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Left Ventricular Diastolic Dysfunction is an Independent Predictor of Late Recurrence After Successful Radiofrequency Catheter Ablation of Persistent or Paroxysmal Atrial Fibrillation

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ABSTRACT

Background: Several echocardiographic parameters assessed before radiofrequency catheter ablation (RFCA) are associated with recurrence of atrial fibrillation (AF). However, data are limited on the associations of changes in these parameters and late recurrence (LR) of AF.

Methods: This study investigated data from 198 consecutive patients with AF (age 63.4 ± 10.5 years; paroxysmal AF 65.7%) who successfully underwent RFCA and maintained sinus rhythm for at least 1 year after RFCA. All patients underwent echocardiography at baseline and at 3 months and 1 year after RFCA. We analyzed associations of LR (any recurrence later than 1 year after RFCA) with changes in echocardiographic parameters, namely, left ventricular ejection fraction, left atrial diameter (LAD), and E/A and E/e' ratios.

Results: During a mean follow-up period of 29.7 ± 11.9 months, 17 patients (8.6%) developed LR. As compared with patients who maintained sinus rhythm, patients with LR had a significantly higher LAD at 1 year after RFCA (36.5 vs 39.2 mm, respectively; $p < 0.001$) and a significantly higher E/e' ratio (10.6 ± 4.1 vs 13.0 ± 3.7 , respectively; $p = 0.017$). Kaplan-Meier and multivariate Cox proportional hazards models revealed that an E/e' ratio >10 (hazard ratio, 4.44; 95% confidence interval, 1.269 – 15.53; $p = 0.020$) and use of antiarrhythmic drugs after RFCA (hazard ratio 2.81; 95% confidence interval, 1.079 – 7.299; $p = 0.034$) were significant predictors of and independently associated with LR, regardless of LAD.

Conclusion: LAD significantly improved in patients who maintained sinus rhythm after RFCA; however, improved LAD was not associated with decreased risk of LR. An E/e' ratio >10 at 1 year after RFCA was significantly associated with LR.

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KEYWORDS: E/e' ratio, left atrial diameter, echocardiography, and pulmonary vein isolation

Many recent studies have reported high success rates for radiofrequency catheter ablation (RFCA) in patients with drug-refractory atrial fibrillation (AF).¹⁻³ Despite improvements in RFCA techniques and devices, the success rate for catheter ablation is only 70% to 80%. AF type (paroxysmal, persistent, or permanent), left atrium (LA) size, age, and presence and severity of underlying cardiac disease are clinical factors associated with recurrence and late recurrence (LR) after successful RFCA.⁴⁻⁷ Left ventricular (LV) diastolic dysfunction was reported to be associated with these factors and has been described as a contributory factor in AF development.⁸ LV diastolic dysfunction can be evaluated by echocardiography or blood testing.⁹ It is unclear whether changes in variables related to LV diastolic dysfunction, such as E/e' ratio, are associated with LR after successful RFCA.

Numerous studies have evaluated long-term outcomes after successful RFCA for AF.^{4-6, 10} Although patients who undergo RFCA for AF are usually carefully followed for 1 year after RFCA, the duration of comprehensive follow-up is shorter for some patients. We examined if changes in echocardiographic parameters after successful RFCA were associated with LR (any AF recurrence later than 1 year after RFCA) of AF and stratified patients in relation to LR risk.

Methods

Study population and design

This retrospective study analyzed data from 338 consecutive patients who underwent RFCA for AF at our center during the period from January 2011 through December 2014. Of these 338 patients, 140 who developed recurrent AF within 1 year after RFCA were excluded. Ultimately, data from 198 patients who successfully underwent RFCA and maintained sinus rhythm (SR) for at least 1 year after RFCA were included in the analysis. The characteristics of these patients are shown in Table 1. AF type and classification, *i.e.*, paroxysmal, persistent, or permanent, were defined according to accepted guidelines.⁶ Paroxysmal AF was defined as recurrent AF (≥ 2 episodes) spontaneously ending within 7 days. Persistent AF was defined as continuous AF of longer than 7 days' duration. Permanent AF was defined as continuous AF that could not be restored to SR.

All patients underwent comprehensive 2-dimensional and Doppler echocardiography at baseline and 3 and 12 months after RFCA. We investigated associations of very

LR of AF after RFCA and changes in echocardiographic parameters, including left ventricular ejection fraction (EF), LV diastolic dimension, and left atrial diameter (LAD) at baseline and follow-up, and E/A and E/e' ratio during follow-up. LR was defined as any recurrence documented by a 24-hr Holter or resting electrocardiogram (ECG) later than 1 year after successful RFCA, as indicated in the relevant guidelines.^{6, 10}

Ethical considerations

The study protocol was approved by the Institutional Review Board of the Toho University Medical Center Omori Hospital (no. M16066). All patients gave their informed consent for the study protocol.

Echocardiography

All patients were imaged with a ultrasound system (GE Vivid E9 ; GE Healthcare, Chicago, IL, USA). Two-dimensional echocardiographic parameters for the LA and LV were measured on the standard parasternal long axis with apical 2- and 4-chamber views. LV diastolic function was evaluated by using the transmitral flow profile from the apical 4-chamber view, *i.e.*, the E/e' ratio – peak early mitral inflow velocity (E) over the early diastolic mitral annular velocity (e') – as determined by pulsed and tissue Doppler. LV mass index was also analyzed because E/e' ratio is associated with LV hypertrophy, which can be estimated by LV mass index.

When patients underwent echocardiography during AF, all echocardiographic parameters were measured with an average of more than 3 beats. When patients had rapid, irregular AF patterns in the pre-state, E/e' ratio was not recorded as an assessment index. Echocardiography was performed before and at 3 and 12 months after RFCA.

RFCA

All antiarrhythmic drugs (AADs) except for amiodarone were discontinued for at least 7 half-lives before RFCA, and all patients were effectively anticoagulated for longer than 1 month. A 7-Fr, 20-pole, 3-site mapping catheter (BeeAT; Japan Life Line Co., Ltd., Tokyo, Japan) was inserted into the coronary sinus via the right jugular vein.

The electrophysiological study and RFCA were performed after sedation with dexmedetomidine and propofol. The transseptal procedure was performed by using fluoroscopic landmarks, and 2 SL0 sheaths (St. Jude Medical, Little Canada, MN, USA) were advanced into the LA. After transseptal puncture, an ablation catheter with an open-irrigated 3.5-mm tip (Thermocool[®], Biosense Webster Inc.,

Table 1 Patient characteristics

	Total	SR group	LR group	<i>P</i>
Male (%)	153 (77.3)	140 (77.3)	13 (76.5)	0.999
Age (years)	63.4 ± 10.5	63.0 ± 10.5	67.0 ± 10.1	0.135
Height (cm)	166.5 ± 8.4	166.5 ± 8.5	165.8 ± 8.2	0.747
Weight (kg)	66.9 ± 12.9	66.9 ± 13.2	67.3 ± 9.6	0.894
BMI (kg/m ²)	24.0 ± 3.8	24.0 ± 3.9	24.4 ± 2.4	0.666
PAF (%)	130 (65.7)	120 (66.3)	10 (58.8)	0.596
CHADS ₂ score	1.4 ± 1.1	1.3 ± 1.1	1.8 ± 1.1	0.110
Duration of AF (months)	60.8 ± 69.4	59.2 ± 69.8	77.2 ± 65.4	0.082
Use of AADs before RFCA	174 (87.9)	158 (87.3)	16 (94.1)	0.700
Use of AADs after RFCA	53 (26.8)	44 (24.3)	9 (52.9)	0.019
Spontaneous echo-contrast (%)	64 (32.3)	61 (33.7)	3 (17.7)	0.277
LAAFV (cm/sec)	49.9 ± 20.7	50.5 ± 20.8	42.7 ± 19.0	0.137
Echocardiography (baseline)				
EF (%)	67.8 ± 10.4	67.4 ± 10.6	71.3 ± 7.7	0.142
LVDs (mm)	30.5 ± 7.1	30.7 ± 7.2	29.0 ± 5.6	0.342
LVDd (mm)	49.3 ± 6.7	49.3 ± 6.7	49.1 ± 6.4	0.906
LVMI (g/m ²)	86.3 ± 24.8	86.7 ± 25.5	82.5 ± 16.6	0.507
LAD (mm)	39.2 ± 6.7	39.1 ± 6.7	40.2 ± 6.4	0.553
MR (>moderate)	9 (4.6)	9 (5.0)	0 (0)	0.999
Laboratory data (baseline)				
Cr (mg/dl)	0.94 ± 0.64	0.94 ± 0.67	0.89 ± 0.17	0.721
eGFR (ml/min)	68.4 ± 48.0	68.8 ± 50.0	64.2 ± 17.3	0.707
BNP (pg/ml)	115.7 ± 166.1	116.7 ± 171.4	104.0 ± 95.4	0.502
HbA1c (%)	5.9 ± 0.57	5.9 ± 0.57	6.0 ± 0.60	0.267
LDL (mg/dl)	116.5 ± 30.4	116.9 ± 30.7	111.4 ± 27.3	0.502
RFCA				
PVI time (mins)	22.2 ± 10.6	22.1 ± 10.5	23.3 ± 11.8	0.633
Total procedure time (mins)	173.0 ± 33.2	171.8 ± 32.1	185.5 ± 42.1	0.103
Irrigation catheter (%)	69 (34.9)	65 (35.9)	4 (23.5)	0.427
First procedure (%)	166 (83.8)	151 (83.4)	15 (88.2)	0.999

Data are expressed as mean ± SD or number (%).

AADs: anti-arrhythmic drugs, AF: atrial fibrillation, BMI: body mass index, BNP: brain natriuretic peptide, EF: ejection fraction, eGFR: estimated glomerular filtration rate, LAAFV: left atrial appendage flow velocity, LAD: left atrial diameter, LVDd: left ventricular diameter diastolic, LVMI: left ventricular mass index, LVDs: left ventricular systolic, MR: mitral regurgitation, PAF: paroxysmal atrial fibrillation, PVI: pulmonary vein isolation, RFCA: radiofrequency catheter ablation, SR: sinus rhythm, LR: late recurrence

Diamond Bar, CA, USA) or 8-mm tip (Ablaze AT, Japan Life Line Co., Ltd.) was used to perform pulmonary vein isolation (PVI) with the double-lasso technique.

RFCA was guided by using a 3-D mapping system (CARTO[®], Biosense Webster Inc. or EnSite[™] NavX[™], St. Jude Medical). Two 5-Fr circular mapping catheters were placed through 2 long sheaths, in the superior and inferior pulmonary veins (PVs). The left- and right-side ipsilateral PVs were circumferentially and extensively ablated.

The endpoint of PVI was elimination of all PV potentials between the LA and PVs at least 30 min after successful

PVI, and elimination of any dormant PV conduction, as revealed by adenosine triphosphate. In addition, incremental isoproterenol infusion (starting at 5 µg, increasing to 10 µg and then 20 µg/min for 2 min) was given before and after PVI, to identify any origination from AF or any non-PV triggers. If frequent premature atrial contractions originating from non-PV sites were present, focal ablation was used to eliminate any non-PV foci. Cavotricuspid isthmus line ablation was performed if any common atrial flutter was detected before or during the procedure.

Post-RFCA follow-up

After the first procedure, all patients were followed-up monthly in the outpatient clinic for 4–6 months and then 1–3 times more during the next 12 months. At each visit, a 12-lead ECG was obtained and symptoms were assessed. After 12 months, a 24-hr Holter ECG was obtained, and symptoms were assessed once or twice a year in the outpatient clinic. Patients with important symptoms or non-PAF were assessed more frequently. Mean duration of follow-up after RFCA was 29.7 ± 11.9 months. The mean number of 24-hr Holter ECGs during follow-up was 8.1 ± 2.4 per patient.

In patients without AF, all anticoagulant treatment was discontinued during follow-up, unless other major risk factors were present. AADs were not resumed in patients with paroxysmal AF; however, patients with persistent AF received AADs for 3 months after ablation.

Freedom from AF was defined as absence of detectable AF/atrial tachycardia (AT) on electrocardiography performed multiple times after the final procedure. AF recurrence was defined as AF/AT longer than 30 second after a 3-month blanking period. AF within the 3-month period after the procedure was considered transient. After the blanking period, a repeat procedure was performed in the event of AF/AT recurrence, if the patient desired.

Statistical analysis

All continuous data are expressed as mean \pm standard deviation, median (interquartile range), or number (%). Comparisons between groups were analyzed by univariate analysis (unpaired *t*-test, Mann-Whitney *U*-test, Fisher exact test, and one-way repeated-measures ANOVA) and multivariate analysis using a Cox proportional hazards model. Associations of AF recurrence with clinical factors were analyzed with the Kaplan-Meier method, and curves were compared with the log-rank test. A *p* value of <0.05 was considered statistically significant. Statistical analyses were performed with Easy R (EZR) (Jichi Medical University, Shimotsuke, Tochigi, Japan), a graphical user interface for R (version 2.13.0; The R Foundation for Statistical Computing, Vienna, Austria).¹¹⁾

Results

Baseline characteristics

The mean age of patients was 63.4 ± 10.5 years, and 153 (77.3%) patients were male. Paroxysmal AF was present in 130 patients (65.7%). Median (interquartile range) AF duration, including paroxysmal and persistent AF, was 36 (12–

84) months. The average CHADS₂ score was 1.4 ± 1.1 points. Mean LA diameter was 39.2 ± 6.7 mm. The baseline characteristics of patients are shown in Table 1.

RFCA procedure and outcomes

RFCA was successfully performed in all patients. The mean follow-up period was 29.7 ± 11.9 months. SR was maintained for at least 1 year after RFCA in 198 patients, and 17 patients (8.6%) developed LR during follow-up. The mean duration of the procedure was 173.0 ± 33.2 min, and the total duration of the RF time was 22.2 ± 10.6 min. LA linear ablation, focal ablation for non-PV foci, and superior vena cava isolation were performed in 13 (6.6%), 51 (25.8%), and 45 (22.7%) patients, respectively. No patient underwent complex fractionated atrial electrogram ablation. Cavotricuspid isthmus line ablation was performed in 184 patients (92.9%). Non-paroxysmal AF was noted in 68 patients. However, AADs were not administered to all these patients during long-term follow-up. Fifty-three patients (26.8%) received additional AAD therapy after successful RFCA (Table 1).

Among the 17 LR patients, 12 underwent re-do RFCA. PV recurrence was detected in 8 (66.7%) patients, and recurrences originating from non-PV foci were detected in 9 (75.0%) patients. AF recurrence due to PV recurrence only was noted in 3 (25.0%) patients.

Echocardiographic parameters at 12 months after RFCA

Characteristics of patients in the SR and LR groups at 12 months after RFCA are shown in Table 2. Data for EF, LV diastolic dimension, and LV diameter-systolic (LVDs) did not significantly differ between groups. LAD (39.7 ± 6.5 vs. 36.2 ± 5.8 mm in LR and SR groups, respectively; *p* = 0.020) and E/e' ratio (13.0 ± 3.7 vs. 10.6 ± 4.1 in LR and SR groups, respectively; *p* = 0.017) were significantly higher in the LR group. Fig. 1 shows changes in echocardiographic parameters: EF significantly improved only in the SR group, but LAD significantly decreased in both groups.

We decided on an E/e' ratio cut-off value of 10, which was used to subdivide the patients into 2 groups. A receiver-operating-characteristic curve comparing E/e' ratio and LR showed an E/e' ratio cut-off value of 10.4 (area under the curve, 0.71; 95% CI, 0.588–0.827) (Fig. 2).

Fig. 3 shows the results of Kaplan-Meier analysis of AF recurrence after RFCA. The Kaplan-Meier curves show that an E/e' ratio >10 was significantly associated with increased risk of LR (log-rank test, *p* = 0.0057).

Table 2 Patient Characteristics at 12 Months after the RFCA, by recurrence status

	SR group	LR group	<i>P</i>
Echocardiography (12 Mo)			
EF (%)	69.8 ± 8.2	72.6 ± 9.2	0.177
LVDs (mm)	29.6 ± 5.7	28.3 ± 4.5	0.357
LVDd (mm)	49.2 ± 6.5	48.9 ± 4.7	0.889
LVMI (g/m ²)	86.1 ± 25.4	89.2 ± 17.8	0.622
LAD (mm)	36.2 ± 5.8	39.7 ± 6.5	0.020
E/A	1.0 ± 0.31	1.1 ± 0.54	0.278
E/e'	10.6 ± 4.1	13.0 ± 3.7	0.017
Laboratory data (at 12 m)			
Cr (mg/dl)	0.93 ± 0.96	0.90 ± 0.20	0.911
eGFR (ml/min)	68.8 ± 15.9	62.5 ± 13.2	0.139
BNP (pg/ml)	36.0 ± 38.1	89.2 ± 142.4	0.089
HbA1c (%)	5.8 ± 0.53	6.0 ± 0.65	0.209

Data are expressed as mean ± SD or number (%).

BNP: brain natriuretic peptide, EF: ejection fraction, eGFR: estimated glomerular filtration rate, LAD: left atrial diameter, LVDd: left ventricular diameter diastolic, LVMI: left ventricular mass index, LVDs: left ventricular systolic, PVI: pulmonary vein isolation, SR: sinus rhythm, LR: late recurrence, RFCA: radiofrequency catheter ablation

Predictors of LR

After adjustment for age, left atrial size at baseline and 12 months after RFCA, and history of non-paroxysmal AF, Cox proportional hazards analysis revealed that E/e' ratio at 12 months (HR, 4.44; 95% CI, 1.269 – 15.53; *p* = 0.020) and use of AADs after RFCA (HR 2.81; 95% CI, 1.079 – 7.299; *p* = 0.034) were significant independent predictors of LR (Table 3).

Discussion

LV diastolic dysfunction and AF recurrence

LAD was significantly improved at 1 year after successful RFCA for AF, although LAD before or after RFCA was not associated with LR. In addition, E/e' ratio at 12 months and use of AADs after RFCA were significantly associated with LR. In particular, an E/e' ratio >10 was significantly positively associated with LR.

An increase in LV diastolic dysfunction worsens LA afterload and LA function. LV diastolic dysfunction might increase LA stiffness and induce LA dilatation.^{12,13} AF alone can lead to worsening of LV diastolic function, which results in atrial stretch and LA enlargement.

E/e' ratio was reported to have the highest predictive accuracy for some echocardiographic parameters of LV diastolic function and LA pressure. The present receiver-

operating-characteristic curve analysis of E/e' ratio and LR showed a E/e' ratio cut-off value of 10.4. Therefore, increased E/e' ratio was defined as an E/e' ratio >10 in the present study. An E/e' ratio of <10 was considered normal for LV diastolic function in past studies.^{9,14-16}

Some studies reported that LV diastolic dysfunction did not predict long-term outcomes of RFCA in AF patients. Further, E/e' ratio was associated with long-term recurrence in the present and past studies.^{8,13,17} Machino et al. found that LA stiffness index, which is related to LV diastolic function, predicts AF recurrence.¹³ In addition, LV diastolic function was improved by successful RFCA and decreased atrial stretch.^{18,19}

The present study analyzed data from patients who maintained SR for at least 1 year after RFCA. E/e' ratio was evaluated in these patients at 3 and 12 months after RFCA, because E/e' ratio strongly correlates with LV diastolic pressure and function during SR. At the baseline echocardiographic assessment, some patients had an AF rhythm; thus, baseline E/e' ratio could not be used to estimate LV diastolic dysfunction and was evaluated at 3 and 12 months. Fig. 1 shows that change in E/e' ratio had no significant effect and that significantly more patients in the LR group had a high E/e' ratio at 3 months after RFCA. In addition, LAD significantly decreased after

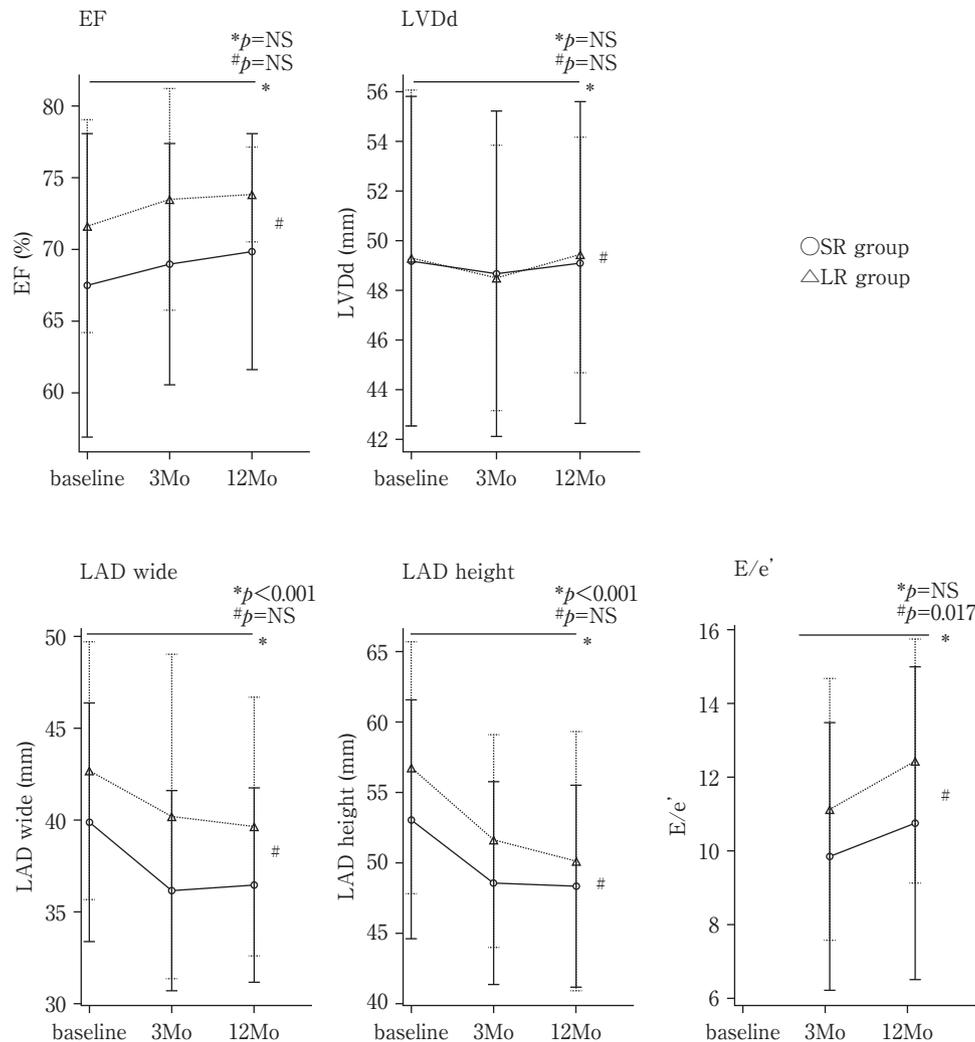


Fig. 1 Change in Echocardiographic Parameters: EF, LVDD, LAD wide, LAD height and E/e' EF significantly improved only in the SR group, but LAD significantly decreased in both groups. E/e' ratio tended to increase, but the change was not significant (NS). Statistical significance was analyzed by one-way repeated-measures ANOVA.

EF: ejection fraction, LVDD: left ventricular diameter diastolic, Mo: months, SR: sinus rhythm, LR: late recurrence, LAD: left atrial diameter

RFCA, possibly because SR maintenance reversed remodeling.

At 1 year after successful RFCA for AF, LAD was significantly improved, although LAD before and after RFCA were not associated with LR. BNP and LAD at 12 months of follow-up tended to be higher in patients with LR than in those with SR. These variables were also associated with LV diastolic dysfunction. However, Cox proportional hazards analysis showed that, regardless of improvement in LAD, E/e' ratio at 1 year after RFCA was the only variable associated with LR.

Mechanism of LR after RFCA

European Society of Cardiology guidelines and data from previous studies indicate that the mechanisms of AF recurrence are reconnections of the PVI and firing from non-PV foci that are not ablated during RFCA.^{6, 20-23} Further, studies reported that detection of AF recurrence is limited by monitoring intensity. Our study included asymptomatic AF patients, and it was therefore difficult to detect AF recurrence in all cases. However, all the present electrocardiographic parameters were assessed more frequently than in previous studies. The 24-hr Holter ECG were obtained at 2 weeks, then monthly for 4–6 months,

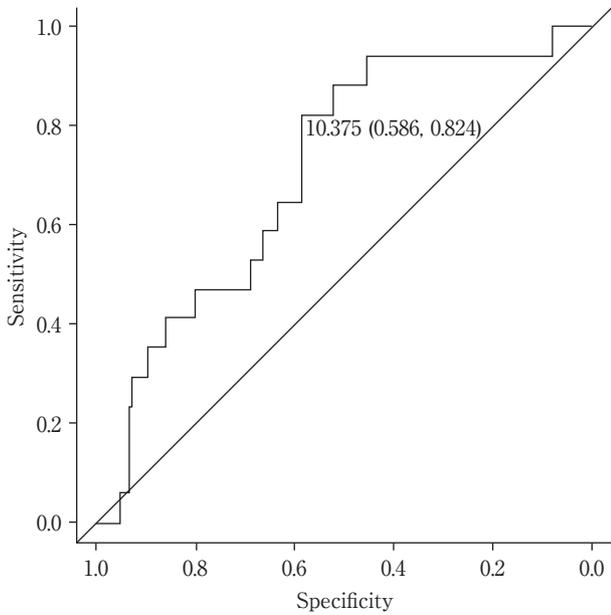


Fig. 2 Receiver-operating-characteristic curves for E/e' ratio and Late Recurrence
 A receiver-operating-characteristic curve comparing E/e' and LR shows a cut-off value of 10.4 (area under the curve, 0.71; 95% confidence interval, 0.588–0.827) for E/e' ratio.

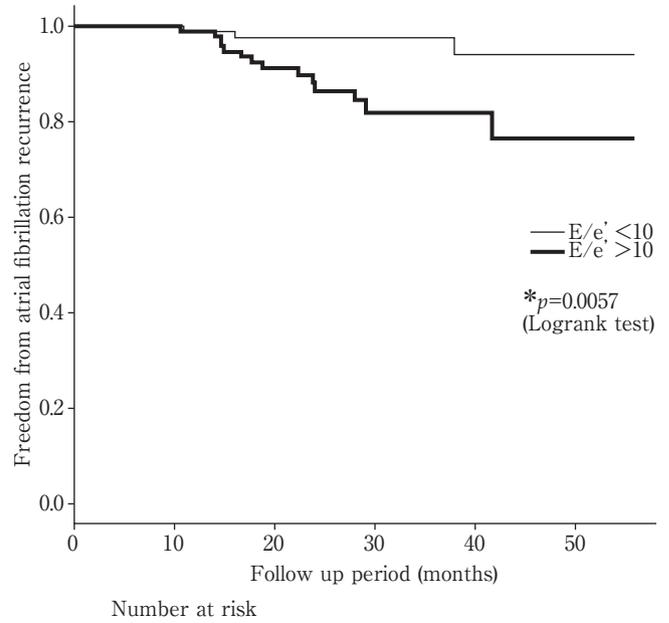


Fig. 3 Kaplan-Meier curves for late recurrence
 Rates of freedom from atrial fibrillation recurrence among patients with an E/e' ratio greater than and less than 10. The bold line represents an E/e' > 10. The normal line represents an E/e' < 10.

	0	10	20	30	40	50
E/e' < 10	99	99	71	46	20	7
E/e' > 10	99	99	72	33	17	5

Table 3 Predictors of late recurrence in univariate and multivariate Cox proportional hazards analysis

N = 198	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
E/e' > 10 (12Mo)	4.91 (1.407–17.07)	0.013	4.44 (1.269–15.53)	0.020
AADs after RFCA	3.20 (1.232–8.283)	0.017	2.81 (1.079–7.299)	0.034
Age > 65	1.45 (0.551–3.808)	0.453	1.32 (0.473–3.660)	0.599
Non-PV foci	2.16 (0.822–5.685)	0.118	2.06 (0.750–5.643)	0.161
Non-PAF	1.47 (0.555–3.868)	0.441	0.40 (0.111–1.466)	0.168
LAD > 45 (baseline)	2.00 (0.702–5.703)	0.195	0.87 (0.233–3.237)	0.833
LAD > 45 (12 Mo)	2.88 (0.938–8.856)	0.065	2.46 (0.719–8.407)	0.151

AADs: anti-arrhythmic drugs, CI: confidential intervals, HR: hazard ratio, LAD: left atrial diameter, PAF: paroxysmal atrial fibrillation, PV: pulmonary vein

and again at 12 months. After 12 months, all ECG variables were checked once or twice a year – more frequently in non-PAF patients.

In the present study, 12 of 17 (70.6%) LR patients underwent re-do RFCA. PV recurrence was detected in 8 (66.7%) patients, and non-PV foci were detected in 9 (75.0%). AF recurrence due to PV recurrence only was noted in 3 (25.0%) patients. This suggests that an increase

in LV diastolic dysfunction may induce an AF substrate, which causes a non-PV foci to develop. We investigated non-PV foci, in particular with the use of incremental isoproterenol infusion before and after PVI during the first and re-do RFCA. However, the mechanism of AF recurrences was detectable in only 70.6% of patients. Recurrence was believed to be due to PV reconnections only. Furthermore, we considered the effects of AAD use after

RFCA, because AAD use might have masked AF recurrence.

Predictors of LRs

Many predictors of AF recurrence have been reported. Clinical factors such as non-paroxysmal AF and longstanding persistent AF, obesity, increased left atrial size, advanced age, and renal dysfunction were found to predict poor outcomes.^{6,24)} Although our study investigated these predictors, the Cox proportional hazards model revealed that only E/e' ratio at 12 months and use of AADs after RFCA were significantly associated with LR.

Non-paroxysmal AF and non-PV foci are believed to be significant factors in AF recurrence. However, neither predicted LR in this study, because patients with these conditions might develop AF recurrence within 1 year after RFCA. Kaplan-Meier curves for freedom from AF recurrence were constructed for all 338 patients who underwent RFCA and showed that non-paroxysmal AF and non-PV foci were significantly associated with increased AF recurrence within 1 year after RFCA (log-rank test, $p < 0.01$). However, use of AADs after RFCA might have prevented AF recurrence within 1 year of RFCA. After RFCA, patients with persistent AF or AF originating from non-PV foci were prescribed AADs, although we reduced or stopped AAD treatment in patients with sustained SR during long-term follow-up. Therefore, use of AADs after RFCA was significantly associated with LR. This and previous studies showed that use of AADs after RFCA masked AF recurrence in patients who ultimately developed LR.²⁵⁻²⁷⁾

Study limitations

This was a retrospective observational study at a single center and thus had some limitations. First, some reports and guidelines recommend that AF patients should be classified as having paroxysmal or non-paroxysmal AF. We thus attempted to assess and follow paroxysmal and non-paroxysmal AF patients separately. Additionally, after adjusting for AF type, Cox proportional hazards analysis revealed that non-paroxysmal AF was not associated with LR. Second, only a small number of patients developed LR, which might have resulted in statistical bias. Further, we were able to detect the mechanisms of LR in only 70% of cases. We also considered the effects of AADs after RFCA, because use of AADs might mask AF recurrence. Third, data on E/e' ratio before RFCA were not available; therefore, serial change in E/e' ratio could not be studied. If patients had rapid and irregular AF before or after

RFCA, E/e' ratio could not be used as an assessment index. Therefore, we could not analyze change in E/e' ratio among patients who developed AF recurrence within 1 year.

Conclusions

LAD improved after successful RFCA but was not associated with LR. E/e' ratio on echocardiography 1 year after RFCA was significantly associated with LR. An E/e' ratio > 10 appears to be a useful cut-off for predicting LR, regardless of AF type.

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References

- 1) Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med.* 1998; 339: 659-66.
- 2) Haïssaguerre M, Shah DC, Jaïs P, Hocini M, Yamane T, Deisenhofer I, et al. Electrophysiological breakthroughs from the left atrium to the pulmonary veins. *Circulation.* 2000; 102: 2463-5.
- 3) Takahashi A, Iesaka Y, Takahashi Y, Takahashi R, Kobayashi K, Takagi K, et al. Electrical connections between pulmonary veins: implication for ostial ablation of pulmonary veins in patients with paroxysmal atrial fibrillation. *Circulation.* 2002; 105: 2998-3003.
- 4) Zhuang J, Wang Y, Tang K, Li X, Peng W, Liang C, et al. Association between left atrial size and atrial fibrillation recurrence after single circumferential pulmonary vein isolation: a systematic review and meta-analysis of observational studies. *Europace.* 2012; 14: 638-45.
- 5) Lee SH, Tai CT, Hsieh MH, Tsai CF, Lin YK, Tsao HM, et al. Predictors of early and late recurrence of atrial fibrillation after catheter ablation of paroxysmal atrial fibrillation. *J Interv Card Electrophysiol.* 2004; 10: 221-6.
- 6) Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al; Heart Rhythm Society Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered

- branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. *Heart Rhythm*. 2012; 9: 632-96.e21.
- 7) Wokhlu A, Hodge DO, Monahan KH, Asirvatham SJ, Friedman PA, Munger TM, et al. Long-term outcome of atrial fibrillation ablation: impact and predictors of very late recurrence. *J Cardiovasc Electrophysiol*. 2010; 21: 1071-8.
 - 8) Kosiuk J, Breithardt OA, Bode K, Kornej J, Arya A, Piorkowski C, et al. The predictive value of echocardiographic parameters associated with left ventricular diastolic dysfunction on short- and long-term outcomes of catheter ablation of atrial fibrillation. *Europace*. 2014; 16: 1168-74.
 - 9) Nagueh SF, Mikati I, Kopelen HA, Middleton KJ, Quiñones MA, Zoghbi WA. Doppler estimation of left ventricular filling pressure in sinus tachycardia. A new application of tissue doppler imaging. *Circulation*. 1998; 98: 1644-50.
 - 10) Hussein AA, Saliba WI, Martin DO, Bhargava M, Sherman M, Magnelli-Reyes C, et al. Natural history and long-term outcomes of ablated atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2011; 4: 271-8.
 - 11) Kanda Y. Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant*. 2013; 48: 452-8.
 - 12) Kim IS, Kim TH, Shim CY, Mun HS, Uhm JS, Joung B, et al. The ratio of early transmitral flow velocity (E) to early mitral annular velocity (Em) predicts improvement in left ventricular systolic and diastolic function 1 year after catheter ablation for atrial fibrillation. *Europace*. 2015; 17: 1051-8.
 - 13) Machino-Ohtsuka T, Seo Y, Tada H, Ishizu T, Machino T, Yamasaki H, et al. Left atrial stiffness relates to left ventricular diastolic dysfunction and recurrence after pulmonary vein isolation for atrial fibrillation. *J Cardiovasc Electrophysiol*. 2011; 22: 999-1006.
 - 14) Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. *Circulation*. 2000; 102: 1788-94.
 - 15) Cha YM, Wokhlu A, Asirvatham SJ, Shen WK, Friedman PA, Munger TM, et al. Success of ablation for atrial fibrillation in isolated left ventricular diastolic dysfunction: a comparison to systolic dysfunction and normal ventricular function. *Circ Arrhythm Electrophysiol*. 2011; 4: 724-32.
 - 16) Kurt M, Wang J, Torre-Amione G, Nagueh SF. Left atrial function in diastolic heart failure. *Circ Cardiovasc Imaging*. 2009; 2: 10-5.
 - 17) Okamatsu H, Ohara T, Kanzaki H, Nakajima I, Miyamoto K, Okamura H, et al. Impact of left ventricular diastolic dysfunction on outcome of catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy. *Circ J*. 2015; 79: 419-24.
 - 18) Nalliah C, Lim TW, Bhaskaran A, Kizana E, Kovoor P, Thomas L, et al. Posterior left atrial isolation for atrial fibrillation in left ventricular diastolic impairment is associated with better arrhythmia free survival. *Int J Cardiol*. 2015; 184: 674-9.
 - 19) Reant P, Lafitte S, Jaïs P, Serri K, Weerasooriya R, Hocini M, et al. Reverse remodeling of the left cardiac chambers after catheter ablation after 1 year in a series of patients with isolated atrial fibrillation. *Circulation*. 2005; 112: 2896-903.
 - 20) Miyazaki S, Taniguchi H, Nakamura H, Takagi T, Iwasawa J, Hachiya H, et al. Clinical significance of early recurrence after pulmonary vein antrum isolation in paroxysmal atrial fibrillation—insight into the mechanism. *Circ J*. 2015; 79: 2353-9.
 - 21) Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. *Circulation*. 2010; 122: 2368-77.
 - 22) Tzou WS, Marchlinski FE, Zado ES, Lin D, Dixit S, Callans DJ, et al. Long-term outcome after successful catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2010; 3: 237-42.
 - 23) Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? *J Am Coll Cardiol*. 2011; 57: 160-6.
 - 24) Li M, Liu T, Luo D, Li G. Systematic review and meta-analysis of chronic kidney disease as predictor of atrial fibrillation recurrence following catheter ablation. *Cardiol J*. 2014; 21: 89-95.
 - 25) Turco P, De Simone A, La Rocca V, Iuliano A, Capuano V, Astarita C, et al. Antiarrhythmic drug therapy after radiofrequency catheter ablation in patients with atrial fibrillation. *Pacing Clin Electrophysiol*. 2007; 30 Suppl 1: S112-5.
 - 26) Leong-Sit P, Roux JF, Zado E, Callans DJ, Garcia F, Lin D, et al. Antiarrhythmics after ablation of atrial fibrillation (5A Study): six-month follow-up study. *Circ Arrhythm Electrophysiol*. 2011; 4: 11-4.
 - 27) Pokushalov E, Romanov A, De Melis M, Artyomenko S, Baranova V, Losik D, et al. Progression of atrial fibrillation after a failed initial ablation procedure in patients with paroxysmal atrial fibrillation: a randomized comparison of drug therapy versus reablation. *Circ Arrhythm Electrophysiol*. 2013; 6: 754-60.