Left Atrial Relaxation Index is an Independent Predictor of the Presence of a Left Atrial Low Voltage Zone in Patients with Atrial Fibrillation

<Original Article>

Left Atrial Relaxation Index is an Independent Predictor of the Presence of a Left Atrial Low Voltage Zone in Patients with Atrial Fibrillation

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Key words: Left atrial remodeling, Relaxation index, Atrial Fibrillation, Low voltage zone, Catheter ablation

ABSTRACT

In atrial fibrillation (AF), low voltage zones (LVZs) on cardiac electro-anatomic mapping reflect atrial fibrosis and are associated with difficulty in maintaining sinus rhythm after catheter ablation (CA). Although left atrial (LA) remodeling is associated with an increment in left atrial pressure (LAP), the importance of assessing LAP and relaxation index as a marker of early left atrial reservoir function in patients who undergo CA for AF is not known. We retrospectively evaluated 102 patients (68 males, age: 67.6 ± 11.4 years) who underwent CA between January and December 2019. We measured LAP during sinus rhythm and the total area of LVZs on the electro-anatomical map during pacing from the coronary sinus, and calculated the relaxation index. We defined LVZs as being significant when they occupied an area of more than 10 % of the entire LA. Seventeen patients (16.7 %) who had significant LVZs were compared with patients without significant LVZs. Age, sex, LA volume index and relaxation index differed significantly between the two groups. In multiple regression analysis, relaxation index was significantly lower in the group with compared to without LVZs (OR 0.22, $p = 0.015$). In conclusion, relaxation index might be a marker of not only early LA reservoir function, but also LVZs, reflecting LA fibrosis.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and correlates with morbidity and mortality [1]. Although catheter ablation (CA) is an effective treatment for AF, recurrence of AF after CA is a common clinical problem [2]. The mechanism of the occurrence and maintenance of AF is complicated [3]. However, it is known to correlate with progressive remodeling of the left atrium (LA). LA remodeling includes electrical and structural remodeling. Electrical remodeling is characterized by up-regulation and down-regulation of ion channels and abnormal expression of gap junctions [4]. On the other hand, structural remodeling is characterized by atrial fibrosis [5], which involves fibroblast and myofibroblast proliferation [6]. Further, atrial fibrosis can become a substrate for AF because of shortening of the action potential and slowing of conduction velocity. On electro-anatomical maps, fibrotic tissue in the LA is recognized as low-voltage zones (LVZs) [7], which have been reported to be associated with the recurrence of AF after CA [8,9]. Previous reports have shown that voltage-based substrate modification after pulmonary vein isolation can improve outcomes

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in patients with AF. However, in clinical practice, LVZs are not investigated in all patients because it is a time consuming procedure, and due to the uncertainty of voltage-based ablation.

LA fibrosis also impairs atrial reservoir function [10]. LA reservoir function is determined by LA relaxation and left ventricular systolic function. LA relaxation, accompanied by an increase in LA volume, occurs in the early LA reservoir phase. The relaxation index (RI), which is calculated based on the LA pressure (LAP) pattern, is a simple indicator of early LA reservoir function [11]. However, this index has rarely been used in clinical practice, because it was so far not possible to measure LAP consistently. Recently, it has become possible to easily measure LAP during CA of AF by trans-septal puncture [12,13]. In the present study, we investigated whether the RI would be useful for identifying AF patients with LVZs in the clinical setting.

METHODS

Study design

This study was a retrospective, single-center, two-arm, observational study conducted by performing a chart review. The study protocol was approved by the institutional review board of our university (1542–5).

Study population

We retrospectively identified 147 AF patients who underwent CA at our university hospital between January and December 2019. We obtained written informed consent for the ablation procedure and participation in the study from all patients. CA for AF was performed according to the guidelines [14]. We excluded 43 of the 147 patients in whom the electro-anatomical map did not provide enough information, and two patients who could not maintain sinus rhythm after completion of CA.

Catheter ablation procedure

CA was performed with the patients under intravenous sedation with dexmedetomidine and using non-invasive positive pressure ventilation (NPPV) to support their respiration. After an 8 + 8 + 4 polar catheter (BeeAT; Japan Lifeline, Tokyo, Japan) was placed in the coronary sinus, we introduced three long sheaths into the left atrium via a single trans-septal puncture. If AF was sustained after trans-septal puncture, we performed internal cardioversion to restore sinus rhythm. All patients underwent circumferential pulmonary vein isolation (CPVI) guided by the electro-anatomical map. A circumferential ablation line was created under the guidance of the three-dimensional (3D) mapping system (CARTO®; Biosense Webster, CA, US). Segmental radiofrequency ablation was performed with an irrigation tip ablation catheter (Thermocool Smarttouch SF; Biosense Webster, CA, US). Cavo-tricuspid isthmus ablation and other additional procedures of superior vena cava isolation, box isolation, mitral isthmus ablation or atrial tachycardia ablation were conducted at the operator's discretion.

LAP measurement

LAP was measured just before finishing the session via the long sheath (Swartz Braided Transseptal Guiding Introducer, Abbott Park, IL, US) under deep sedation and NPPV. We measured an average of two beats at the end of expiration. We measured four components of LAP, peak a, c, v and x descent, and mean pressure and time from the a-wave to x-descent. We described the a-wave pressure as "P(a)", and the time from the a-wave to x-descent as "t(x-a)". The "a-wave" was defined as the protruding part from the baseline in the LAP waveform between the beginning of the P-wave and the peak of the QRS complex in the electrocardiogram (**Figure 1**). RI was quantified as (P(a)-P(x)/P(a))/t(x-a) [11].

Three-dimensional geometry and voltage maps

A 3D geometry and voltage map of the LA and pulmonary veins was created just before CPVI during CS pacing if sinus rhythm was maintained. If it was difficult to maintain sinus rhythm, they were created after CPVI. We created a high-density map using a 20-pole Pentaray Nav Eco mapping catheter (Biosense Webster, CA, US), and Carto3 auto-mapping system (Biosense Webster, CA, US). We defined LVZs as areas with bipolar peak-to-peak voltage amplitudes of < 0.5 mV [15]. LVZs were expressed as a percentage of the total mapped area, excluding the pulmonary veins and LA antrum. LVZs were considered as being significant if they occupied more than 10 % of the total LA surface area (**Figure 2**) [16]. We divided the patients into two groups based on the presence of LVZs: the "LVZ group", which had LVZs over more than 10

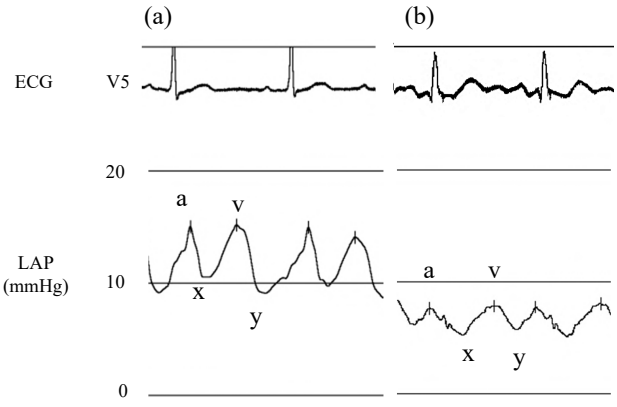

Figure 1 Example of LAP patterns with high RI and low RI with sinus rhythm; (a) LAP pattern of high RI (RI = 2.78 10^{-3}/ms); (b) LAP pattern of low RI (RI = 0.89 10^{-3}/ms).
LAP, left atrial pressure; RI, relaxation index

% of the entire LA, and the "non-LVZ group", in which LVZs occupied < 10 % of the LA area.

Echocardiography and blood sampling

Echocardiography was performed using standard ultrasound equipment (Vivid E9, GE-Vingmed, Horten, Norway; EPIQ 7G, Philips Healthcare, Andover, Massachusetts; Artida, Canon Medical Systems, Tokyo, Japan). Cardiac size and function were evaluated by two-dimensional imaging; left atrial diameters, left atrial volume, interventricular septum thickness (IVST), posterior LV wall thickness (PWT), left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVDs), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF) were measured using the modified Simpson's method. Left atrial volume index (LAVI) was estimated by the biplane area-length method, using measurements in the apical 4- and 2-chamber views at end-systole, and indexed by body surface area. LV mass (LVM) was calculated using the formula: $0.8 \times 1.04 \times [(IVST + LVDd + PWT)^3 - LVDd^3] + 0.6$. LVM index was calculated as the ratio of LVM to body surface area [17].

In all the subjects, a blood sample was collected on admission for routine laboratory determination of serum creatinine and brain natriuretic peptide (BNP) levels. Estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine level, age, and sex [18].

Statistical analysis

Categorical variables are shown as numbers (%) and were compared using the Chi-square test or Fisher's exact test. Variables were expressed as medians with interquartile ranges (IQR). Variables that were normally distributed were compared between groups using Student's t tests, and those that were not normally distributed were compared using Mann–Whitney U tests. Factors associated with LVZs (> 10 %) were investigated using univariate and multivariate logistic regression analysis. A value of $p < 0.05$ was used to define statistically significant values. Data were analyzed using SPSS Statistics version 26.0 (IBM Corp. Armonk, NY, USA).

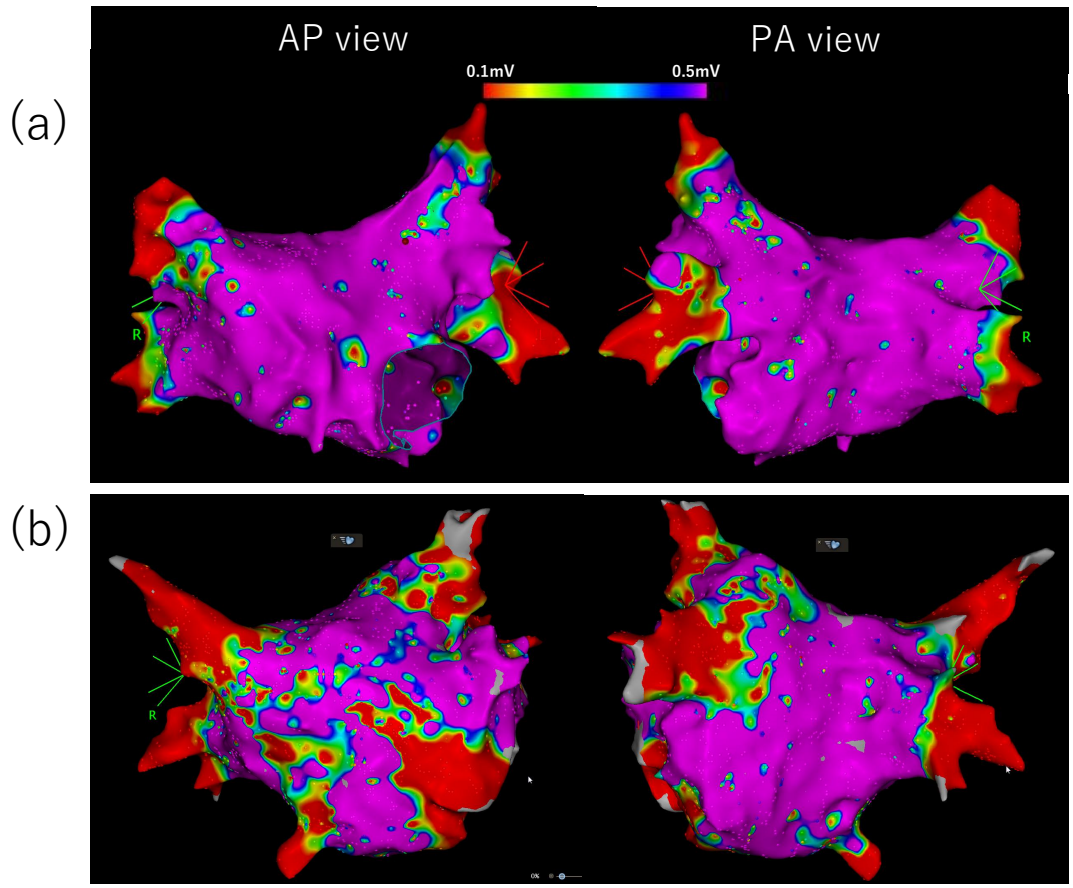

Figure 2 Example of LA voltage map with and without LVZs. In each map, the color gradation indicates serial changes in the electrogram amplitude, from purple at > 0.5 mV to red at < 0.1 mV. (a) indicates the map without LVZs. (b) indicates the map with LVZs in the anterior and septal parts of the LA.
LA, left atrium; LVZ, low voltage zone; AP, anterior-posterior; PA, posterior-anterior

RESULTS

Among 102 patients evaluated, 17 patients (17 %) belonged to the LVZ group and 85 (83 %) patients belonged to the non-LVZ group. The baseline characteristics of the patients are shown in **Table 1**. There were no significant differences in body mass index, AF type, cardiovascular risk factors, BNP levels, and LVEF between the two groups. The LVZ group included significantly more elderly patients, females, patients with a longer duration between diagnosis of AF and CA, and those with low eGFR. On echocardiogram, LAVI was greater in the LVZ group than in the non-LVZ group. In

Table 1 Patients' characteristics

variables	non-LVZ group				LVZ group				*p* value
n	85				17				
Age (yrs)	68.0	(57.5	—	74.5)	76.0	(72.0	—	82.0)	<0.001
Sex (M), *n* (%)	62	(72.9		)	6	(35.3		)	0.004
Persistent AF, *n* (%)	41	(48.2		)	7	(41.2		)	0.79
Diagnosis to CA (month)	5.0	(2.0	—	28.0)	19.0	(10.0	—	42.5)	0.03
Multiple ablation procedure, *n* (%)	16	(18.8		)	4	(23.5		)	0.66
Body mass index (kg/m^2)	23.8	(22.2	—	26.7)	23.5	(21.8	—	25.4)	0.33
Comorbidity									
Hypertension, *n* (%)	51	(60.0		)	11	(64.7		)	0.79
Diabetes mellitus, *n* (%)	12	(14.1		)	1	(5.9		)	0.69
Dyslipidemia, *n* (%)	36	(42.4		)	9	(52.9		)	0.44
Heart failure, *n* (%)	23	(27.1		)	7	(41.2		)	0.26
Thrombolism, *n* (%)	3	(3.5		)	1	(5.9		)	0.52
Coronary artery disease, *n* (%)	10	(11.8		)	3	(17.6		)	0.51
Structual heart disease, *n* (%)	13	(15.3		)	3	(17.6		)	0.81
Echocardiographic data									
LAD (mm)	43.0	(40.0	—	46.0)	46.0	(41.8	—	52.3)	0.046
LAVI (ml/m^2)	37.0	(30.0	—	50.0)	57.5	(40.3	—	66.8)	0.001
LVEDV (ml)	72.5	(62.3	—	83.3)	70.5	(51.0	—	78.3)	0.23
LVESV (ml)	27.0	(22.0	—	33.0)	28.5	(18.8	—	34.3)	0.85
LVEF (%)	63.0	(55.0	—	67.0)	57.5	(40.3	—	66.8)	0.14
E/e'	9.9	(8.2	—	14.5)	14.7	(9.3	—	17.9)	0.22
LVMI (g/m^2)	87.0	(69.0	—	101.0)	84.0	(73.5	—	105.0)	0.60
≧ 3 degree MR, *n* (%)	1	(1.2		)	3	(17.6		)	0.014
Labolatory data									
Estimated GFR (ml/min/1.73m^2)	62	(54	—	71)	54.5	(48.8	—	66.5)	0.038
BNP (pg/dl)	85.1	(26.8	—	188)	122	(73.2	—	225.5)	0.064
Medication									
Class I antiarrhythmic drugs, *n* (%)	26	(30.6		)	12	(70.6		)	0.005
Amiodarone, *n* (%)	4	(4.7		)	0	(0		)	0.36
Beta blocker, *n* (%)	46	(54.1		)	10	(58.8		)	0.79

AF, atrial fibrillation; Diagnosis to CA, duration between diagnosis of AF and catheter ablation; LAD, left atrial diameter; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVZ, low voltage zones; MR, mitral regurgitation; GFR, glomerular filtration rate; BNP, brain natriuretic peptide; Class I antiarrhythmic drugs, class I antiarrhythmic drugs according to Vaughan Williams classification.

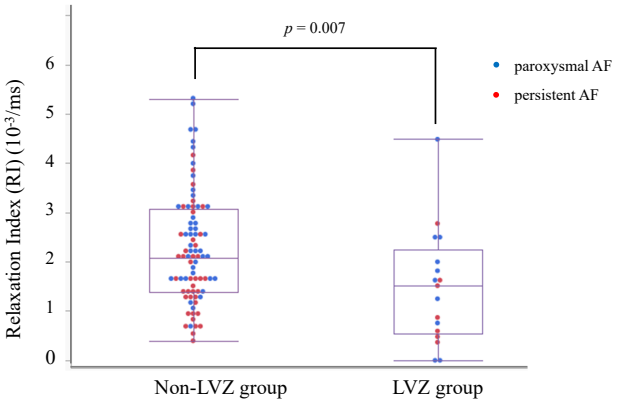

Figure 3 Differences in RI between the non-LVZ and LVZ groups. The red points show persistent AF and the blue points show paroxysmal AF. RI, relaxation index; LVZ, low voltage zone; AF, atrial fibrillation

addition, the LVZ group had a higher frequency of class I antiarrhythmic drug usage.

LA pressure data are shown in **Table 2**. There were no significant differences in *P* (a), *P* (x), *P* (v), *P* (m) and t (x-a) between the LVZ and non-LVZ groups. The LVZ group had lower *P* (a) – *P* (x) and RI than the non-LVZ group, although *P* (v) – *P* (x) was not different between the two groups. As seen in the box plot in Figure 3, the RI value did not seem to change depending on whether the patient had paroxysmal or persistent AF, although it seemed to be greatly affected by the presence or absence of LVZs. Logistic regression analysis was performed to evaluate the correlation between the observed factors and the presence of LVZs. In univariate analysis, the presence of LVZs correlated with age, sex, LAD, LAVI and RI (**Table 3**). In multivariate analysis, LVZs were independently associated with low RI adjusted for age, sex and LAVI (**Table 3**).

Table 2 Left atrial pressure during catheter ablation

variables	non-LVZ group						LVZ group						*p* value
n			85						17				
P (a) (mmHg)	14	(	10	–	18	)	13	(	10	–	18.5	)	0.91
P (c) (mmHg)	13	(	10	–	17	)	13	(	11	–	19	)	0.58
P (x) (mmHg)	8	(	6	–	12	)	10	(	6	–	17	)	0.13
P (v) (mmHg)	14	(	10	–	20	)	17	(	13	–	24	)	0.061
P (m) (mmHg)	10	(	7	–	14	)	10	(	9	–	17	)	0.207
P (a) - *P* (x) (mmHg)	5	(	3	–	6	)	3	(	1	–	4	)	0.001
P (v) - *P* (x) (mmHg)	6	(	4	–	9	)	8	(	5	–	11	)	0.23
t (a-x) (ms)	160	(	120	–	230	)	160	(	120	–	200	)	0.14
Relaxation Index (10^{-3}/ms)	2.08	(	1.39	–	3.07	)	1.51	(	0.54	–	2.25	)	0.007

P (a), left atrial pressure at a wave; *P* (c), left atrial pressure at c wave; *P* (x), left atrial pressure at x descent; *P* (v), left atrial pressure at v wave; *P* (m), mean left atrial pressure; t (a-x), time from a wave to x descent

Table 3 Univariate and multivariate linear regression analysis of parameters predicting the presence of LVZs

	univariate							multivariate						
	OR		95 % CI				*p* value	OR		95 % CI				*p* value
Age (yrs)	1.15	(	1.053	–	1.26	)	0.002	1.19	(	1.047	–	1.34	)	0.007
Female	4.94	(	1.64	–	14.9	)	0.005	6.33	(	1.14	–	35.4	)	0.036
PeAF	0.75	(	0.26	–	2.16	)	0.6							
Body mass index (kg/m^2)	0.90	(	0.78	–	1.05	)	0.19							
Heart failure	1.88	(	0.64	–	5.55	)	0.25							
LAVI (ml/m^2)	1.06	(	1.02	–	1.1	)	0.003	1.025	(	0.97	–	1.079	)	0.36
LVEF (%)	0.99	(	0.95	–	1.05	)	0.89							
LVMI (g/m^2)	1.003	(	0.98	–	1.02	)	0.75							
eGFR (ml/min/1.73m^2)	0.97	(	0.93	–	1.001	)	0.059							
BNP (pg/dl)	1.003	(	0.99	–	1.007	)	0.14							
Diagnosis to CA (month)	1.007	(	0.99	–	1.02	)	0.42							
Relaxation index (10^{-3}/ms)	0.47	(	0.25	–	0.85	)	0.013	0.22	(	0.065	–	0.75	)	0.015

OR, odds ratio; CI, confidence interval; PeAF, persistent atrial fibrillation; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; Diagnosis to CA, duration between diagnosis of AF and catheter ablation.

DISCUSSION

In the present study, we found that LVZs (burden of LVZs > 10 %) were detected in 17% of AF patients, and the presence of LVZs was associated with a lower RI, higher LAVI, low eGFR, female sex and older age. On multivariate analysis, lower RI and age were independently associated with the presence of LVZs. To the best of our knowledge, this is the first study to examine the association between LVZs and LA reservoir function in the clinical setting.

The recent development of a 3D mapping system and consequent high-quality imaging of the LA has facilitated calculation of LVZs, with an LVZ proportion of > 10 % reflecting LA fibrosis [7]. Several studies have evaluated the presence of LVZs and reported that the presence of LVZs after CA for AF is a powerful predictor of AF recurrence [8,19–21]. This could be because the presence of LVZs facilitates macro re-entrant atrial tachycardia and serves as an intramural re-entry area that drives AF [22,23]. It has also been reported that non-pulmonary vein triggers arise from the LVZ and correlate with AF recurrence [24]. In addition, various ablation strategies associated with LVZs have been reported, and it has been suggested that these strategies (LVZ guided ablation, in addition to CPVI) improve the outcomes compared to CPVI alone, suggesting that LVZs have arrhythmogenic properties and are involved in the refractoriness and persistence of AF. Therefore, information on the presence of LVZs is very useful for CA operators.

Previous studies have shown that predictive factors for the presence of LVZs include older age, female sex, LAVI, E/e', and persistent AF [25,26]. On the other hand, increased LAP provokes the occurrence and persistence of AF [27]. Elevated LAP leads to stretching and dilatation of the LA to compensate for the rising atrial wall stress, which might subsequently result in AF. Although LAP can be measured directly during CA, there have been no reports to date evaluating LAP waveforms for the detection of LVZs. In this study, the LVZ group did not differ in the frequency of persistent AF, although the time from diagnosis of AF to CA was significantly longer, perhaps reflecting the left atrial enlargement. However, multivariate analysis showed that RI was associated with the presence of LVZs independent of these parameters, which might have high diagnostic significance.

The LA affects cardiac performance in a variety of ways: as a booster, a reservoir, and a conduit. Using a circulatory model, Suga et al. hypothesized that LA reservoir capacity contributes to maintaining cardiac output [28]. Barbier et al. described LA reservoir function in detail, dividing it into two phases (early and late) by referring to the transition of the LA area change rate [11]. They demonstrated that LA early reservoir function was determined by active LA contraction and relaxation, and LA late reservoir function by LA stiffness and LV longitudinal fiber shortening. In the present study, LVZs were associated with the RI calculated from the early phase of LAP. Although previous reports showed that mean or maximum LAP is associated with AF recurrence after CA, in those studies LAP was affected by LA preload and heart rate [12,13]. In the present study, the presence of LVZs was not associated with max and mean LAP. Additionally, measurement of RI is very easy, and its value is not affected by heart rate and/or volume overload [29].

Our findings indicate that RI is associated with LVZs in patients with AF, whether persistent or paroxysmal. RI is useful not only for assessing LA reservoir function, but also for predicting the presence of LVZs.

Clinical implication

LAP can be easily and rapidly measured during CA, and the RI derived from LAP can predict the presence of LVZs more easily and quickly than other methods (e.g., voltage map of the entire left atrium, LA strain, MRI or 3D mapping). When the presence of LVZs is suspected from the RI, investigations for abnormal LA substrates and/or the occurrence of scar-related atrial tachycardia should be conducted to determine the need for additional CA. In the clinical setting, easy measurement of LAP at the end of a CA session would help to determine if an additional session is needed. In addition, LAP measurement is useful for evaluating heart failure, and, in fact, it has been reported that elevated LAP after CA is associated with heart failure events without AF recurrence [30]. Thus, we believe that calculation of the RI from LAP during CA is useful for predicting the presence of LVZs, the likelihood of recurrence of AF, and heart failure outcomes.

Limitations

The present study has several limitations. First, this was a small, single-center study. Second, the invasive and non-invasive markers were not measured at the same time. Therefore, laboratory data and echocardiogram parameters might not have directly reflected LAP. However, these parameters were assessed within one month of each other. Third, we measured LAP after completion of CA because some patients could not maintain sinus rhythm before CPVI. Therefore, we did not know the RI until the end of the CA session. Additionally, LAP is affected by volume overload and/or heart rate. However, as mentioned above, assessment of the RI would be beneficial by allowing easier determination of the need for additional CA as compared to the labor-intensive color mapping method. Furthermore, as also mentioned above, RI is less affected by volume overload and/or heart rate [29]. Finally, this study did not examine the prognosis of these patients. As previously described, low LA reservoir function predicts poor outcomes in terms of AF recurrence, cardiovascular events and LA reverse remodeling. In the future, it is necessary to prospectively investigate the association between RI and these outcomes.

CONCLUSION

We evaluated the association between RI and the presence of LVZs, which is an indicator of LA fibrosis. Future studies should assess the prognosis of AF recurrence, cardiovascular events and LA reverse remodeling in patients with a low RI after CA for AF.

ACKNOWLEDGEMENTS

We thank Ms. Megumi Hashimoto, Hitomi Iwai, and Taeko Ishikawa for their excellent technical support.

DISCLOSURE STATEMENT

None

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Received August 15, 2022
Accepted October 11, 2022