

Incremental Value of Left Atrial Geometric Remodeling in Predicting Late Atrial Fibrillation Recurrence After Pulmonary Vein Isolation: A Cardiovascular Magnetic Resonance Study

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Background—Left atrial (LA) enlargement is a marker for increased risk of atrial fibrillation (AF). However, LA remodeling is a complex process that is poorly understood, and LA geometric remodeling may also be associated with the development of AF. We sought to determine whether LA spherical remodeling or its temporal change predict late AF recurrence after pulmonary vein isolation (PVI).

Methods and Results—Two hundred twenty-seven consecutive patients scheduled for their first PVI for paroxysmal or persistent AF who underwent cardiovascular magnetic resonance before and within 6 months after PVI were retrospectively identified. The LA sphericity index was computed as the ratio of the measured LA maximum volume to the volume of a sphere with maximum LA length diameter. During mean follow-up of 25 months, 88 patients (39%) experienced late recurrence of AF. Multivariable Cox regression analyses identified an increased pre-PVI LA sphericity index as an independent predictor of late AF recurrence (hazard ratio, 1.32; 95% confidence interval, 1.07–1.62, $P=0.009$). Patients in the highest LA sphericity index tertile were at highest risk of late recurrence (highest versus lowest: 59% versus 28%; $P<0.001$). The integration of the LA sphericity index to the LA minimum volume index and passive emptying fraction provided important incremental prognostic information for predicting late AF recurrence post PVI (categorical net reclassification improvement, 0.43; 95% confidence interval, 0.16–0.69, $P=0.001$).

Conclusions—The assessment of pre-PVI LA geometric remodeling provides incremental prognostic information regarding late AF recurrence and may be useful to identify those for whom PVI has reduced success or for whom more aggressive ablation or medications may be useful. (*J Am Heart Assoc.* 2018;7:e009793. DOI: 10.1161/JAHA.118.009793.)

Key Words: atrial fibrillation • cardiovascular magnetic resonance • late recurrence • left atrial sphericity index • left atrial volume • pulmonary vein isolation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and has a significant impact on heart failure, thromboembolism, and mortality.^{1–3} Among patients with AF, the distress caused by symptom onset can be severe and result in a major reduction in quality of life.^{4,5} Pulmonary vein isolation (PVI) is an established therapy for symptomatic AF patients and provides symptom improvement and a better quality of life,⁶ but recurrence of AF following PVI remains

relatively high.⁷ Currently, several risk factors of AF recurrence have been identified, including hypertension,⁸ complex valvular disease,⁹ older age, persistent AF,¹⁰ long-standing persistent AF,^{9–11} left atrial (LA) size,^{12–14} untreated obstructive sleep apnea,¹⁵ and increasing plasma B-type natriuretic peptide level.¹⁶ However, the associations are generally weak and are not routinely incorporated to guide decision making regarding the decision to perform PVI and/or the use of post-PVI antiarrhythmic drugs. Thus, further identification of predictive tools for AF recurrence is an unmet clinical need.

Several investigators have reported that LA geometry has an important role in assessing AF incidence and recurrence using various cardiac imaging modalities.^{17–20} However, LA geometry is not part of the standard assessment of AF recurrence. Noninvasive cine cardiovascular magnetic resonance (CMR) is accurate, reproducible, and is widely considered the noninvasive gold standard for morphologic and functional assessment of the heart. Accordingly, the purpose of this study was to evaluate whether CMR LA geometry parameters or their temporal change after PVI provides

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Received May 15, 2018; accepted August 10, 2018.

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Clinical Perspective

What Is New?

- Pre-PVI LA geometric parameter is strongly associated with recurrent AF after the first PVI procedure after adjusting for LA volume index and the established clinical predictor.
- The integration of LA sphericity index to the LA minimum volume index and passive emptying fraction provides additional prognostic information regarding recurrent AF.

What Are the Clinical Implications?

- A cine cardiovascular magnetic resonance –derived LA sphericity index can be derived without the cost of additional scan time or the need for gadolinium contrast.
- Prospective, large multicenter studies are necessary to examine this easily obtained LA geometric parameter in the selection of patients receiving multiple PVI procedures and aggressive medical therapy.

additive predictive value for late recurrence of AF in patients undergoing their first PVI.

Methods

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

We queried the Beth Israel Deaconess Medical Center clinical CMR database and identified 238 consecutive patients who had undergone their first PVI for paroxysmal or persistent AF and had a comprehensive CMR study before and within 6 months after their PVI. We investigated late recurrence of AF over a 12-month follow-up period following their PVI. Eleven patients were excluded because of early (<90 days) AF recurrence with redo ablation or cardioversion (n=4) or missing follow-up data (n=7), leaving 227 patients for the final analysis. Patient demographics and clinical follow-up records from the hospital electronic medical records were reviewed, and no patients with valvular disease requiring surgery were included. Paroxysmal AF was defined as AF that spontaneously terminates within 7 days. Persistent AF was defined as AF that is sustained beyond 7 days or that lasts <7 days but necessitates pharmacologic or electrical cardioversion. Long-standing persistent AF was defined as AF of >1 year in duration in which cardioversion has either failed or not been attempted. The study was carried out with Beth Israel Deaconess Medical Center Institutional Review Board approval which waived a written informed consent.

Image Acquisition

All CMR images were acquired with a 1.5 Tesla CMR scanner (Achieva, Philips Medical Systems, Best, The Netherlands) equipped with a 5-element or 32-element cardiac-surface coil. To assess left ventricular (LV)/right ventricular myocardial function, geometry, and mass, 10 to 12 short-axis stack images and a 4-chamber long axis image were acquired using a cine steady-state free precession sequence (TR=3.1 ms, TE=1.5 ms, slice thickness=8 mm, gap=2 mm, in-plane spatial resolution=2×2 mm, 30 ms temporal resolution).²¹

Image Analysis

CMR images were analyzed by a blinded investigator using commercial workstations (Extend MR WorkSpace, version 2.3.6.3, Philips Healthcare; OsiriX environment, Pixmeo, Geneva, Switzerland). At end diastole and end systole, epi- and endocardial LV borders were manually traced in contiguous short-axis cine images covering the apex to mitral valve plane to calculate end-diastolic volume and end-systolic volume, stroke volume, and ejection fraction. LV mass was calculated as the sum of the myocardial volume multiplied by the specific gravity (1.05 g/mL) of myocardial tissue. For LA analysis, all parameters were measured at end diastole using the frame immediately before the opening of the mitral leaflets. LA maximum volume was measured using the area-length method with atrial length (from the back wall to the line across the hinge points of the mitral valve) and border excluding the atrial appendage and pulmonary veins in the 2- and 4-chamber views with the following formula: LA maximum volume=(4ch-LA area)×(2ch-LA area)×0.848/[(4ch-LA length+2ch-LA length]/2).²² Sphericity index was calculated as the ratio of LA maximum volume to the volume of a sphere with maximum LA length diameter among atrial length and transverse length (perpendicular to the atrial length) from the 2- and 4-chamber image (Figure 1). Volumetric and geometric reverse remodeling were defined as the change in LA maximum volume and sphericity index at the CMR follow-up, respectively. In the subgroup analysis of 147 patients with sinus rhythm at the time of scan, LA minimum volume and LA total/passive/active emptying fractions were also calculated with the following formula: LA total emptying fraction=(LA maximum volume–LA minimum volume)/LA maximum volume×100, LA passive emptying fraction=(LA maximum volume–LA volume before LA contraction)/LA maximum volume×100, LA active emptying fraction=(LA volume before LA contraction–LA minimum volume)/LA volume before LA contraction×100. In addition, 20 healthy control subjects matched in age and sex (14 men; age, 59 years) were compared to validate the LA sphericity index. To evaluate inter- and intraobserver reproducibility, measurements of the LA sphericity index from a random sample of 10 AF patients

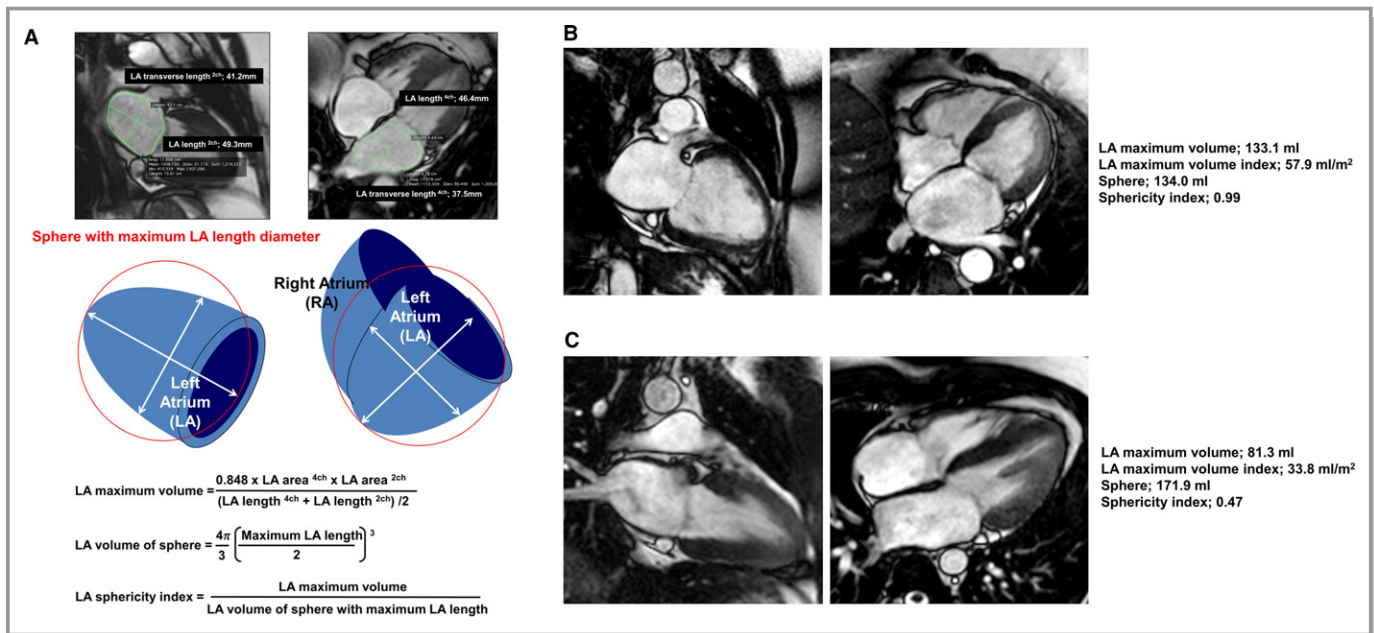


Figure 1. Measurements of LA maximum volume and sphericity index. Left atrial (LA) maximum volume and sphericity index were measured at the LA end-diastole frame immediately before the opening of the mitral leaflets using 2- and 4-chamber cine images. LA maximum volume was measured from the area-length method using atrial length (from the back wall to the line across the hinge points of the mitral valve) and border excluding atrial appendage and pulmonary veins in the 2- and 4-chamber views. The volumetric LA sphericity index was calculated as the ratio of LA maximum volume to the volume of a sphere with maximum LA length diameter among atrial length and transverse length (perpendicular to the atrial length) from the 2- and 4-chamber image. LA length 2ch of 49.3 mm is chosen as the maximum LA length in this case (A). Representative cases with and without increased LA sphericity index (B and C).

were independently assessed by 2 observers, and 1 observer measured LA sphericity index twice on 2 separate days with a washout period of at least 2 weeks.

PVI Protocol

PVI was performed using the recommendation of the Heart Rhythm Society.⁶ Briefly, point-by-point radiofrequency ablation was created to encircle the left and right pulmonary veins and was confirmed by recording within the veins using a circular multipolar catheter to confirm entrance block into the veins. For patients with persistent AF, additional linear LA ablation and/or complex fractionated atrial electrogram ablation were performed, based on operator judgment and preference. If sinus rhythm could not be restored with ablation alone, administration of ibutilide or external direct convert cardioversion was considered to restore sinus rhythm.

Follow-Up

All patients underwent follow-up CMR (51 ± 35 days after PVI) and were followed at clinic visits with 3- to 6-month intervals after PVI. All had resting electrocardiography at all clinical visits. Extended outpatient cardiac monitoring was performed only in patients with symptoms. The primary end point was

late recurrence of AF or atrial flutter lasting >30 seconds defined as occurring >3 months after a PVI blanking period and confirmed by either ECG, cardiac monitoring, or online medical records. Optimal medical therapy was adjusted at the discretion of the clinical physician, who was blinded to CMR findings. However, continuation of antiarrhythmic drugs beyond 3 months after PVI was based on documented AF recurrence or symptoms without any documented arrhythmia.

Statistical Analysis

We computed the power analysis using the comparison of 2 conditional probabilities: the probability of having late recurrence given that the patient belongs to the high level of LA sphericity index category versus the probability of having late recurrence given that the patient belongs to the low LA sphericity index category. We assumed these estimated probabilities to be 50% versus 30%. With type I error of 0.05, and power of 0.80, the required sample size was 190. We accounted for up to 10% attrition rate, which then brought the sample size to 210. Thus, our study sample size of 227 used in this analysis was sufficient to detect the desired effect size. Statistical analyses were performed using SPSS (version 19, IBM Corporation, Armonk, NY) and R (version 3.2.3, R Project for Statistical Computing). Continuous variables are

Table 1. Patients Characteristics

Characteristics	All Patients (n=227)	No AF Recurrence (n=139)	Recurrent AF (n=88)	P Value
Age, y	59±10	57±11	60±9	0.051
Male sex, n (%)	164 (72)	103 (74)	61 (69)	0.43
Race				0.49
White	209 (92)	129 (92)	80 (91)	
Black	11 (5)	6 (4)	5 (6)	
Asian	2 (1)	2 (2)	0	
Unknown/missing	5 (2)	2 (2)	3 (3)	
BMI, kg/m ²	29.4±5.7	29.4±5.4	29.0±6.1	0.63
BSA, m ²	2.11±0.26	2.11±0.27	2.09±0.24	0.57
Blood pressure				
Systolic, mm Hg	146±29	146±30	144±29	0.59
Diastolic, mm Hg	67±12	66±12	67±13	0.52
NYHA >II	172 (76)	101 (73)	71 (81)	0.17
Heart failure (%)	53 (23)	24 (17)	29 (33)	0.006
Hypertension (%)	108 (48)	58 (42)	50 (57)	0.027
Diabetes mellitus (%)	22 (10)	10 (7)	12 (14)	0.11
Dyslipidemia (%)	89 (39)	56 (40)	33 (38)	0.68
Obesity (%)	88 (39)	55 (40)	33 (38)	0.76
Obstructive sleep apnea (%)	31 (14)	21 (15)	10 (11)	0.42
Coronary artery disease (%)	21 (9)	15 (11)	6 (7)	0.31
Prior PCI or CABG (%)	11 (5)	8 (6)	3 (3)	0.42
Valvular heart disease (%)	25 (11)	11 (8)	14 (16)	0.061
eGFR, mL/min per 1.73 m ²	81±19	81±19	80±19	0.67
AF type				0.001
Paroxysmal	192 (85)	126 (91)	66 (75)	
Persistent	35 (15)	13 (9)	22 (25)	
Long-standing persistent	21 (9)	3 (2)	18 (21)	
Medication use, n (%)				
ACEI or ARB	47 (21)	22 (16)	25 (28)	0.023
β-Blocker	92 (41)	48 (35)	44 (50)	0.021
Calcium-channel blocker	46 (20)	20 (14)	26 (30)	0.006
Number of failed antiarrhythmics				0.28
No drugs	129 (57)	75 (54)	54 (61)	
1 drug	91 (40)	58 (42)	33 (38)	

Continued

Table 1. Continued

Characteristics	All Patients (n=227)	No AF Recurrence (n=139)	Recurrent AF (n=88)	P Value
2 drugs	7 (3)	6 (4)	1 (1)	
Statin	57 (25)	34 (25)	23 (26)	0.78
Digoxin	18 (8)	10 (7)	8 (9)	0.61
Diuretics	38 (17)	19 (14)	19 (22)	0.12
Length of follow-up, months	25±20	28±20	21±18	0.009

ACEI indicates; angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blockers; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

expressed as mean±standard deviation or median (quartiles) if not normally distributed, and compared using an unpaired Student *t* test or Mann-Whitney nonparametric test as appropriate. Categorical variables were reported as counts and percentages and compared using a chi-square test. To compare the relationship between the changes of LA parameters and LA parameters at baseline, Spearman correlation analysis was performed. All tests were 2-sided, and *P*<0.05 was considered significant. Kaplan-Meier curves were used to estimate the distribution of time to the first episode of late AF recurrence. Differences between time-to-event curves between the 2 groups were compared with the log-rank test. Univariable Cox regression analysis was used to assess the association between each variable and the primary end point. For multivariable modeling (Model 1), we decided to include 5 of the most significant variables from the univariable models (long-standing AF, hypertension, valvular heart disease, LA maximum volume index, and LA sphericity index) and 2 covariates (age and sex). Using the rule of thumb of having between 5 and 10 outcomes per predictor (we had 88 with AF recurrence), Model 2 was additionally adjusted for coronary artery disease, obstructive sleep apnea, and number of failed antiarrhythmic drugs as established risk factors for AF recurrence. All reported associations in this study are hazard ratios and their corresponding 95% confidence intervals (CIs). For purposes of clinical applicability, we determined the cutoff value of the LA sphericity index by the area under the receiver operating characteristic curve analysis and assessed the additive value of LA sphericity in predicting AF recurrence 1 year after PVI in the subgroup analysis of 147 patients with sinus rhythm at scan time. A 2-fold cross-validation approach was used to calculate the cross-validated C-statistic and assess the stability of this parameter estimates. Reclassification of patients was determined using net reclassification improvement analysis for recurrent AF and obtained by adding

Table 2. CMR Parameters of the Study Population

Characteristics	No AF Recurrence (n=139)	Recurrent AF (n=88)	P Value (Recurrence vs No Recurrence)
AF at CMR scan, n (%)			
Baseline	47 (34)	33 (38)	0.57
Follow-up	0*	13 (15)*	0.04
LV EDV, mL			
Baseline	168±51	168±44	0.93
Follow-up	169±41	168±40	0.86
LV EDV index, mL/m ²			
Baseline	78±17	80±19	0.45
Follow-up	80±14	80±15	0.71
LV ESV, mL			
Baseline	69±27	71±32	0.60
Follow-up	69±23	69±26	0.92
LV stroke volume, mL			
Baseline	97±28	96±22	0.82
Follow-up	100±23	99±22	0.69
LV ejection fraction, %			
Baseline	59±9	59±9	0.80
Follow-up	60±7	59±8	0.74
LV mass index, g/m ²			
Baseline	53±12	53±14	0.74
Follow-up	52±12	54±13	0.37
LV mass/LV EDV, g/mL			
Baseline	0.69±0.17	0.68±0.16	0.68
Follow-up	0.66±0.15 [†]	0.67±0.15	0.51
RV EDV, mL			
Baseline	171±45	169±40	0.73
Follow-up	167±40	165±36	0.77
RV EDV index, mL/m ²			
Baseline	81±18	81±18	0.95
Follow-up	79±15	79±15	0.92
RV ESV, mL			
Baseline	78±26	77±26	0.62
Follow-up	75±33	71±23 [†]	0.40
RV stroke volume, mL			
Baseline	93±25	93±20	0.97
Follow-up	91±34	93±23	0.61

Continued

the LA sphericity index to the clinical model (Model 2), and the LA minimum volume index and passive emptying fraction. Because no conventional cutoff values exist for late AF recurrence, risk categories were used to stratify patients into

Table 2. Continued

Characteristics	No AF Recurrence (n=139)	Recurrent AF (n=88)	P Value (Recurrence vs No Recurrence)
RV ejection fraction, %			
Baseline	55±7	55±7	0.53
Follow-up	57±6*	57±7 [†]	0.89
LA maximum volume, mL			
Baseline	100±30	118±36	<0.001
Follow-up	92±29*	111±37*	<0.001
LA maximum volume index, mL/m ²			
Baseline	47±13	57±17	<0.001
Follow-up	44±13*	53±17*	<0.001
LA sphericity index			
Baseline	0.79±0.11	0.84±0.10	<0.001
Follow-up	0.76±0.10*	0.81±0.09 [†]	<0.001

Variables given are mean± standard deviation or N (%). A P value is calculated using either the t test for continuous variables or chi-squared test for categorical data. AF indicates atrial fibrillation; CMR, cardiovascular magnetic resonance; EDV, end-diastolic volume; ESV, end-systolic volume; LA, left atrial; LV, left ventricular; RV, right ventricular. *P<0.01 vs baseline. [†]P<0.05 vs baseline.

low-risk (0% to <10%), low-intermediate-risk (10% to <30%) and high-intermediate-risk (30% to <50%) categories. Categorical net reclassification improvement was computed together with integrated discrimination improvement. Intra- and interobserver reliability of LA sphericity index measurements were assessed with the intraclass correlation coefficient.

Results

Patient Population

Table 1 summarizes the baseline patient characteristics of the study population. During the mean follow-up of 25 months, 88 patients (39%) experienced recurrent AF. Patients with recurrent AF were older (P=0.05) and more likely to have history of heart failure (P=0.006) and hypertension (P=0.03), with a trend for diabetes mellitus (P=0.11) and valvular heart disease (P=0.06). There was no significant difference regarding sex, race, body mass index, history of dyslipidemia, obstructive sleep apnea, and coronary artery disease. Eighteen of 21 (86%) patients with long-standing persistent AF had recurrent AF (P=0.001). There was higher usage of angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, β-blockers, and calcium-channel blockers in patients with recurrent AF (P=0.02, 0.02, and 0.006, respectively).

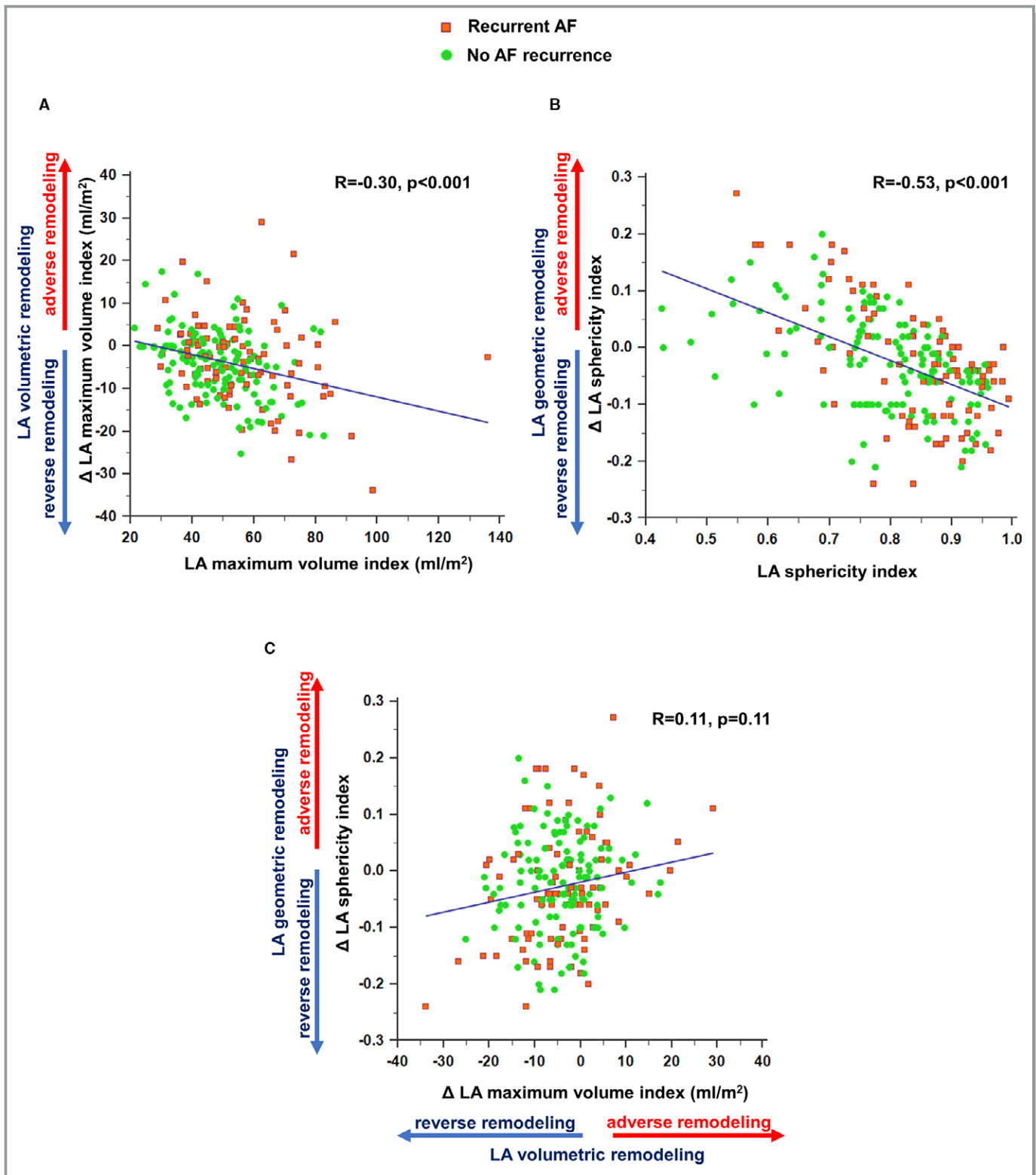


Figure 2. Correlation between LA volumetric/geometric remodeling and LA parameters at baseline. A, Changes in LA volume after PVI are mildly negatively correlated with LA volume at baseline ($r=-0.30$; $P<0.001$). B, Similar to LA volumetric changes, there was a moderate and negative association between changes in the LA sphericity index after PVI and the LA sphericity index at baseline ($r=-0.53$; $P<0.001$). C, Change of LA volume and sphericity index showed no correlation ($r=0.11$; $P=0.11$). AF indicates atrial fibrillation; LA, left atrial; PVI, pulmonary vein isolation.

Table 3. Univariable and Multivariable Analysis for the Association With Recurrent AF

Characteristics	Univariable			Multivariable (Model 1)			Multivariable (Model 2)		
	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value
Age, y	1.02	0.99 to 1.04	0.16	1.00	0.98 to 1.03	0.84	1.01	0.98 to 1.03	0.74
Male	0.77	0.49 to 1.22	0.27	0.79	0.48 to 1.30	0.35	0.82	0.50 to 1.36	0.44
BMI	0.98	0.95 to 1.02	0.37						
Persistent AF	2.29	1.41 to 3.71	0.001						
Long-standing persistent AF	4.00	2.38 to 6.75	<0.001	3.68	2.13 to 6.34	<0.001	3.68	2.13 to 6.34	<0.001
Congestive heart failure	1.16	0.74 to 1.81	0.53						
Hypertension	1.50	0.98 to 2.29	0.06	1.63	1.05 to 2.51	0.028	1.63	1.05 to 2.51	0.028
Diabetes mellitus	1.63	0.88 to 3.00	0.12						
Obstructive sleep apnea	0.81	0.42 to 1.57	0.53				0.75	0.37 to 1.52	0.43
Valvular heart disease	2.01	1.13 to 3.56	0.017	1.98	1.11 to 3.54	0.021	1.98	1.11 to 3.54	0.021
Coronary artery disease	0.54	0.24 to 1.24	0.15				0.57	0.24 to 1.37	0.21
eGFR	1.00	0.99 to 1.01	0.84						
Number of failed antiarrhythmic drugs	0.71	0.43 to 1.15	0.16				1.09	0.72 to 1.64	0.69
Baseline CMR parameters									
LV EDVI	1.00	0.99 to 1.01	0.87						
LV ESV	1.00	0.99 to 1.01	0.79						
LV EF, per 1% decrement	0.99	0.97 to 1.02	0.67						
LV mass/LV EDV, per 0.1 increase	0.97	0.85 to 1.10	0.64						
RV EDVI	1.00	0.99 to 1.01	0.70						
RV ESV	1.00	0.99 to 1.00	0.25						
RV EF, per 1% decrement	0.98	0.96 to 1.01	0.27						
LA maximum volume	1.01	1.00 to 1.01	0.055						
LA maximum volume index	1.02	1.01 to 1.03	0.007	1.01	0.99 to 1.02	0.26	1.01	0.99 to 1.02	0.25
LA sphericity index, per 0.1 increase	1.38	1.13 to 1.69	0.001	1.32	1.07 to 1.62	0.009	1.32	1.07 to 1.62	0.009
Changes of CMR parameters									
Δ LV mass/LV EDV	1.01	0.99 to 1.02	0.39						
Δ RV ESV	1.00	0.99 to 1.00	0.74						
Δ RV EF	0.99	0.98 to 1.01	0.32						
Δ LA maximum volume index	1.02	0.99 to 1.05	0.14						
Δ LA sphericity index, per 0.1 increase	0.95	0.75 to 1.20	0.66						

HR (hazard ratio) refers to the ratio of hazards of the presence of the characteristic to the reference (absence), or to the change of 1 unit (continuous variable). Model 1 included age, sex, long-standing persistent AF, hypertension, valvular heart disease, LA maximum volume index, and LA sphericity index. Model 2 was additionally adjusted for coronary artery disease, obstructive sleep apnea, and number of failed antiarrhythmic drugs. AF indicates atrial fibrillation; BMI, body mass index; CI, confidence interval; CMR, cardiovascular magnetic resonance; EDV, end-diastolic volume; EDVI, end-diastolic volume index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESV, end-systolic volume; LA, left atrial; LV, left ventricular; RV, right ventricular.

Changes in CMR function and geometric parameters are summarized in Table 2. Follow-up CMR scans were performed during the AF rhythm in 13 of 88 (15%) of patients with recurrent AF. In both groups, LA maximum volume, LA maximum volume index, and LA sphericity index were reduced and right ventricular ejection fraction increased at follow-up (nonrecurrent AF group, all $P<0.01$; AF recurrent group, $P<0.01$, $P<0.01$, $P<0.05$, $P<0.05$, respectively). LV mass/LV

end-diastolic volume improved only in the nonrecurrent AF group ($P<0.05$). Figure 2 illustrates the association between LA volumetric/geometric remodeling and LA parameters at baseline. In the whole population, changes in LA maximum volume mildly and negatively correlated with LA maximum volume at baseline ($r=-0.30$; $P<0.001$), with greater reduction in patients with a larger LA maximum volume regardless of AF recurrence. Similar to volumetric changes, there is a

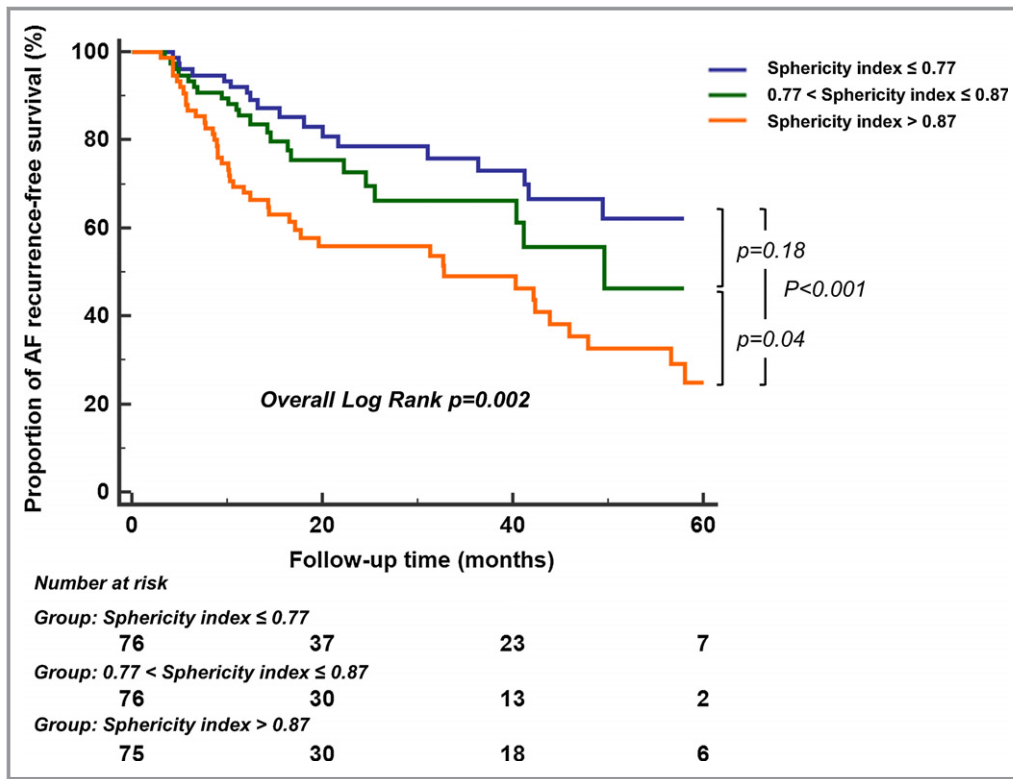


Figure 3. Survival curve for late AF recurrence events after pulmonary vein isolation. Patients with the greatest LA sphericity index (orange line) had the highest recurrence rate during a mean follow-up of 25 months. Selected *P* values for comparisons between 2 groups are also shown. AF indicates atrial fibrillation; LA, left atrial.

moderate and negative association between the change in LA sphericity index and LA sphericity index at baseline ($r=-0.53$, $P<0.001$), indicating greater geometric reverse remodeling in patients with severe adverse geometric remodeling at baseline. However, there was no relationship between change of LA maximum volume and LA sphericity index ($r=0.11$; $P=0.11$).

LA Geometric Parameter and Late Recurrent AF

Univariable and multivariable analyses of clinical and CMR parameters for recurrent AF are summarized in Table 3. In multivariable analysis adjusted for age, sex, long-standing persistent AF, hypertension, valvular heart disease, and LA maximum volume index, increased LA sphericity index was the independent predictor of recurrent AF (hazard ratio, 1.32; 95% CI, 1.07–1.62; $P=0.009$). When additionally adjusted for coronary artery disease, obstructive sleep apnea, and number of failed antiarrhythmic drugs, the LA sphericity index remained significantly associated with recurrent AF. After at least 12 months of follow-up, recurrent AF for patients in the highest LA sphericity index tertile (more spherical remodeling) was 44 of 75 (59%), while only 21 of 76 (28%) for the lowest LA sphericity index tertile. The observed difference in

recurrence rate for patients with a high versus low sphericity index was 31% (59%–28%). In the power analysis, we hypothesized that the expected effect size was at least 20% (50%–30%); therefore, this difference was confirmed in our sample. Kaplan-Meier curves showed the worst recurrence-free survival in patients with an LA sphericity index of >0.87 ($P=0.002$) (Figure 3). The LA sphericity index provided the better risk stratification for recurrent AF beyond the clinical model (Model 2) (categorical net reclassification index, 0.14; 95% CI, 0.02–0.26; $P=0.03$). Although an increased LA maximum volume index was an important predictor of recurrent AF in univariable analysis, LA maximum volume index was no longer significant in multivariable analysis. The LA maximum volume index had a weak correlation with the LA sphericity index ($r=0.30$; $P<0.01$) (Figure 4). However, the test of multicollinearity revealed variance inflation factors of <1.3 for all variables, suggesting that multicollinearity did not affect the analysis.

Incremental Value of LA Sphericity Index

Table 4 summarizes measured LA parameters at baseline in 147 patients with sinus rhythm at scan time. For purposes of clinical applicability, we assessed the additive value of the LA

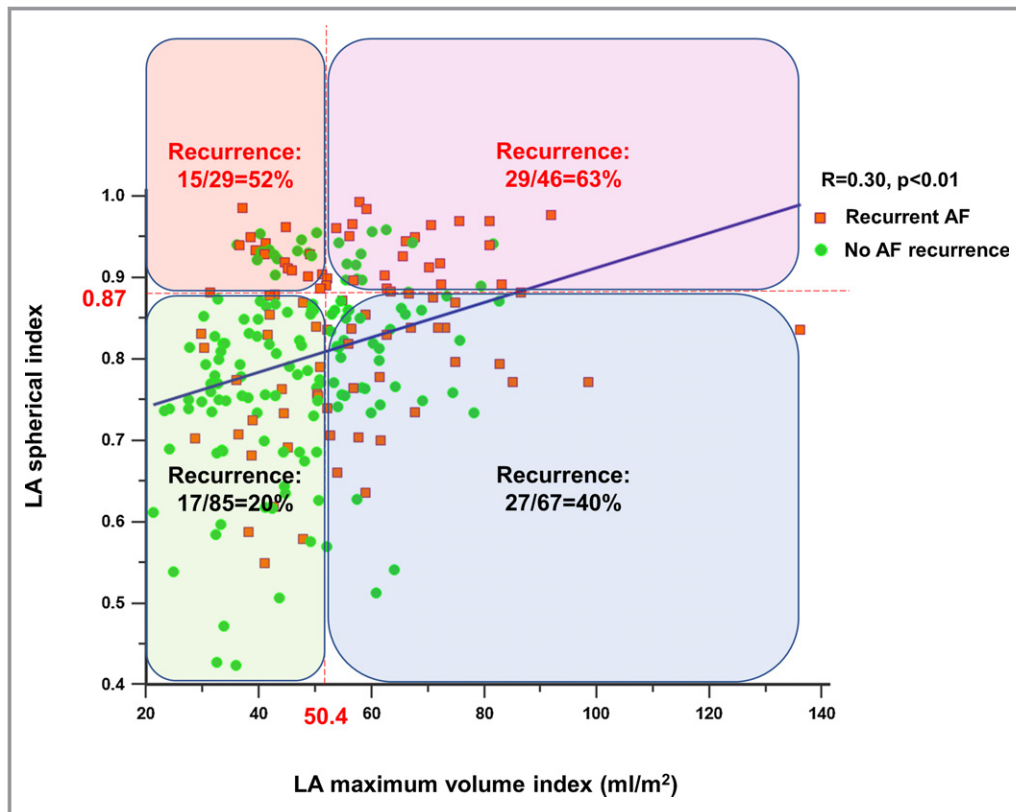


Figure 4. Association of LA sphericity index to LA maximum volume index and schematic for AF recurrence using LA sphericity and LA maximum volume index. There was a weak correlation between the LA sphericity index and the LA maximum volume index. LA maximum volume index >50.4 mL/m² was determined by receiver operating characteristic curve analysis to predict AF recurrence, while a LA sphericity index of 0.87 showed the highest LA sphericity index tertile. The subgroup with smaller LA maximum volume and higher LA sphericity index (left-top) had a higher AF recurrence rate compared with the subgroup with a larger LA maximum volume and lower LA sphericity index (right-bottom) (52% vs 40%). AF indicates atrial fibrillation; LA, left atrial.

sphericity index for predicting recurrent AF 1 year after PVI. The C-statistic of the LA sphericity index for predicting recurrent AF was 0.72 (95% CI, 0.61–0.82), with 88% sensitivity and 59% specificity when using a cutoff value of 0.84 for the LA sphericity index (Table 5). The cross-validated C-statistic was 0.70 (95% CI, 0.56–0.82). When the LA sphericity index was combined with the LA passive emptying fraction and LA minimum volume index, we observed a greater C-statistic than either variable used individually (C-statistic, 0.78 versus 0.69, Delong’s test; $P=0.05$, C-statistic, 0.76 versus 0.69, Delong’s test; $P=0.1$, respectively) (Figure 5A and 5B). Furthermore, integration of the LA sphericity index into the LA minimum volume index and passive emptying fraction provided a better C-statistic for prediction of AF recurrence (C-statistic, 0.80; 95% CI, 0.70–0.89; and C-statistic, 0.73; 95% CI, 0.63–0.84, respectively, Delong’s test; $P=0.07$) (Figure 5C). Combined assessment of the LA sphericity index, minimum volume index, and passive emptying fraction yielded 10 correct (up) reclassifications and 2 incorrect (down) reclassifications in the 25 patients with AF

recurrence. Additionally, 29 correct (down) reclassifications and 16 incorrect (up) reclassifications occurred in the 122 patients without recurrent AF. Overall, the integration of the LA sphericity index provided improvement in risk stratification for predicting recurrent AF 1 year after the first PVI (categorical net reclassification index, 0.43; 95% CI, 0.16–0.69; $P=0.001$).

Validation and Reproducibility of LA Sphericity Index

The LA sphericity index measurement was suitable for analysis in all patients. The mean LA sphericity index in controls was 0.74 ± 0.09 , and no controls had an LA sphericity index of >0.87 . In patients with AF, the mean LA sphericity was 0.81 ± 0.11 , which was significantly higher than that in controls ($P=0.01$). The intraclass correlation coefficients for inter- and intraobserver measurements of the LA sphericity index were 0.93 (95% CI, 0.75–0.98) and 0.96 (95% CI, 0.85–0.99), respectively.

Table 4. Comparison of LA Parameters in Patients With Sinus Rhythm at Scan Time

Characteristics	All Patients (n=147)	No AF Recurrence (n=92)	Recurrent AF (n=55)	P Value
LA maximum volume, mL	104±33	97±29	116±37	<0.001
LA maximum volume index, mL/m ²	51±16	47±12	57±19	<0.001
LA minimum volume, mL	56±19	51±14	65±22	<0.001
LA minimum volume index, mL/m ²	28±9	25±7	32±11	<0.001
LA total emptying fraction, %	46±6	47±6	44±5	0.002
LA passive emptying fraction, %	20±5	21±5	18±5	0.002
LA active emptying fraction, %	32±6	33±7	31±4	0.19
LA sphericity index	0.82±0.11	0.80±0.11	0.86±0.09	<0.001

AF indicates atrial fibrillation; LA, left atrial.

Discussion

In this retrospective study of 227 consecutive patients referred for CMR before and after the first PVI procedure, we demonstrate that (1) cine CMR-derived LA spherical remodeling is the independent predictor of recurrent AF, (2) LA sphericity index >0.87 is associated with a higher risk of recurrent AF, and (3) the integration of the LA sphericity index to the LA minimum volume index and passive emptying fraction provides additional prognostic information regarding recurrent AF. However, a temporal change of the LA sphericity index

Table 5. Comparison of Area Under the ROCs of Measured LA Parameters for Predicting 1-Year AF Recurrence

Characteristics	AUC (95% CI)	P Value
LA maximum volume index	0.67 (0.55–0.78)	0.01
LA minimum volume index	0.69 (0.58–0.80)	0.004
LA total emptying fraction	0.61 (0.50–0.72)	0.08
LA passive emptying fraction	0.70 (0.58–0.81)	0.002
LA active emptying fraction	0.52 (0.42–0.63)	0.75
LA sphericity index	0.72 (0.61–0.82)	0.001

AF indicates atrial fibrillation; AUC, area under the curve; CI, confidence interval; LA, left atrial; ROC, receiver operating characteristic.

before and after PVI showed no incremental performance in predicting late AF recurrence. Our findings are consistent with a recent study by Bisbal et al that PVI leads to spherical reverse remodeling.²³ LA volumetric and geometric remodeling are present before PVI. Therefore, early detection of these changes in individuals at higher risk for late recurrence after PVI has a great clinical impact. More importantly, cine CMR-derived LA sphericity index can be derived without the cost of additional scan time or the need for gadolinium contrast.

Similar to LV spherical remodeling as a trigger for ventricular arrhythmia,^{24,25} LA spherical remodeling can be associated with increased atrial stretch. Chronic atrial stretch is a common etiologic factor in AF,²⁶ and the electrophysiologic sequelae of it include slowing of conduction; prolongation of the effective refractory period, areas of low voltage, and electrical scarring; double potentials and fractionated electrograms; and increased inducibility of AF.^{27–30} Greater understanding of atrial spherical remodeling in addition to size and function helps predict late recurrence of AF, although AF has also been attributed to LA functional and architectural changes, such as focal myocyte hypertrophy and fibrosis. Our study result is consistent with the recent study by Bisbal et al that magnetic resonance angiography-derived LA sphericity is useful for predicting AF recurrence.¹⁷ However, their method requires a 3-dimensional LA reconstruction, which can be time consuming. Gadolinium contrast would also remain a crucial problem, and there is an increasing interest in exploring the clinical utility of alternative noncontrast imaging. The present study demonstrated that cine CMR-derived spherical measurement can be an effective alternative method when taking no additional scan and analysis time and noncontrast material requirement into consideration. The measurement of the LA sphericity index by 2-dimensional cine CMR depends on geometric assumptions. Thus, relatively small measurement errors can lead to some differences in the sphericity index cutoff value between 2-dimensional cine CMR and volumetric reconstruction using MR angiography.

It remains to be clarified whether a reduction in the LA volume occurs only after a successful PVI procedure.^{23,31–35} In accordance with previous studies,^{23,33,35} the results in our current study demonstrated a similar reduction of LA maximum volume in most patients, regardless of the ablation outcome. This is supported by results in both animal and human studies that demonstrate that LA structural remodeling, especially in the earlier stages, could be reversible after using certain medications or PVI.³⁶ Several investigators attempted to provide the best risk stratification to predict recurrent AF. In a recent study by Marrouche et al, atrial tissue fibrosis on late gadolinium enhancement images were assessed.³⁷ We have also previously reported the association between LA fibrosis and AF recurrence.³⁸ However, given the anatomic location of the left atrium, the fibrosis of the thin

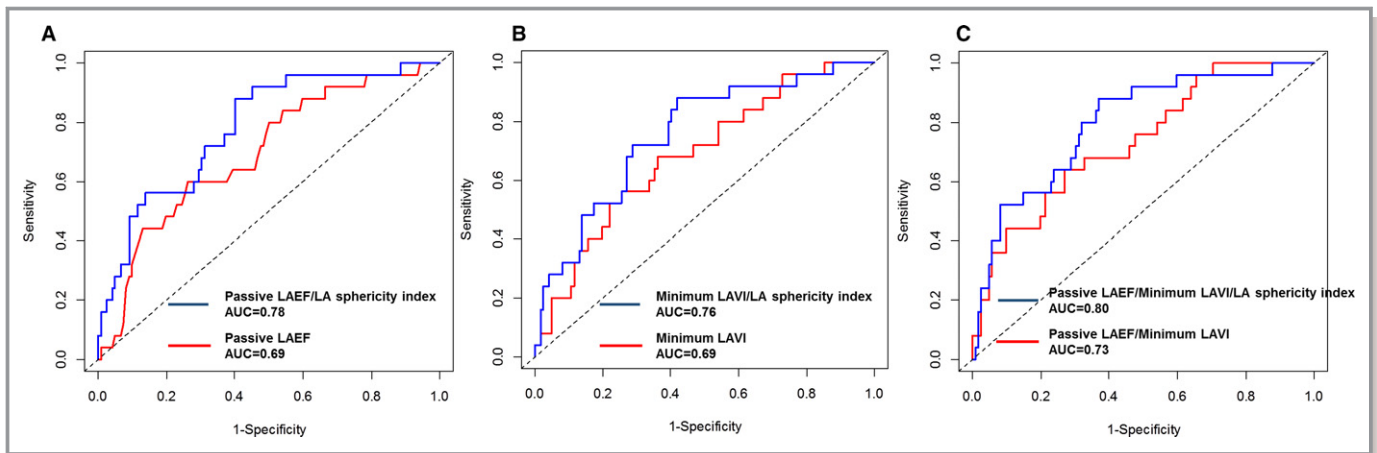


Figure 5. Comparison of the ROC curves for late AF recurrence events. Receiver operating characteristic (ROC) curve and corresponding area under the curve (AUC) describing the incremental value of integration of the left atrial (LA) sphericity index (blue line) and the LA passive emptying fraction (passive LAEF) (red line) (A), LA minimum volume index (minimum LAVI) (red line) (B), and combination of passive LAEF and minimum LAVI (red line) (C) to predict late AF recurrence.

atrial wall can still be challenging in a routine clinical setting. LA function assessment of cine CMR may also be useful for predicting late AF recurrence.^{39–41} However, quantitative function analysis cannot be applicable to patients with AF at the time of the scan. In addition, LA strain assessment by using tissue tracking software is time consuming and might be dependent on image quality. We found that cine CMR volumetric, functional, and geometric quantification of the left atrium provided better risk stratification to predict late AF recurrence beyond both LA minimum volume and passive emptying fraction. The advantage of LA spherical remodeling assessment is that geometric data can easily be derived from 2-dimensional cine images.

Study Limitations

Our study has several limitations. It is a retrospective study with a relatively moderate sample size. We studied patients undergoing PVI spanning a period of 6 years, and medical management might have changed over the course of this follow-up period. Also, the PVI procedure was not standardized and was left to the discretion of the operator. We used the biplane area-length method to measure LA volume. Therefore, the calculated volumes might be an overestimation or an underestimation of the true volumes by 1.4% to 2.5%, depending on the alignment of the acquired slice with true LA orientation.^{42,43} However, the small differences in LA maximum volume may not be of great significance in calculating the LA sphericity index. AF recurrence was identified on the basis of a review of online medical records, which may underestimate AF diagnosis, given that some AF cases are asymptomatic. However, the late AF recurrence rate in the current study was higher compared with the published data.

Conclusion

The cine CMR–derived LA geometric parameter is strongly associated with recurrent AF after the first PVI procedure after adjusting for the LA volume index and the established clinical predictor, and provides additive risk stratification for patients at risk for recurrent AF after PVI. Prospective, large multicenter studies are necessary to examine this easily obtained LA geometric parameter in the selection of patients receiving multiple PVI procedures and aggressive medical therapy.

Acknowledgments

We thank Jennifer Rodriguez for reviewing the manuscript and editorial assistance.

Sources of Funding

Nakamori received a scholarship from Mie University Foundation International. Nezafat received grant support from NIH 1R21HL127650, 1R01HL129185, AHA 15EIA22710040.

Disclosures

None.

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