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ORIGINAL PAPER

Assessment of left atrial remodeling in paroxysmal atrial fibrillation with speckle tracking echocardiography: a study with an electrophysiological mapping system

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Abstract

This study aimed to evaluate left atrial (LA) remodeling and fibrosis in paroxysmal atrial fibrillation (AF) using speckle tracking echocardiography (STE) based on the findings with radiofrequency catheter ablation (RFCA) so as to predict atrial remodeling prior to ablation. A total of 40 patients with paroxysmal AF were enrolled and divided into two groups based on LA bipolar voltage detected during RFCA: those with low-voltage zone (LVZ) (LV group, $n=19$) and those without LVZ (non-LV group, $n=21$). The segmental and global LA reservoir, conduit and contractile strain (εs, εe, εa) were analyzed using two-dimensional STE before RFCA. The segmental and global εs, εe, εa (%) decreased in the LV group. Especially, the εs in anteroseptal upper (18.32 ± 7.94 vs. 31.61 ± 9.39) and lower segments (16.60 ± 7.23 vs. 29.23 ± 9.81), posteroseptal upper (22.24 ± 6.65 vs. 32.23 ± 10.57) and lower segments (18.24 ± 6.49 vs. 26.40 ± 7.12), and the global εs (23.85 ± 6.74 vs. 30.48 ± 8.67) significantly decreased in the LV group than in the non-LV group (all $P<0.05$). The $\varepsilon s\leq24.07$ in the anteroseptal upper segment was an effective parameter to differentiate the LV group (sensitivity, 84%; specificity, 81%, $P<0.001$). Besides, global εs tended to be an independent determinant of the LVZ (odds ratio 1.347, $P=0.046$). STE enables a noninvasive method to evaluate LA remodeling prior ablation.

Keywords Atrial fibrillation · Left atrium · Remodeling · Speckle tracking echocardiography · Strain · Substrate

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias. It is responsible for left atrial (LA) remodeling and affects LA function. Traditional cardioversion drugs with low efficacy and high recurrence make radiofrequency catheter ablation (RFCA), usually circumferential pulmonary vein isolation (CPVI), more suitable for treating AF. However, still a number of patients suffer a recurrence. Under these circumstances, the ablation based on the substrate becomes important and is considered as one of the decisive strategies [1]. The low-voltage zone (LVZ) detected by the CARTO3 system suggests the disordered areas and electrical remodeling in electrophysiology testing. It is also related to LA fibrosis and recurrence of AF. Therefore, predicting LA remodeling and fibrosis before the operation is of great significance. Based on two-dimensional (2D) images with high-frequency imaging, speckle tracking echocardiography (STE) can detect myocardial velocity, strain, and ventricle twist deformation more correctly [2]. Recent studies on STE have also shown the importance of evaluating LA function and predicting recurrence after ablation in patients with AF [3–5]. Most studies focused on LA mechanical function but seldom correlated to the findings with electrophysiological study. This study aimed to investigate the relationship between mechanic remodeling and electrical remodeling so as to evaluate the value of LA fibrosis using STE.

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Methods

Study population

A total of 40 patients with paroxysmal AF (PAF) (aged 18–75 years) at the Department of Cardiology, RenJi Hospital, School of Medicine, Shanghai Jiao Tong University, from May 2015 to June 2016 were enrolled. PAF was defined according to the guidelines of ACC/AHA 2014 on AF: it was defined as AF that terminates spontaneously or with intervention within 7 days of onset [6]. The exclusion criteria included other severe arrhythmias such as atrioventricular block, severe ischemic heart disease, valvular disease and cardiomyopathy, pacemaker implantations, and left ventricular systolic dysfunction (ejection fraction $< 50\%$). Patients with inadequate acoustic windows, especially those with incomplete images of LA, were also excluded. This study was approved by the ethics committee of Jiaotong University.

Echocardiography

Transthoracic echocardiography including 2D, M-mode, pulsed-wave, continuous-wave, color tissue Doppler was performed routinely 1 or 2 days prior to the PVI procedure in the sinus rhythm using the Vivid E9 Echo-system (General Electric Medical Health) equipped with an M4S probe. The atrial thrombus was excluded using transesophageal echocardiography. All images were obtained in the parasternal short- and long-axis views or the apical two-, three-, and four-chamber views according to the American Society of Echocardiography guidelines [7]. Experienced echocardiographers conducted all echocardiographic examinations and analyzed echocardiographic parameters.

Regular echocardiographic parameters included were as follows:

LA maximal volume (LA Vmax): end-systolic LA volume prior to the opening of the mitral valve
LA minimal volume (LA Vmin): end-diastolic LA volume prior to the closing of the mitral valve
Left atrial ejection fraction (LAEF) = (Vmax − Vmin)/Vmax
Left atrial volume index (LAVi) = LA maximal volume/body surface area

Peak early (E-wave) and late (A-wave) diastolic LV filling velocities, E-wave deceleration time, and E/A velocity ratios were determined using standard Doppler imaging. Pulse-waved tissue Doppler imaging was used to measure the mitral annular velocity. A sample volume was placed in the septal and lateral corners of the mitral annulus in the apical four-chamber view, and peak diastolic velocity during early diastolic filling (E′) at the mitral medial annular corner was measured. The ratio of the peak of LV early diastolic filling using Doppler and the velocity of the moving medial mitral annulus using pulse tissue Doppler (E/E′) were calculated for each participant.

LA strain area analysis

Two-dimensional speckle imaging was analyzed using a commercialized software (EchoPAC 13.0; GE Medical Systems), using apical four-, two-, and three-chamber views. Two-dimensional images of a representative cardiac cycle were selected, and the LA endocardial surface was manually traced using a point-and-click approach. An epicardial surface tracing was automatically generated by the system, creating a region of interest (ROI), which was manually adjusted to cover the full thickness of the LA wall. The software divided the ROI into six segments and generated averages of the values and the curves of strain.

According to a previous study [8], for estimating the LA segmental function, each atrial wall was divided into two segments (upper and lower) from apical four-, two-, and three-chamber views. The LA roof segment in each view was excluded in this study due to the discontinuity of the LA wall at the connection to the pulmonary veins (Fig. 1). The LA STE curves were obtained using the R-wave onset of the electrocardiogram as a reference point. The first peak-positive strain (εs), second peak strain (εa) and εe (= εs − εa) were measured as the LA segmental strain from corresponding curves. Each parameter correlates with LA reservoir, contractile and conduit function. The curves of the segmental LA strain are shown in Fig. 2. The global εs, εe, εa were defined as the average of all segmental LA strains.

Electrophysiological study and RFCA

The patients were in a conscious state with a continuous intravenous injection of fentanyl for analgesia. Double transseptal punctures were performed. Then, Decapolar Circular Mapping Catheter (Lasso, Biosense Webster Inc., CA, USA) and ThermoCool SmartTouch Catheter (Biosense Webster Inc.) were placed into the left atrium for mapping and ablation. Bipolar intracardiac electrograms and 12-lead surface electrocardiogram (ECG) were recorded simultaneously on a computerized digital amplifier system (Cardiolab, GE, USA). Bipolar intracardiac electrograms were filtered at the range of 30–500 Hz.

Before performing CPVI, the catheter was manipulated to acquire 200–400 points in the left atrium with a stable sinus rhythm. The points were carefully taken with the optimal contact force range defined as 10–20 g. Bipolar voltage was

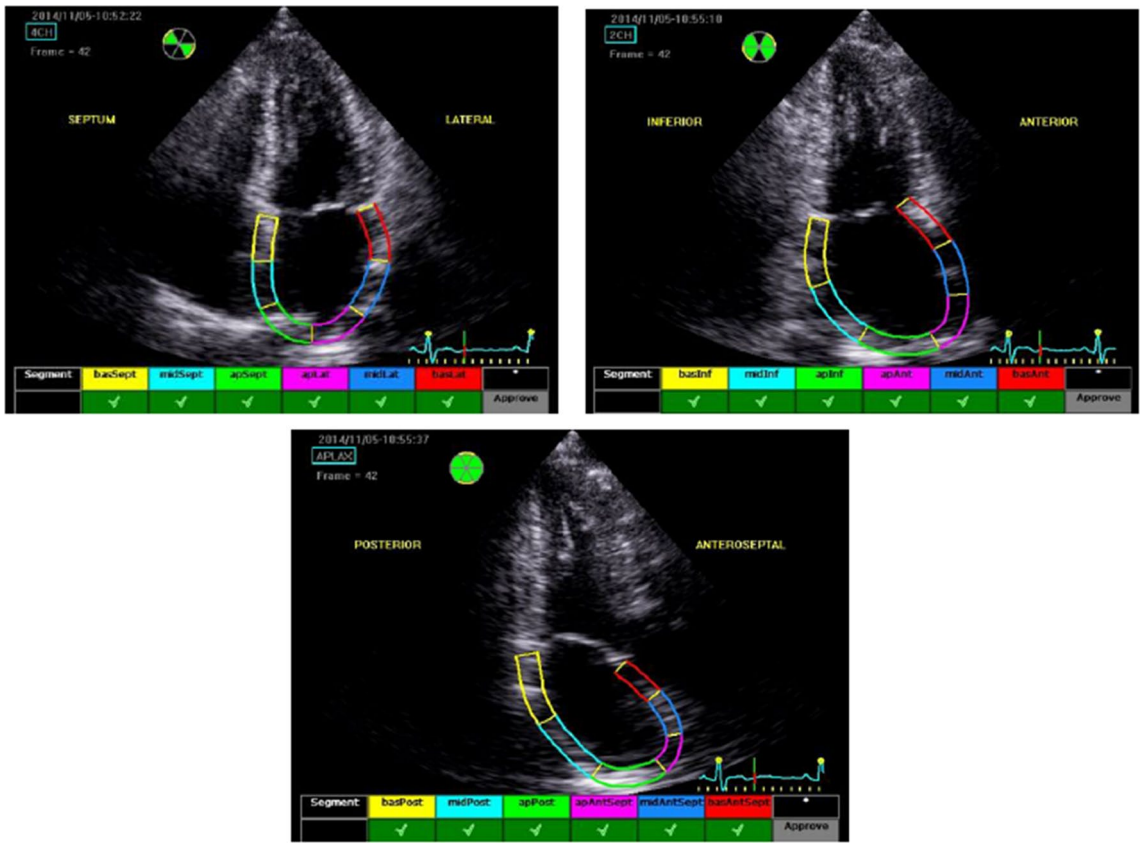

Fig. 1 Four-, two-, and three-chamber views of STE for estimating the LA segmental function. The LA roof segment (green and pink segments) was excluded due to the discontinuity of LA wall at the connection to the pulmonary veins

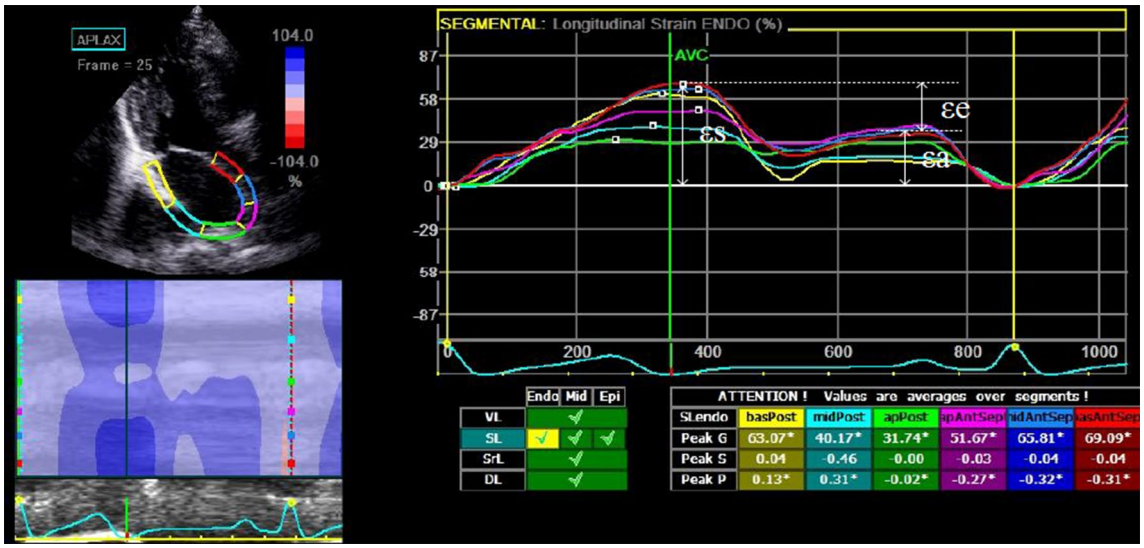

Fig. 2 Example of LA segmental strain curves during a cardiac cycle. The first positive peak strain (εs), the second positive peak strain (εa) and the εe = εs − εa represent the total amount of LA reservoir, contractile and conduit function

defined as the amplitude from the peak-positive to peak-negative deflection of bipolar electrograms. In LA voltage mapping, the LVZ was defined as bipolar voltage < 0.5 mV and displayed in red, normal area defined as bipolar voltage ≥ 1.0 mV and displayed in purple, and borderline area defined as bipolar voltage between 0.5 and 1.0 mV and displayed in variegation, based on a previous study [9, 10] (Fig. 3). Patients with AF were divided into two groups based on the results of bipolar voltage: LV group (bipolar voltage < 0.5 mV) including 19 patients of whom LVZ was observed, at extensive anterior wall (including anterior and septum wall) in 5 patients, septum wall in 7 patients, and anterior wall in 7 patients; and non-LV group (bipolar voltage > 0.5 mV) including 21 patients.

After voltage mapping, CPVI was performed using the CARTO3 system (Biosense Webster Inc.). The endpoint of CPVI was the elimination of PV potentials or the dissociation of PV potentials with atrial electrical activity.

Statistical analysis

The statistical analyses were performed using the SPSS software v.22.0 and MedCalc. Continuous variables were expressed as the mean ± standard deviation. The Kolmogorov–Smirnov test was used to analyze the distribution of continuous variables. Further, continuous variables were analyzed using the Student *t* test or Mann–Whitney *U* test when appropriate. Categorical variables were expressed as a percentage and analyzed using the Chi square test or Fisher exact test between the two groups. Receiver operating characteristic (ROC) curves were constructed. Univariate and multivariate forward stepwise logistic regression analyses were employed to find the independent determinant for assessing patients with AF having an LVZ. A *P* value less than 0.05 was considered statistically significant.

Results

Clinical characteristics

Forty patients were included in the study. The clinical characteristics are summarized in Table 1. The two groups were comparable in terms of age and sex distribution. No significant differences were found in morbidity profiles.

Echocardiographic parameters

Echocardiographic characteristics of both groups are listed in Table 2. The LV group presented significantly lower LAEF compared with the non-LV group. No significant differences were found in the other conventional echocardiographic parameters between the two groups.

LA segmental and global strain using STE

LA segmental and global strain results and ROC curves are presented in Tables 3 and 4, respectively. The septal and global

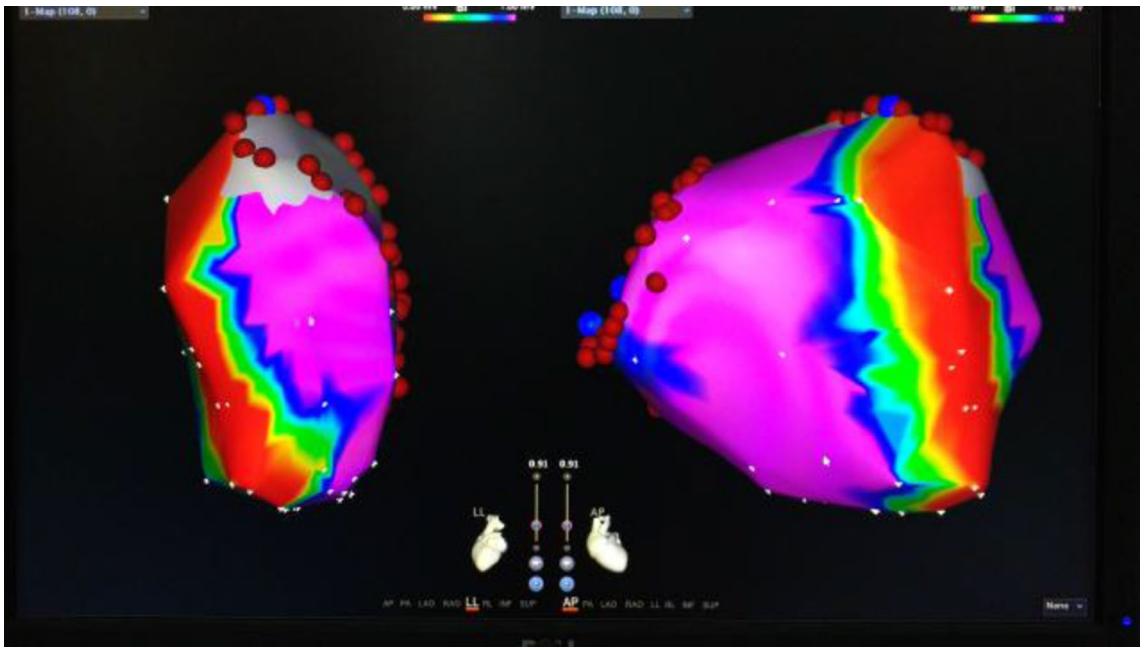

Fig. 3 Example of left atrial voltage mapping. The low-voltage zone (red area) was observed in the septum and anterior of the LA. *AP* anteroposterior, *LL* left lateral

Table 1 Clinical characteristics

	Non-low-voltage group	Low-voltage group	*P* value
Group number	21	19	–
Gender (male)	11 (52%)	8 (42%)	0.516
Age	60.76 ± 10.57	64.47 ± 7.52	0.213
CHADS VASC score	1.62 ± 1.28	2.42 ± 1.64	0.120
Hypertension	9 (42.86%)	12 (63.16%)	0.199
Diabetes mellitus	4 (19.05%)	2 (10.53%)	0.451
Coronary heart disease	4 (19.05%)	4 (21.05%)	0.874
History of stroke	0	2 (10.53%)	0.127

Table 2 Echocardiographic parameters between the two groups

	Non-low-voltage group	Low-voltage group	*P* value
LV end-diastolic volume (mL)	87.57 ± 20.11	78.53 ± 25.52	0.219
LV end-systolic volume (mL)	30.38 ± 8.67	27.05 ± 10.68	0.163
LVEF (%)	65.43 ± 4.91	65.68 ± 4.68	0.867
LA diameter (cm)	39.10 ± 3.58	40.95 ± 4.75	0.169
LA Vmax (mL)	57.48 ± 19.94	56.31 ± 14.47	0.836
LA Vmin (mL)	23.81 ± 12.38	28.95 ± 8.97	0.145
LAEF (%)	59.71 ± 10.64	49.16 ± 8.15	0.001
LAVi (mL/m^2)	32.34 ± 11.67	32.55 ± 7.47	0.473
E-wave velocity (m/s)	0.80 ± 0.30	0.86 ± 0.25	0.467
A-wave velocity (m/s)	0.68 ± 0.21	0.60 ± 0.17	0.401
E/A	1.33 ± 0.61	1.51 ± 0.46	0.326
E′ septal (m/s)	0.08 ± 0.02	0.09 ± 0.02	0.501
E′ lateral (m/s)	0.10 ± 0.03	0.11 ± 0.02	0.167
E/E′ septal	10.37 ± 3.78	9.94 ± 2.56	0.691
E/E′ lateral	8.77 ± 3.72	8.13 ± 2.62	0.776
DT (ms)	214.33 ± 39.86	207.16 ± 43.39	0.591

εs were significantly lower in the LV group than in the non-LV group. The ROC analysis showed that the septal and global strains presented high sensitivity and/or specificity. For εe parameters, significant decrease was observed in septal segments. And for εa parameters, besides the septal and global strain, we also found significant decrease in posterior upper segment. The ROC analysis also showed high sensitivity and/or specificity in septal, posterior and global segments. The univariate and multivariate logistic regression analysis results for identifying patients with LA LVZ are shown in Table 5. The findings indicated that the LA global reservoir strain (εs) had a tendency to be an independent determinant of the LVZ (odds ratio 1.347; 95% confidence interval 1.005–1.807; $P = 0.046$).

Discussion

Major findings

In the present study, the LA reservoir, conduit and contractile strain in septal segments significantly decreased in the LV group than in the non-LV group, which was correlated to the substrate area detected using the electrophysiological examination. Also, significantly high sensitivity and specificity of strain results were found in septal segments, as well as global strain, to predict the LA LVZ through the ROC analysis. Univariate and multivariate analyses showed that the LA global reservoir strain had a tendency to be the only independent determinant to predict the LA LVZ.

AF substrate

Atrial fibrosis is a common feature of clinical AF. In animal models, atrial fibrosis causes localized slowing of conduction, increases conduction heterogeneity, and provides an AF substrate [11]. The fundamental mechanisms underlying AF have long been debated. However, electrical remodeling, contractile remodeling, and structural remodeling are important synergistic contributors to the AF substrate [12].

Electroanatomic bipolar voltage mapping has been described to define the relationship between anatomic and electrophysiological abnormalities [13]. It is now used for

Table 3 LA segmental and global strain (%) results between the two groups

Segment	εs			εe			εa		
	Non-low-voltage group	Low-voltage group	*P* value	Non-low-voltage group	Low-voltage group	*P* value	Non-low-voltage group	Low-voltage group	*P* value
Anteroseptal									
Upper	31.61 ± 9.39	18.32 ± 7.94	0.001	16.07 ± 7.23	9.11 ± 4.63	0.001	15.53 ± 8.21	9.20 ± 6.14	0.009
Lower	29.23 ± 9.81	16.60 ± 7.23	0.001	14.73 ± 5.66	7.38 ± 3.79	0.001	14.50 ± 9.32	9.22 ± 6.07	0.044
Anterior									
Upper	22.72 ± 10.83	18.21 ± 7.33	0.129	9.79 ± 4.84	9.30 ± 4.15	0.732	12.93 ± 7.90	8.92 ± 4.96	0.065
Lower	26.13 ± 14.58	20.48 ± 7.67	0.140	12.92 ± 6.52	11.47 ± 5.05	0.440	13.21 ± 9.82	9.01 ± 4.84	0.100
Lateral									
Upper	22.48 ± 10.87	22.27 ± 9.79	0.948	11.23 ± 7.75	12.89 ± 6.84	0.477	11,25 ± 5.02	9.37 ± 5.82	0.279
Lower	30.41 ± 11.94	28.88 ± 10.39	0.989	17.08 ± 9.77	18.01 ± 6.31	0.725	13.33 ± 5.75	10.86 ± 7.89	0.263
Inferior									
Upper	36.45 ± 12.70	30.56 ± 9.10	0.113	20.02 ± 9.18	17.13 ± 5.23	0.235	16.43 ± 6.01	12.66 ± 6.03	0.055
Lower	36.45 ± 12.90	29.79 ± 8.65	0.103	21.19 ± 9.52	18.44 ± 6.99	0.308	15.26 ± 5.75	12.12 ± 6.84	0.061
Posterior									
Upper	32.84 ± 14.55	27.42 ± 9.65	0.228	16.95 ± 10.21	16.77 ± 6.48	0.948	15.89 ± 6.55	10.64 ± 6.88	0.018
Lower	38.87 ± 19.23	33.24 ± 12.09	0.280	21.05 ± 12.55	20.74 ± 9.32	0.930	17.82 ± 9.53	12.50 ± 7.84	0.063
Posteroseptal									
Upper	32.23 ± 10.57	22.24 ± 6.65	0.001	17.15 ± 7.16	12.57 ± 5.36	0.029	15,08 ± 6.02	9.68 ± 5.74	0.006
Lower	26.40 ± 7.12	18.24 ± 6.49	0.001	14.27 ± 5.29	10.36 ± 5.59	0.029	12,12 ± 5.03	7.88 ± 4.06	0.006
Global strain	30.48 ± 8.67	23.85 ± 6.74	0.008	16.04 ± 5.56	13.68 ± 3.63	0.125	14.45 ± 5.15	10.17 ± 4.79	0.010

Table 4 ROC curves of LA strain (%)

	Segment	AUC	*P* value	Cutoff point	Sensitivity	Specificity
εs	Anteroseptal					
	Upper	0.87	0.0001	≤ 24.07	84	81
	Lower	0.86	0.0001	≤ 16.89	63	100
	Posteroseptal					
	Upper	0.81	0.0001	≤ 26.2	74	81
	Lower	0.80	0.0001	≤ 20.64	68	81
	Global strain	0.73	0.004	≤ 34.84	100	38
εe	Anteroseptal					
	Upper	0.79	0.001	≤ 16.35	100	48
	Lower	0.85	0.001	≤ 11.96	95	71
	Posteroseptal					
	Upper	0.68	0.037	≤ 17.59	84	52
	Lower	0.69	0.033	≤ 12.48	74	71
εa	Anteroseptal					
	Upper	0.74	0.003	≤ 9.13	68	76
	Lower	0.69	0.036	≤ 10.35	74	71
	Posterior					
	Upper	0.74	0.004	≤ 14.76	84	62
	Lower	0.69	0.035	≤ 11.45	63	81
	Posteroseptal					
	Upper	0.75	0.002	≤ 16.08	94	52
	Lower	0.74	0.003	≤ 11.17	84	71
	Global strain	0.74	0.003	≤ 12.88	79	62

Table 5 Univariate and multivariate logistic regression analysis for identifying patients with the LA low-voltage zone

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.049	0.972–1.131	0.217			
LVEF	1.012	0.886–1.155	0.863			
LA diameter	1.117	0.953–1.310	0.171			
LA Vmax	0.996	0.960–1.033	0.831			
LA Vmin	1.046	0.984–1.112	0.148			
LAEF	0.891	0.822–0.966	0.005	0.864	0.704–1.057	0.154
LA stroke	1.001	0.512–1.955	0.999			
LAVi	1.002	0.940–1.069	0.946			
E/A	1.839	0.554–6.108	0.320			
Anteroseptal upper	0.839	0.753–0.934	0.001	1.012	0.756–1.354	0.938
Anteroseptal lower	0.810	0.710–0.924	0.002	0.925	0.679–1.261	0.622
Anterior upper	0.947	0.881–1.018	0.139			
Anterior lower	0.952	0.889–1.019	0.158			
Lateral upper	0.998	0.938–1.061	0.946			
Lateral lower	0.987	0.932–1.045	0.660			
Inferior upper	0.971	0.872–1.081	0.588			
Inferior lower	0.950	0.892–1.012	0.112			
Posterior upper	0.963	0.912–1.017	0.18			
Posterior lower	0.977	0.937–1.019	0.280			
Posteroseptal upper	0.852	0.755–0.961	0.009	0.896	0.664–1.209	0.472
Posteroseptal lower	0.817	0.709–0.943	0.006	0.925	0.679–1.261	0.622
Global strain	0.890	0.808–0.979	0.017	1.347	1.005–1.807	0.046

substrate description in clinical electrophysiological studies. The atria of patients with AF and clinically similar characteristics can present differently during electroanatomic mapping. Even patients with the worst (bi-)atrial substrate may present with paroxysmal (instead of persistent) AF [14]. AF fibrosis should be related to human age or other cardiovascular diseases. However, previous studies could not detect any correlation between patient age and increase in the extent of fibrosis [15]. Besides, the degree of LA structural remodeling was also found to be completely independent of comorbidities such as hypertension [16]. The present study also found no significant difference in age, hypertension, and history of stroke between the LV and non-LV groups.

Speckle tracking echocardiography

Previous studies found LA low voltage and LA mechanical dysfunction to be correlated with LA fibrosis estimated by LA delayed-enhancement area on magnetic resonance imaging [17, 18]. Kuppahally found that the echocardiographic assessment of LA structural and functional remodeling was related to LA wall fibrosis, using delayed-enhancement MRI, which would be a quick and feasible technique considering MRI as an expensive, time-consuming method. The present study also revealed using 2D STE the correlation between LA strain and substrates. The findings suggested the following.

(1) LA strain could be an index reflecting LA reservoir, conduit and contractile functional remodeling. To date, most studies were examining LA reservoir function. Reduced LA reservoir function was found to markedly increase the propensity for AF [19]. Hong et al. [20] reported that LA functional remodeling assessed using the LA strain was associated with an impairment of LA intrinsic myocardial properties and the early recurrence of AF after ablation in lone AF. Other studies also proved that LA reservoir function remodeling was the major pathogenesis for the occurrence, progression, and recurrence of AF [21, 22]. In our study, besides reservoir strain, we also found the decrease of other two atrial strains. The results indicated that all LA functions including reservoir, contractile and conduit would be affected in AF patients with LVZ.

(2) The LA strain can indicate segmental and global mechanical dysfunction. This may be a result of the regional fibrosis of the LA myocardial tissue. Regional fibrosis may lead to the heterogeneity of LA wall stiffness, resulting in dysfunction in the reservoir phase [23]. Recent study from Huo et al. [24] discovered that the most frequent localization of LVZ was anterior wall, septum and posterior wall. In our study, the LVZ was localized at anterior and/or septum wall, and LA strain showed a decrease in related segments:

notably a significant decline in septum segments. We also observed a decrease of posterior upper segment contractile strain. We thought that it might be resulting from the enlargement of anterior and septum wall, given that we have 5 patients with LVZ at extensive anterior wall. Although regional strain analysis has not been studied as rigorously as global strain, it might have potential value to quantify LA function and indicate LVZ. Sarvari et al. [25] studied segmental dyssynchrony with STE and proved it to be a predictor of AF recurrence after RFCA.

(3) The segmental mechanical dysfunction corresponded to the atrial substrate, suggesting that LA mechanical and electrical dysfunction coexisted in the early phase of LA remodeling even prior to LA enlargement. Watanabe et al. [26] also obtained same results, reporting that 3D STE could enable the noninvasive estimation of LA electrical remodeling and AF substrate even in an early phase. However, 3D STE requires high-quality imaging, and segmental atrial remodeling using 3D STE has not been reported yet. Hugo et al. [27] showed that LA strain impairment was an independent predictor of postoperative AF and might serve as a surrogate marker for biological processes involved in establishing the substrate for POAF. Furthermore, the coexistence of dysfunction in the mechanical and electrical remodeling areas might suggest that the atrial fibrosis area could be predicted in advance by STE, while no such study has been reported yet.

Study limitations

The present study had several limitations. First, the study involved a small sample size from only a single institution in a nonrandomized retrospective manner. Therefore, the findings need to be validated through conducting large, prospective, and multicenter studies in the future. Second, the software for specifically evaluating the LA strain is not yet available, and thus, the LA strain was analyzed using the software for analyzing the LV strain.

Conclusions

LA segmental and global strain decreased in patients with PAF having an LVZ in this study, indicating that STE parameters could identify the LVZ from controls. Moreover, this study evaluated the early phase of electrical and mechanical remodeling using a noninvasive technique, which suggest that STE may be a potential tool to assess LA remodeling and fibrosis prior to ablation.

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Data availability The data set supporting the results of this article are included within the article.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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