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ORIGINAL ARTICLE

The association between left atrial stiffness and low-voltage areas of left atrium in patients with atrial fibrillation

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Abstract

The low-voltage areas of left atrium (LA-LVA) have recently been of significant focus. However, very few studies have focused on the association between LA function and LA-LVA, and the mechanism of appearance of LA-LVA remains unclear. We investigated the marker for the existence of LA-LVA using automated 3-D mapping system. We studied 92 patients (75 males, 68 ± 9 years, 47 non-paroxysmal AF) who received CA for AF and 40 control patients without AF. Echocardiography was performed before the CA, and high-density voltage mapping during sinus rhythm after pulmonary isolation was performed in AF patients. LA-LVA was defined as < 0.5 mV, and LA stiffness index (LASI) was defined as the ratio of *E*/*e*′ to LA peak strain. LA-LVA (LVA burden > 10%) was detected in 19/92 AF patients (21%). Patients with LA-LVA were associated with higher LASI (1.64 ± 1.70 vs. 0.61 ± 0.46, $p < 0.0001$), larger LA volume, non-paroxysmal AF, higher brain natriuretic peptide, structural heart disease, and older age. On multivariate analysis, LASI, LA volume, and age were independently associated with the existence of LA-LVA. Of these markers, the highest area under curve was obtained with LASI. The rate of high LASI (≥ 0.552) was highest in AF patients with LA-LVA. Moreover, the existence of LVA in anterior LA wall was associated with higher LASI. High LA stiffness index was associated with the presence of LA-LVA. The LA-LVA might be attributed to LA functional remodeling rather than LA anatomical remodeling.

Keywords Left atrial stiffness · Low-voltage area · Atrial fibrillation

Introduction

Catheter ablation (CA) has been proven to be efficacious for atrial fibrillation (AF), especially paroxysmal AF (PAF). However, CA for persistent AF (PeAF) is less effective [1]. Approximately one half of patients with PeAF undergoing CA will experience a recurrence of AF, even after multiple procedures [2]. PeAF is a chronic disease with progressive atrial fibrosis and development of pulmonary and non-pulmonary vein (PV) triggers [3]. A recent clinical trial has failed to demonstrate the efficacy of CA with substrate modification for PeAF [2].

It is known that atrial remodeling due to AF causes an increase in fibrosis, which is associated with a reduction in conduction velocity, and a consequent increase in vulnerability to AF [4]. In addition, Kottkamp et al. proposed "fibrotic atrial cardiomyopathy", which is characterized by extensive bi-atrial fibrosis in patients with lone AF [5]. Fibrotic infiltration of the atrium is one of major determinants of the pathogenesis and progression of AF [6]. The existence of low-voltage areas (LVA), as surrogates of atrial fibrosis, has recently been of significant focus. The extent of LVA appears to be associated with atrial arrhythmia recurrence after CA [7]. Recently, various ablation strategies associated with LVA have been reported [8]. Their results suggested that these LVA ablation in addition to PVI improved procedural outcomes in patients with AF. Moreover, some studies reported that the existence of LVA (more than 10% of the LA total surface area) in voltage mapping strongly predicts AF recurrence in patients with PAF [9]. Therefore, we believe that the assessment of predictors of LVA of LA (LA-LVA) is essential.

Various predictive factors of LA-LVA using 3-D mapping system have been reported [7]. Clinically, some patients with a normally sized or moderately enlarged LA have LA-LVA during 3-D mapping. However, very few

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studies have focused on the association between LA function and LA-LVA, and the mechanism of appearance of LA-LVA remains unclear. Our aim was to investigate the marker (including LA function) for the existence of LA-LVA using the automated 3-D mapping system.

Methods

Patient population

This study included 100 patients with non-valvular AF who underwent transthoracic echocardiography (TTE) before CA and high-density voltage mapping during sinus rhythm after CA at the Hyogo College of Medicine between September 2016 and September 2017. Patients requiring box isolation were excluded from our study because voltage mapping cannot be performed adequately in these patients. From this initial population, patients requiring hemodialysis ($n=4$), had a previous cardiac device implantation ($n=1$), or patients who underwent cardiac surgery ($n=3$) were excluded from the study. There were no patients who could not maintain sinus rhythm after the CA procedure. The remaining 92 patients (75 males, age 68 ± 9 years, 47 non-paroxysmal AF) were included in retrospective study analyses (Fig. 1). This study also included 40 control patients without AF (22 men, age 69 ± 8 years). Control patients consisted of those individuals who underwent TTE and catheter ablation for paroxysmal supraventricular tachycardia but in whom no structural heart disease was found. Antiarrhythmic drugs were discontinued for at least five half-lives before CA. The clinical and echocardiographic variables were retrospectively assessed. All patients were older than 18 years of age and provided written informed consent to the procedures. The research protocol was approved by the appointed local ethics committee.

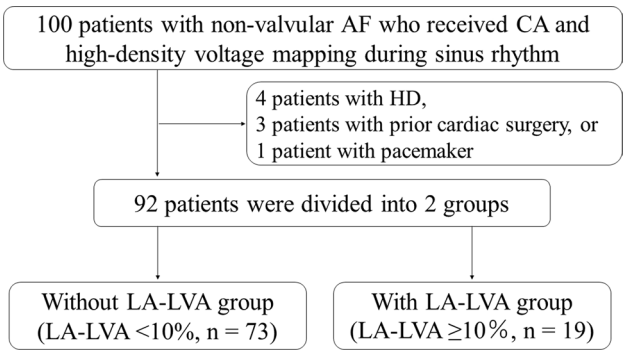

Fig. 1 Flow chart of the study patients. *AF* atrial fibrillation, *CA* catheter ablation, *HD* hemodialysis *LA-LVA* low voltage area of left atrium

Echocardiographic imaging

All patients underwent TTE within the month preceding their CA procedure using a Prosound F75 (Hitachi Aloka Medical, Tokyo, Japan) with a 3.88-MHz transducer probe. Left atrial (LA) diameter, LA volume, left ventricular (LV) diameter during end-diastole, and LV ejection fraction were assessed during TTE. LA volumes were measured by the biplane area-length method. Minimum LA volume (LAV_{min}) was measured at the closure of the mitral valve in end-diastole. Maximum LA volume (LAV_{max}) was measured just before the opening of the mitral valve in end-systole. LA systolic function was assessed with the: (a) LA emptying volume $=LAV_{max}-LAV_{min}$, and (b) LA emptying fraction $=[(LAV_{max}-LAV_{min})/LAV_{max}]\times100$. As described previously [10], three consecutive cardiac cycles were gained and averaged from the apical two-and four-chamber views with frame rates of 50–80 Hz. The LA endocardium was traced first, followed by the LA endocardium. The areas of interests of specific wall thickness were then marked. The peak LA strain was taken from longitudinal LA strain curves. The ratio of *E*/*e*′ to LA peak LA longitudinal strain (PALS) was used to obtain the LA stiffness index [LA stiffness index = (*E*/*e*′ ratio)/PALS]. The PALS was measured three times by one experienced cardiologist in all patients. The measurements of PALS showed $<5\%$ intra-observer variability. An average of three PALS measurements was used to determine the LA stiffness index during sinus rhythm.

Catheter ablation procedure

Patients were studied under deep sedation. A temperature probe was introduced into the esophagus for continuous real-time monitoring of the intraluminal temperature (Sensitherm; Abbott Medical, Abbott Park, IL, USA). Cardiac catheterization was performed as described previously [11]. All patients underwent circumferential pulmonary vein isolation (CPVI) guided by electroanatomical mapping combined with image integration. The circumferential ablation lines were created under the guidance of a 3-D mapping system (EnSite Velocity NavX System; Abbott Medical). Segmental radiofrequency application was performed with a 4-mm externally irrigated-tip quadripolar ablation catheter (Flex-Ablity; Abbott Medical). Administration of adenosine triphosphate was carried out to provoke a reconnection of the PVs (dormant PV conduction) at least 20 min after successful wide CPVI. Upon observation of any dormant PV conduction, additional radiofrequency energy was applied at the earliest PV activation site until the absence of any

dormant PV conduction. The endpoint was the establishment of bidirectional conduction block between the LA and the PV. Cavotricuspid isthmus ablation and the other additional procedures of superior vena cava isolation, mitral isthmus ablation, or atrial tachyarrhythmia ablation were conducted at the operator's discretion. The procedure ended when there was no immediate recurrence of AF after cardioversion with isoproterenol infusion (5–10 μg/min). If there were mappable AF triggers or atrial premature beats, we carefully mapped and ablated these non-PV foci as much as possible.

Voltage mapping

After PV isolation, a detailed bipolar voltage map of left atrium was acquired during sinus rhythm using a 20-polar circumferential catheter (Lasso; Biosense-Webster). Automated 3-D mapping system (EnSite AutoMap module; Abbott Medical) was used to construct the LA geometry and voltage map. To ensure the highest accuracy of the acquired atrial geometry by the 3-D mapping system, respiratory gating was performed, and the atrial geometry was acquired at high adjustment settings. In addition, high-density mapping was added at sites where LA-LVA was recorded to exactly define the extent of the LVA. Endocardial contact was ensured by fluoroscopy, electrogram stability, and the 3-D mapping system. The band pass filter was set at 30–500 Hz. Each acquired point was classified according to the peak-to-peak electrogram, as follows: ≥ 0.5 mV, healthy; and < 0.5 mV, LA-LVA [7]. The lowest number of points acquired for the LA endocardial map was 2000. The proportion of the mapped LA surface exhibiting low voltage was expressed as a percentage of the overall mapped LA surface area within the isolation line, not including the ablation lesions in LA surface area and anatomical structures such as the pulmonary vein and left atrial appendage. Figure 2 shows representative voltage maps demonstrating high and low proportions of LA-LVA in patients mapped in SR. Every LA map was divided into six segments for analysis: anterior, posterior, inferior, roof, septal, and posterolateral wall (Fig. 2). The existence of LA-LVA was defined as more than 10% of the LA total surface area.

Statistical analysis

All data are expressed as the mean value ± standard deviation. Statistical comparisons were made using Student's *t* test. Differences between categorical variables were evaluated using the chi-square test or the Fisher's exact

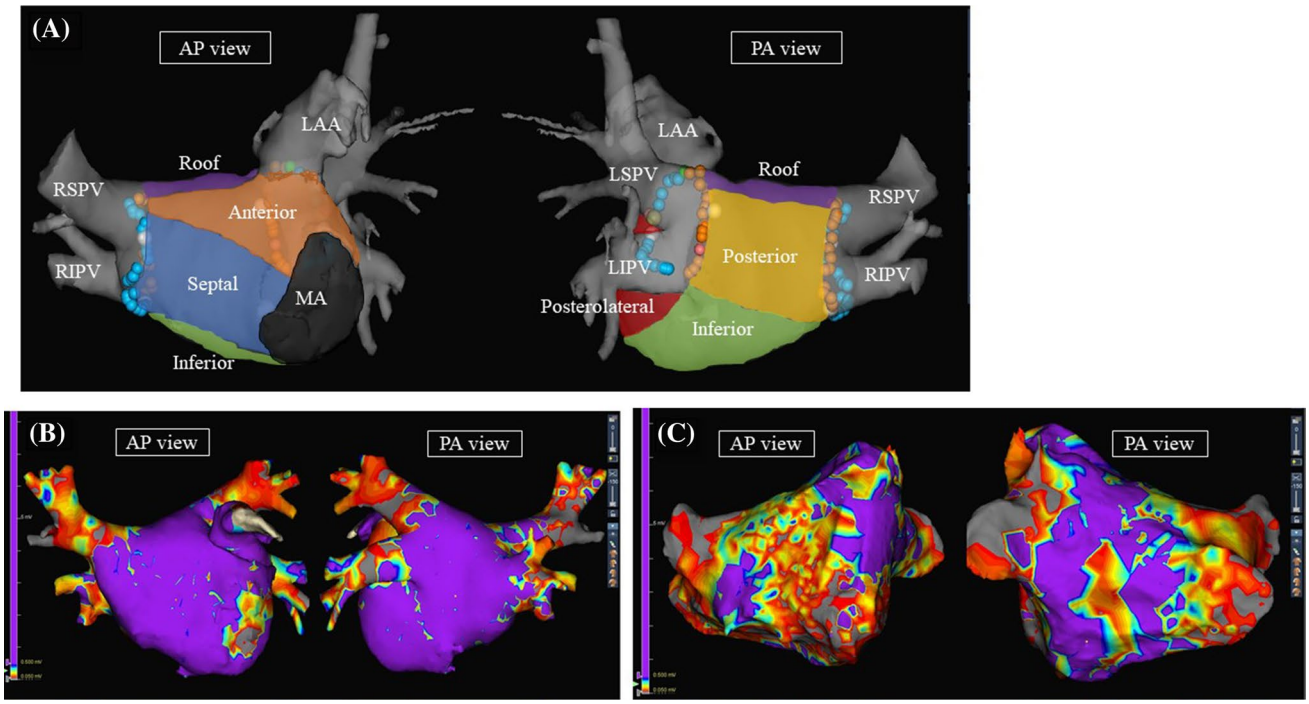

Fig. 2 **a** Schematic representation of six LA anatomical regions exhibiting the prevalence of LVA. **b** Representative normal LA voltage map. The color gradient reflects the graded changes in electrogram amplitude from purple at > 0.5 mV to red LVA at < 0.05 mV. LA-LVA; 0% and LA stiffness index was 0.38. **c** Representative LVA case. LVA shown in the anterior, septal, inferior, posterior walls, and roof. LA-LVA; 51.4% and LA stiffness index was 2.15. *AP* anterior–posterior, *LA* left atrial, *LAA* left atrial appendage, *LA-LVA* low voltage area of left atrium, *LIPV* left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *LVA* low voltage area, *PA* posterior–anterior, *RIPV* right inferior pulmonary vein, *RSPV* right superior pulmonary vein

test. A *P* value of less than 0.05 was considered statistically significant. Univariate analyses were performed. The variables that were found to be significant in univariate analysis were entered into a multivariate analysis. The independent association with AF recurrence after CA was evaluated using multivariate analysis. Receiver operating characteristic (ROC) curves were generated to obtain the area under the ROC curve (AUC) values with 95% confidence intervals (CI), along with the sensitivity and specificity of each variable as a predictor of LA-LVA. All analyses were performed using the JMP Pro statistical software (version 10, SAS Inc, Cary, NC, USA) and Microsoft Excel.

Results

All 92 patients (age 68 ± 9 years, 75 males, 47 non-paroxysmal AF) were enrolled in the study according to specific inclusion and exclusion criteria (Fig. 1). Of the 92 patients, LA-LVA (the burden of LA-LVA > 10%) was detected in 19 patients (21%). We divided all patients into two groups as follows: with LA-LVA group ($n = 19$) and without LA-LVA group ($n = 73$). Baseline characteristics of the patients are listed in Table 1. The LA-LVA group had a significant higher prevalence of non-paroxysmal AF and structural heart disease than the without LA-LVA group. The age and levels of brain natriuretic peptide were significantly higher in the with LA-LVA group than those in the without LA-LVA group. Echocardiographic findings and medication therapy

Table 1 Baseline characteristics

	Without LA-LVA ($n = 73$)	With LA-LVA ($n = 19$)	*P* value
Male, *n* (%)	62 (85%)	13 (68%)	0.0986
Age (years)	67.0 ± 9.5	71.8 ± 7.6	0.0453
Body mass index (kg/mm^2)	24.0 ± 3.4	22.9 ± 2.2	0.1868
Non-paroxysmal AF, *n* (%)	30 (41%)	17 (89%)	0.0002
Brain natriuretic peptide (10^2 pg/mL)	1.11 ± 1.37	3.98 ± 7.55	0.0027
Creatinine (mg/dL)	0.96 ± 0.99	0.96 ± 0.38	0.9989
Hypertension, *n* (%)	46 (63%)	11 (58%)	0.6822
Dyslipidemia, *n* (%)	19 (26%)	7 (37%)	0.3510
Diabetes mellitus, *n* (%)	21 (29%)	4 (21%)	0.5007
Prior stroke/TIA, *n* (%)	7 (10%)	3 (16%)	0.4254
Structural heart disease, *n* (%)	16 (22%)	10 (53%)	0.0081
$CHADS_2$ score	1.4 ± 1.1	1.9 ± 1.4	0.0882
HAS-BLED score	1.3 ± 0.9	1.2 ± 0.6	0.6072
Echocardiographic findings			
LA diameter (mm)	41.7 ± 6.4	46.6 ± 3.5	0.0018
LA volume (mL)	69.7 ± 22.2	93.9 ± 20.0	< 0.0001
LA stiffness index	0.61 ± 0.46	1.64 ± 1.70	< 0.0001
LA emptying volume (mL)	22.5 ± 12.4	20.5 ± 11.1	0.5785
LA emptying fraction (%)	32.8 ± 12.5	21.8 ± 9.6	0.0041
LV diameter during end-diastole (mm)	49.7 ± 4.8	50.8 ± 7.4	0.4037
LV ejection fraction (%)	62.2 ± 10.2	58.2 ± 16.7	0.1942
Medication therapy			
β blocker, *n* (%)	35 (48%)	13 (68%)	0.1115
ACE-I, *n* (%)	8 (11%)	5 (26%)	0.1328
ARB, *n* (%)	28 (38%)	5 (26%)	0.4251
Calcium channel blocker, *n* (%)	28 (38%)	7 (37%)	1
Statin, *n* (%)	19 (26%)	6 (32%)	0.7727
Antiarrhythmic drug, *n* (%)	27 (37%)	9 (47%)	0.4088
Amiodarone, *n* (%)	8 (11%)	3 (16%)	0.6912

Values are given as no. (%) or mean ± SD

ACE-I angiotensin-converting enzyme inhibitor, *AF* atrial fibrillation, *ARB* angiotensin receptor blocker, *LA* left atrial, *LV* left ventricular, *TIA* transient ischemic attack

are listed in Table 1. The with LA-LVA group had significant larger LA diameter, larger LA volume, lower LA emptying fraction, and higher LA stiffness index than the without LA-LVA group. Baseline medication use did not differ between the with LA-LVA group and the without LA-LVA group.

Table 2 lists the procedural findings of the study groups. All patients had successful CPVI [first session: 80 patients (87%), second session: 12 patients (13%)]. Sixty patients (65%) underwent cavotricuspid isthmus ablation, and 12 patients (13%) underwent additional procedures (superior vena cava isolation, mitral isthmus ablation, or AT ablation). The with LA-LVA group had significant higher rate of CTI ablation, longer procedural time/radiofrequency time, higher radiofrequency energy than the without LA-LVA group. LA voltage mapping was completed in all patients, with a mean number of acquired mapping points of 2398 ± 1091 per patients. In the with LA-LVA group, total area with a LA-LVA was 27.0 ± 13.5 cm^2, and the percentage of LA-LVA on the total LA surface area was 33.9 ± 16.2%. Total area of LA surface did not differ between the with LA-LVA group and the without LA-LVA group. Table 2 lists the distribution of LA-LVA. The LA-LVA was most frequently observed in the anterior region. On multivariate analysis, LA stiffness index, LA volume, and age were independently associated with the existence of LA-LVA (Table 3). LA diameter was not entered into a multivariate analysis because LA diameter is equivalent to LA volume.

Then, AUC analysis was performed to determine the best cut-off values for related factors in the prediction of the existence of LA-LVA. We compared 3 ROC curves (LA stiffness index, LA volume, and age) using AUC comparison analysis. The higher AUC was obtained with LA stiffness index (AUC 0.8417, $P < 0.0001$) with a best cut-off value of 0.552 (sensitivity 94.7%, specificity 61.6%) than LA volume (AUC 0.7909, sensitivity 63.2%, specificity 87.8%) and age (AUC 0.6341, sensitivity 94.7%, specificity 26.0%). Moreover, all patients were divided into three groups based on the prevalence of AF and LA-LVA; Group 1 [$n = 40$, AF (−)], Group 2 [$n = 73$, AF (+)/LA-LVA < 10%], and Group 3 [$n = 19$, AF (+)/LA-LVA ≥ 10%]. The LA stiffness index was 0.245 ± 0.090, 0.606 ± 0.463, and 1.644 ± 1.701 in Group 1, Group 2, and Group 3, respectively. The rate of high LA stiffness index (≥ 0.552) was highest in group 3 (Fig. 3). The regional distribution of LA stiffness index is shown in Fig. 4. Patients with LA-LVA in the anterior wall had a higher LA stiffness index than those without LA-LVA. In the other regions, there were no differences of LA stiffness index between both groups.

Table 2 Procedural findings

	Without LA-LVA ($n = 73$)	With LA-LVA ($n = 19$)	*P* value
1st session, *n* (%)	61 (84%)	19 (100%)	0.0581
PV isolation, *n* (%)	73 (100%)	19 (100%)	1
CTI ablation, *n* (%)	41 (56%)	19 (100%)	0.0004
SVC isolation, *n* (%)	9 (12%)	1 (5%)	0.6812
Additional procedure, *n* (%)	1 (1%)	1 (5%)	0.3722
Procedural time (min)	126 ± 38	149 ± 42	0.0261
Radiofrequency time (min)	23 ± 13	33 ± 8	0.0028
Radiofrequency energy (10^2 J)	400 ± 216	515 ± 124	0.0320
Number of mapping point	2296 ± 1092	2788 ± 1023	0.0801
Total area of LA (cm^2)	72.5 ± 18.4	80.3 ± 16.9	0.0955
LA-LVA area (cm^2)	0.9 ± 2.2	27.0 ± 13.5	< 0.0001
Burden of LA-LVA (%)	1.1 ± 2.6	33.9 ± 16.2	< 0.0001
Number of LA-LVA (regions)	0.2 ± 0.5	3.2 ± 1.4	< 0.0001
Distribution of LA-LVA			
Anterior, *n* (%)	4 (5%)	13 (68%)	< 0.0001
Roof, *n* (%)	3 (4%)	9 (47%)	< 0.0001
Septal, *n* (%)	2 (3%)	10 (53%)	< 0.0001
Posterior, *n* (%)	5 (7%)	9 (47%)	< 0.0001
Inferior, *n* (%)	3 (4%)	8 (42%)	< 0.0001
Posterolateral, *n* (%)	0 (0%)	7 (37%)	< 0.0001

Values are given as no. (%) or mean ± SD

CTI cavo tricuspid isthmus, *LA-LVA* low-voltage area of left atrium, *PV* pulmonary vein, *SVC* superior vena cava

Table 3 Univariate and multivariate analyses

	Univariate analysis	Multivariate analysis	
	P value	*P* value	OR (95% CI)
LA stiffness index	< 0.0001	0.0142	10.021† (1.264–19.96)
LA volume	< 0.0001	0.0124	1.120† (1.023–1.208)
Age	0.0453	0.0397	1.142† (1.007–1.266)
LA emptying fraction	0.0041	0.0523	
Non-paroxysmal AF	0.0002	0.5724	
Brain natriuretic peptide	0.0027	0.7924	
Structural heart disease	0.0081	0.1767	

AF atrial fibrillation, *CI* confidence interval, *LA* left atrial, *OR* odds ratio

†For each 1 unit increase in the LA stiffness index/LA volume/age

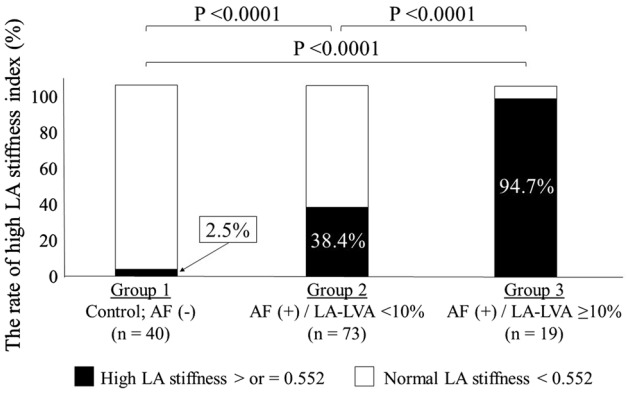

Fig. 3 The rate of patients with high LA stiffness index (≥0.552). Three groups based on the existence of LA-LVA and AF; group 1 (control group, $n=40$), group 2 [AF (+)/LA-LVA < 10%, $n=73$], and group 3 [AF (−) ≥10%, $n=19$]. *AF* atrial fibrillation, *LA* left atrial, *LA-LVA* low voltage area of left atrium

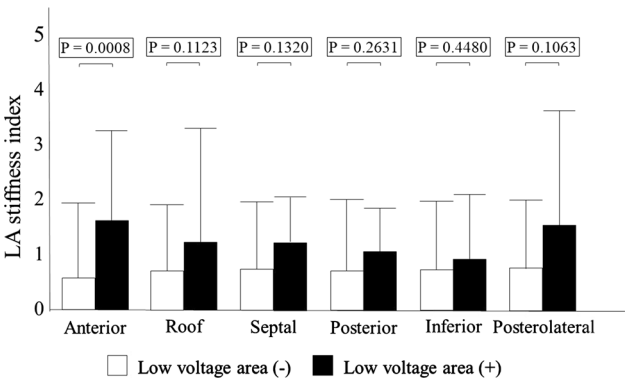

Fig. 4 LA stiffness index comparisons between two groups (patient without LA-LVA group vs. with LA-LVA group) in each anatomical region; anterior ($n=17$): 0.66 ± 0.50 vs. 1.51 ± 1.87, $P=0.0008$; roof ($n=12$): 0.76 ± 0.95 vs. 1.23 ± 0.93, $P=0.1123$; septal ($n=12$): 0.76 ± 0.96 vs. 1.21 ± 0.86, $P=0.1320$, posterior ($n=14$): 0.77 ± 0.99 vs. 1.09 ± 0.76, $P=0.2631$, inferior ($n=11$): 0.79 ± 1.00 vs. 1.03 ± 0.56, $P=0.4480$; posterolateral ($n=7$): 0.77 ± 0.95 vs. 1.38 ± 1.02, $P=0.1063$. *LA* left atrial, *LA-LVA* low voltage area of left atrium

Discussion

This is a retrospective study of a predictive factor for the existence of LA-LVA in AF patients using a single-center database. Our study showed that LA-LVA (the burden of LA-LVA > 10%) was detected in 21% AF patients, and patients with LA-LVA were associated with higher LA stiffness index, non-paroxysmal AF, larger LA volume, higher brain natriuretic peptide, structural heart disease, and older age. On multivariate analysis, higher LA stiffness index, LA volume, and age were independently associated with the existence of LA-LVA. Of these markers, the highest AUC was obtained with LA stiffness index. Moreover, the rate of high stiffness index (≥0.552) was highest in the patients with AF/LA-LVA ≥ 10% compared to the patients with AF/LA-LVA < 10% or control group. Moreover, the existence of LVA in the anterior LA wall was associated with higher LASI.

It is well-known that an abnormal atrial substrate, such as atrial fibrosis, is associated with AF. Recent studies have reported that cardiac magnetic resonance imaging (MRI) is useful for the detection of abnormal LA substrates. They suggested that atrial tissue fibrosis identified by MRI is associated with AF recurrence after CA [12]. Some studies have shown that LA fibrosis detected by MRI correlates with low endocardial voltage [13]. However, MRI is not the gold standard method for the detection of abnormal LA substrate because of several limitations (time consumption, limited reproducibility, and poor accuracy). On the other hand, with the development of a 3-D mapping system and consequent high-quality imaging of the LA, several studies on the LA-LVA have been investigated. A previous study has reported that the existence of LA-LVA after CA for AF is a powerful predictor of AF recurrence [7]. In addition, various ablation strategies associated with LA-LVA have been reported, and they suggested that these strategies (LA-LVA guided ablation in addition to CPVI) improve the outcomes compared to CPVI alone [8]. Moreover, recent expert consensus showed

that the 3-D mapping system is highly applicable clinically and is superior in defining atrial substrates that lead to the development of AF [14]. As such, there has been significant focus on the LA-LVA.

Previous studies have shown evidence of LA-LVA in patients with several markers [7]. Recently, Pablo et al. studied the characterization of LA-LVA in 104 patients with AF (69 paroxysmal and 35 persistent AF). Their study indicated that age and LA volume were associated with the presence of LA-LVA, and AF classification (persistent or paroxysmal) was not a marker of an abnormal LA substrate [15]. Ammar-Busch et al. also studied the markers of LA-LVA in patients with 70 non-paroxysmal AF (34 persistent and 36 long-standing AF). They indicated that, after adjustment for several clinical factors, age, female sex, and LA surface area remained associated with LA-LVA detected by 3-D mapping during AF rhythm [16]. Age and LA volume were thus associated with the existence of LA-LVA regardless of AF classification, findings that corroborate our results. On the other hand, a limited number of studies have reported LA function and LA remodeling. One study reported the association between the extent of LA-LVA and LA function in 22 patients with AF. They found that structural (i.e. LA volume) and functional (i.e. LA emptying fraction and LA strain) parameters of the LA correlate with the extent of LVA [17]. Their results, in which LA strain (surrogate of LA conduit/reservoir function) is associated with the extent of LA-LVA, could support our findings because LA stiffness index consists of LA peak strain.

In our study, LA stiffness index was the most useful marker of LA-LVA. LA stiffness index, which is a surrogate of LA diastolic function, may be a useful marker to estimate LA remodeling. A few clinical studies have reported LA stiffness. Irfan et al. reported a novel measure of LA diastolic dysfunction, the LA stiffness index, which is based on a combination of noninvasive volume measurements from cardiac magnetic resonance imaging and invasive pressure measurements at the time of CA [18]. They found that the LA stiffness index is associated with persistent AF, history of CA, and age, and is a strong independent predictor of AF recurrence after CA. Their method is useful for evaluating LA diastolic function. However, this method would be difficult to implement in the clinical setting. Most studies on LA stiffness have used echocardiographic speckle tracking to assess strain and indirectly evaluate myocardial compliance [10]. Kurt et al. studied the association between LA function and diastolic heart failure in 64 patients undergoing right heart catheterization. They showed that non-invasive LA stiffness index, as was the ratio of *E/e′* to LA peak strain, correlated well with pulmonary artery systolic pressure [10]. These findings indirectly suggest that chronic stretch due to high LA pressure may lead to an increase in the LA-LVA.

To best of our knowledge, this is the first study illustrating that LA stiffness index based on non-invasive LA strain can predict the existence of LA-LVA in patients with AF.

However, it is still a matter of debate if stiff LA / LA fibrotic changes are the cause or consequence of AF. Various mechanisms of stiff LA/LA fibrotic changes have been suggested. First, LA remodeling, such as LA enlargement, might lead to stiff LA/LA fibrotic changes. It is well established that aging results in LA remodeling and increases the risk of AF. Further, it has been established that AF increases the predisposition to LA remodeling in a so-called "AF begets AF" manner. Second, LA enlargement might occur secondary to stiff LA/LA fibrotic change. It is easy to elevate LA pressure in patients with a stiff LA because a stiff LA has a smaller change in LA volume filling in a more compliant LA. Consequently, elevated LA pressures lead to LA remodeling such as LA enlargement. In addition, it is well-known that the maintenance of AF results in LA remodeling such as LA enlargement. One study reported that 16 patients with paroxysmal AF had a higher mean LAP at baseline (8.3 ± 4.7 vs. 5.1 ± 3.1 mmHg, $P = 0.048$), compared to 11 control patients [19]. Their findings suggested that patients with paroxysmal AF have a stiff LA, compared to those without. Recently, "fibrotic atrial cardiomyopathy" was originally proposed by Kottkamp et al. [5] Clinically, some patients with lone AF might have underdetected chronic substrates such as fibrotic atrial cardiomyopathy. Previous studies reported that fibrotic atrial cardiomyopathy leads to atrial arrhythmias and sinus node dysfunction [5]. Furthermore, Teh et al. reported clinical data about progressive atrial remodeling 10 months after successful CA for AF in patients without structural heart disease [20]. They showed that even successful elimination of AF by CA fails to halt the progression of fibrosis, suggesting that LA abnormal substrate is not the result of arrhythmia alone. Thus, the mechanisms of stiff LA/LA fibrotic changes remains controversial. We speculate that LA stiffness index could be helpful to understand these mechanisms. Given the current data, further investigation is necessary to determine the validity of these mechanisms.

Our findings indicate that LA stiffness is the most useful marker to predict the existence of LA-LVA in patients with AF. The prediction of LA-LVA as an LA abnormal substrate is important for the estimation of the outcome after CA. Patients with LA-LVA typically have a poor outcome and may require aggressive additional procedures/provocation tests. LA stiffness index based on LA strain is non-invasive and simpler than the other methods (MRI or 3-D mapping system). A prediction of LA substrate using LA stiffness index could be helpful to predict the outcome and provide an appropriate strategy for CA. Moreover, LA stiffness index might be helpful for monitoring the reverse remodeling of LA abnormal substrate after CA.

There were several limitations in our study. First, this is a retrospective study with a small number of patients in a single center. Second, our study completed atrial voltage mapping after CA. This approach may fail to identify LA-LVA present in the PV antrum. Third, previous studies used variable criteria for defining LA-LVA. However, an atrial voltage < 0.5 mV is most appropriate to detect LA-LVA according to previous studies. Therefore, we used this definition of the LA-LVA. Fourth, LA stiffness index is a hybrid measure of *E/e'* ratio and LA strain. However, there is no direct marker of LA stiffness. Fifth, LA voltage map could not be obtained in patients in control group. Finally, most previous studies about LA-LVA used a conventional 3-D mapping technique (manual and point-by-point) while we used a new automated 3-D mapping system.

Conclusions

High LA stiffness index was associated with the presence of LA-LVA. The LA-LVA might be attributed to LA functional remodeling rather than LA anatomical remodeling.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest on the part of authors.

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