **Masato Okada:** Data curation, Formal analysis, Writing - review & editing. **Issei Yoshimoto:** Data curation, Formal analysis, Writing - review & editing. **Ryo Kitagaki:** Data curation, Formal analysis, Writing - review & editing. **Atsunori Okamura:** Investigation, Project administration, Writing - review & editing. **Katsuomi Iwakura:** Conceptualization, Project administration, Writing - review & editing. **Yasushi Sakata:** Conceptualization, Supervision, Writing - review & editing. **Kenshi Fujii:** Project administration, Supervision, Writing - review & editing. **Koichi Inoue:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

K.I. has received honoraria from Bayer, Medtronic, Johnson and Johnson KK, Bristol-Myers Squibb, Daiichi-Sankyo, and Boehringer Ingelheim. K.I. has received honoraria from Boehringer Ingelheim. Other authors (T.O., Y.K., K.T., Y.H., N.T., M.O., I.Y., R.K., A.O., K. Iwakura, and K.F.) have no financial conflicts of interest to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100588.

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