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Evaluation of the atrial substrate based on low-voltage areas and dominant frequencies after pulmonary vein isolation in nonparoxysmal atrial fibrillation

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Abstract

Background: This study aimed to evaluate the atrial substrate in the left atrium (LA) by low-voltage areas (LVAs) and high-dominant frequencies (DFs) after circumferential pulmonary vein isolation (PVI) in nonparoxysmal atrial fibrillation (AF).

Methods: In 70 patients with nonparoxysmal AF patients (41 persistent AF), LA voltage maps were created during sinus rhythm by external cardioversion after PVI and DF mapping. The patients were divided into AF-free and AF-recurrent groups.

Results: The AF freedom rate without antiarrhythmic drugs was 69.0% after PVI after 1 procedure during a 12-month follow-up. There was a significant difference in the LVA (<0.5 mV)/LA surface area after PVI between the AF-free and AF-recurrent groups (15% vs 23%, $P = .033$). AF freedom was significantly greater in those with LVAs of ≤24% than in those with LVAs of >24% during 12 months of follow-up (78.6% vs 53.8%, Log-rank test $P = .020$). Fifty-six (72%) of the 78 high-DF sites (≥8 Hz) overlapped with LVAs. Thirty-one (55%) of 56 high-DF sites overlapped with LVAs that existed at LVA border zones. There were no significant differences in number of high-DF sites that overlapped with LVAs in the LA between the two groups. However, in persistent AF patients, the max-DF value in the LA exhibited a significant difference between the two groups ($P = .008$).

Conclusions: LVAs were associated with AF recurrences after PVI in nonparoxysmal AF patients and overlapped with many high-DF sites. PVI alone may be enough to treat patients with mild-to-moderate extent (≤24%) of LVAs.

KEYWORDS
atrial fibrillation, catheter ablation, dominant frequencies, low-voltage areas, pulmonary vein isolation

1 | INTRODUCTION

Circumferential pulmonary vein isolation (PVI) has become an established approach for atrial fibrillation (AF) ablation.[1] PVI is insufficient as a lone strategy for persistent AF, and additional substrate modification is the creation of linear lesions in the left atrium and focal ablation to eliminate atrial signals that demonstrate complex fractionated atrial electrograms (CFAEs) during AF.[2,3] However, no

reduction in the rate of recurrent AF has been found when either linear ablation or ablation of CFAEs was performed in addition to PVI.[4] Meanwhile, atrial sites that represent local electrograms with high-dominant frequencies (DFs≧8 Hz) may be associated with AF maintenance.[5] Spectral analysis and frequency mapping identify localized sites of high-frequency activity during AF in humans in paroxysmal and permanent AF. Ablation at these sites results in prolongation of the AFCL and termination of paroxysmal AF (who may have relatively less LVAs), indicating their role in the maintenance of AF.[6] Therefore, high-DF sites as surrogates for localized sources maintaining AF were potential AF ablation targets. A recent study reported that a high-DF site ablation following PVI was effective in paroxysmal AF patients and nonparoxysmal AF patients with continuous AF for a duration of a few years.[5] However, the significance of DF-guided ablation is controversial.[7] Meanwhile, localized electrical sources (rotor and focal impulse) have been reported to be prevalent sustaining mechanisms of human AF using a specific computational mapping device.[8] The patients who underwent a FIRM (focal impulse and rotor modulation)-guided ablation maintained a higher freedom from AF.

Low-voltage areas (LVAs) as detected by LA voltage mapping have been shown to be a predictor of atrial tachycardia and AF recurrence after AF ablation.[9,10] LVAs indicate atrial structural remodeling involving atrial fibrosis and scar tissue. Although various additional LVA-guided substrate modifications after PVI have been reported in nonparoxysmal AF patients with LVAs, the outcome and approach vary widely according to the size and distribution of the LVAs.[11–13] A tailored LVA-guided ablation may need a personally adapted large or complicated lesion design in some patients. However, it is difficult to modify the diffuse fibrotic atrial areas or massive fibrosis. Whether all LVA sizes should be potential targets for modification or not remains unclear.

Further, high-DF sites can be recorded not only in LVAs but also healthy atrial myocardium. The relationship of the atrial substrate between LVAs and sites with high-DFs has not yet been evaluated. This study aimed to evaluate relationship of the LA atrial substrate between LVAs and high-DFs sites after circumferential pulmonary vein isolation in nonparoxysmal AF.

2 | METHODS

2.1 | Study population

This study included 70 patients (65 ± 9 years) with AF who underwent catheter ablation at our institution between July 2014 and December 2015. The patients included 41 with persistent AF and 29 with long-standing persistent AF (mean duration 22 ± 31 months). Persistent AF was defined as AF lasting ≥7 days but <1 year and long-standing persistent AF as continuous AF lasting ≥1 year.[14] All antiarrhythmic drugs were discontinued for at least 5 half-lives, and no patients received any oral amiodarone therapy before the electrophysiological study. The protocol for this research project has been approved by a suitably constituted Ethics Committee of the Institution of Gunma Prefectural Cardiovascular Center (Date of IRB approval; January 23, 2017; Approval number, 28017) and it conforms to the provisions of the Declaration of Helsinki. All patients provided written informed consent for the electrophysiological study, ablation procedure, and use of their anonymized data in this study.

2.2 | Electrophysiological study

A NavX system (St. Jude Medical Inc., St. Paul, MN) was used for catheter ablation. A 5-french deflectable catheter was inserted into the coronary sinus (CS) via the right femoral vein. The trans-septal procedure was performed using fluoroscopic landmarks, and three 8-F SL0 sheaths (St. Jude Medical, Inc.) were advanced into the LA. After the trans-septal procedure, a single bolus of 5000U of heparin was administered. A continuous infusion with heparinized saline was delivered to maintain an activated clotting time of 300 to 350s. The 3D biatrial geometry was created on the NavX system, and sequential contact mapping was performed using a 7-F decapolar circular catheter (Lasso, Biosense-Webster, Inc., Diamond Bar, CA). The LA was divided into nine areas (pulmonary veins [PVs], roof, left atrial appendage [LAA], LA septum, lateral, anterior, bottom, posterior, and CS) and RA into seven (lateral, anterior, posterior, cavotricuspid isthmus, superior vena cava, inferior vena cava, and RA septum) for a location analysis of the AF substrate.[5] The points in each region were similar in number and nearly equally distributed.

2.3 | Ablation procedure

The PVI was performed guided by two 7-F decapolar circular catheters (Lasso, Biosense-Webster, Inc.) positioned at the ipsilateral PV ostia. At the anterior aspect of the left PVs, an ablation line was created along the ridge between the LAA and PV ostium. Each radiofrequency (RF) energy application was delivered for 40s. A 3.5 mm irrigated tip RF catheter (Safire, St. Jude Medical Inc.) was used with the temperature limited to 42°C and power to 30W (with a flow rate of 13 mL/min). A maximum power of ≤25W was used while delivering energy to sites near the esophagus. After the elimination or dissociation of the PV potentials, exit block was confirmed by pacing from circular catheters placed within the PVs.

After the PVI, frequency analyses were performed. And LA voltage map was constructed during sinus rhythm (SR) after external cardioversion. The procedure was completed with a cavotricuspid isthmus ablation in all patients who regained sinus rhythm.

2.4 | Frequencies analysis

DF mapping was performed during AF after PVI. The fast Fourier transform (FFT) method has been described previously.[5,6,15] Recordings at each site were 5 seconds in length using a high-density (HD) 20-pole mapping circular catheter (St. Jude Medical, Inc.). Signals were truncated to 5 seconds at sampling rates of 1000 Hz, providing 4096 points for analysis (resolution 0.50 Hz). The signals were rectified and processed by a Hanning window function and filtered from

2 to 20 Hz. A manual entry of the DF value was used into the NavX system. The point DF was determined as the frequency associated with the maximum peak power of the spectrum. Only DF points with a regularity index >0.2 were included.[6,15] The high-DF sites were defined as DFs of ≥8 Hz.[5,6]

2.5 | LVAs mapping and analysis

After circumferential PVI, a detailed bipolar LA voltage map was constructed during SR after external cardioversion. The method of LVA mapping has been described previously.[11] The mapping points were systematically acquired with a decapolar circular catheter (Inquiry Optima or Reflexion Spiral; St. Jude Medical). An interpolation threshold of 10 mm was used for the surface color projection. Filling all color gaps provided a minimal map density in all parts of the LA. Adequate endocardial contact was assessed by stable electrograms and consideration of the distance to the geometry surface. Only true sinus beats were selected. Bipolar electrograms were filtered by a bandpass to frequencies between 30 and 500 Hz. In accordance with previous studies[9,16] LVA was defined as area with bipolar peak-to-peak electrogram amplitude <0.5 mV and electrical scar areas <0.1 mV, and covering >5% of the LA body surface area. The LA surface area was defined as the LA body area without the PV antrum regions inside the PVI line.

All patients underwent a prospective electrocardiogram (ECG)-gated computed tomography (CT) scan with a dual source 64-slice multidetector computed tomography (MDCT)-scanner (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany; 0.33s gantry rotation time, 120 kV, and 320 mA) before the catheter ablation. Then, fusion of the MDCT image and electro-anatomical mapping was performed, and the overlap between the LVAs and high-DF sites was evaluated manually by 2 independent blinded observers. As a definition of high-DF sites overlapping with LVAs, high-DF sites were located within LVAs or at their border zones.[17]

2.6 | Postprocedure care and follow-up

A clinical interview, surface ECG, and 24-h Holter monitoring were performed 1 day after the procedure and repeated 1, 3, 6, 9, and 12 months after the catheter ablation. Antiarrhythmic medications were continued for at least 3 months to prevent any early recurrences. AF recurrence was defined as sustained AF lasting more than 30 seonds, which occurred more than 3 months after the catheter ablation.[14]

2.7 | Statistical analysis

The continuous variables are presented as the mean ± standard deviation together with 95% confidence intervals. Categorical variables are expressed as numbers and percentages. The significance of any differences between two groups was analyzed with an unpaired *t* test and Mann-Whitney *U* test for continuous variables, and with a Fisher's exact probability test for categorical variables. A predictive analysis of AF recurrence during the follow-up period was assessed using multivariate Cox proportional hazard regression models. A multivariate analysis with multivariate Cox proportional hazard regression models was performed to isolate the independent criteria of AF recurrence after ablation. Only the variables with significant *P*-values in the univariate analysis were included in the multivariate Cox proportional hazard regression. A Kaplan-Meier event-free survival analysis was conducted to assess the cumulative freedom from AF recurrence. A value of $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

The patient characteristics are shown in Table 1. The mean age of all patients was 65 ± 9 years old. A total of 70 consecutive AF patients including 41 (58%) with persistent AF and 29 (42%) with long-standing persistent AF were enrolled. The body mass index (BMI) and body surface area were 21.2 ± 2.9 kg/m^2 and 1.78 ± 0.16 m^2, respectively. None except for 3 (2 with old myocardial infarctions, and 1 with hypertrophic cardiomyopathy) had structural heart disease. The BNP level was elevated in almost all patients.

3.2 | Outcome of the catheter ablation

A PVI was successfully achieved in all PVs. AF freedom off AADs was 68.3% and 69.0%, respectively, in the persistent and long-standing AF patients after 1 procedure over a 12-month follow-up period. The patients were divided into two groups, those in whom AF was prevented by catheter ablation (AF-free group, n = 48) and those in whom AF recurred (AF-recurrent group, n = 22). The patient characteristics and laboratory data did not differ between the two groups except for the LA diameter in the AF-recurrent group as compared to the AF-free group (Table 1). The SR ratio at the start of the procedure and AF termination during ablation did not differ between the two groups (Table 2). In 2 patients, the PVI was performed under SR after cardioversion due to unstable hemodynamic conditions. The RF time for the PVI and total procedure time did not differ between the two groups. There were no cases of cerebral infarctions, cardiac perforations, tamponades, PV stenosis, or atrial-esophageal fistulae.

3.3 | LVAs and frequencies analysis

The characteristics of the LVAs and frequencies are shown in Table 2. LA voltage maps were created during SR in all patients with 1175 ± 363 mapping points per patient. There was a significant difference in the LA LVAs (<0.5 mV) after PVI between the AF-free and AF-recurrent groups among all patients with persistent and long-standing persistent AF (14 cm^2 vs 23 cm^2, $P = .018$; 15% vs 23%, $P = .033$). No LVAs were identified in 13 (19%) patients. LVAs

TABLE 1 Patient characteristics

	All N = 70)	AF-free group (n = 48)	AF-recurrent group (n = 22)	*P* value
Age, y	65 ± 9	64 ± 8	66 ± 9	.299
Men, n (%)	54 (77)	38 (79)	16 (73)	.554
Duration of AF, mo	22 ± 31	19 ± 22	25 ± 42	.641
Persistent AF, n (%)	41 (58)	28 (58)	13 (59)	.952
Long-standing persistent AF, n (%)	29 (42)	20 (42)	9 (41)	
CHA2DS2-VASc score	2.2 ± 1.6	2.1 ± 1.5	2.6 ± 1.7	.248
Hypertension, n (%)	48 (69)	33 (69)	15 (68)	.962
Structural heart disease, n (%)	3 (4)	2 (4)	1 (5)	.943
BMI (kg/m^2)	21.2 ± 2.9	21.0 ± 3.4	21.7 ± 1.4	.622
Body surface area (m^2)	1.78 ± 0.16	1.78 ± 0.16	1.79 ± 0.17	.8
LA diameter (mm)	44 ± 5.2	43 ± 4.4	46 ± 5.9	.031
LVEF (%)	58 ± 9.5	56 ± 10	60 ± 7.8	.291
LAA flow velocity (cm/s)	46 ± 20	49 ± 19	43 ± 20	.18
BNP (pg/mL)	223 ± 189	223 ± 196	224 ± 184	.593
Number of failed AADs	1.4 ± 0.7	1.4 ± 0.8	1.3 ± 0.5	.925

AF, atrial fibrillation; AADs, antiarrhythmic drugs; BMI, body mass index; BNP, B-type natriuretic peptide; LA, left atrium; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; RA, right atrium.

were frequently identified at the septum, anterior, inferior, and posterior wall of the LA. There were significant differences in the LVAs at the anterior, lateral, and posterior wall of the LA between the two groups. A cut-off of 24% for the LVAs was determined for the freedom from AF recurrence with a 52.2% sensitivity and 78.0% specificity (area under the receiver operating characteristic curve of 0.654, $P = .035$). A Kaplan-Meier event-free survival analysis was conducted to assess the cumulative freedom from AF recurrence. AF freedom was significantly greater in those with LVAs of ≤24% than in those with LVAs of>24% after 1 procedure during 12 months of follow-up (78.6% vs 53.8%, log-rank test $P = .020$; Figure 1). AF freedom in patients without LVAs was 12 (93%) of 13.

TABLE 2 Mapping and ablation results

	All (N = 70)	AF-free group (n = 48)	AF-recurrent group (n = 22)	*P* value
SR at procedure begin, n, %	9 (13)	8 (17)	1 (4)	.163
AF termination, n, %	13/61 (21)	6/40 (15)	7/21 (33)	.099
Distribution of LVAs				
Anterior, %	4.3	3.6	5.8	.04
septum, %	4.4	3.9	5.8	.123
lateral, %	1.9	1.3	3.3	.011
posterior, %	2.8	2.4	3.8	.02
inferior, %	3	2.7	3.8	.133
roof, %	1.8	1.7	2.2	.206
LAA, %	1.4	1.1	2	.123
LVA area, median (Q1-Q3), cm^2	16 (7-31)	14 (5-23)	23 (12-43)	.018
LVA area/LA surface area after PVI, median (Q1-Q3), %	16 (6-28)	15 (5-24)	23 (12-32)	.033
Max-DF value in LA, Hz	9.8 ± 1.1	9.7 ± 1.1	9.9 ± 1.2	.533
Max-DF value in RA, Hz	9.6 ± 1.0	9.6 ± 1.0	9.6 ± 1.1	.832
Inducibility after PVI, n, %	16/65(25)	10/48 (21)	6/17 (35)	.234
Total procedure time, min	201 ± 37	197 ± 28	213 ± 52	.282
RF time for PVI, min	35 ± 9	34 ± 7	37 ± 12	.556

AF, atrial fibrillation; DF, dominant frequency; LAA, left atrial appendage; LVAs, low-voltage areas; PVI, pulmonary vein isolation; RA, right atrium; SR, sinus rhythm.

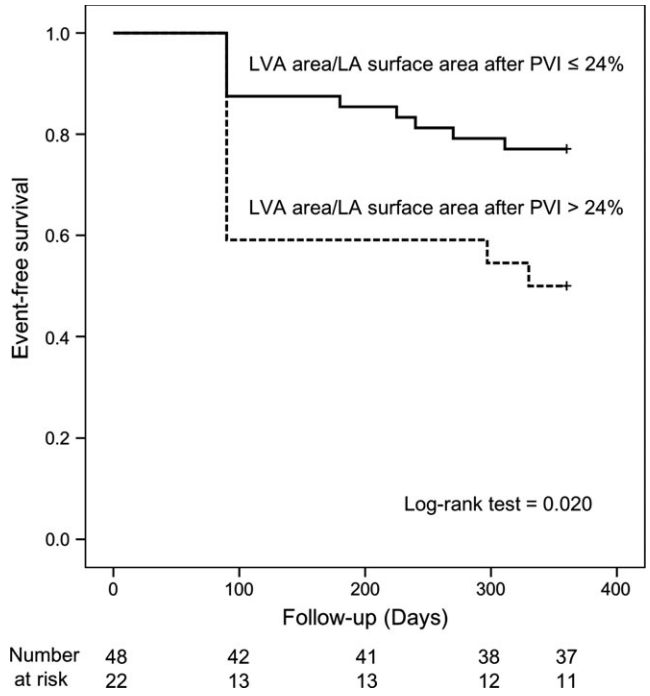

FIGURE 1 Kaplan-Meier event-free survival analysis for the cumulative freedom from AF/AT recurrence. AF/AT freedom was significantly greater in those with LVAs of ≤24% than in those with LVAs of>24% after 1 procedure during 12 mo of follow-up (78.6% vs. 53.8%, log-rank test $P = .020$)

Table 3 shows the overlap between the LVAs and high-DF sites. High-DF sites were found in 39 (85%) of 46 patients in whom DF mapping was performed during AF after the PVI. The number of the high-DF sites in the LA and RA was 1.7 and 0.6 per patient after the PVI, respectively. The max-DF value was found at the LVAs in 31 (79.5%) of 39 patients with high-DF sites. The max-DF value in the LA and RA did not differ between the AF-free and AF-recurrent groups (Table 2).

Figure 2 shows the distribution of the LVAs and high-DF sites in the LA after the PVI. Twenty-two (28%) of 78 high-DF sites in the LA were found in healthy atrial myocardium. Fifty-six (72%) of 78 high-DF sites in the LA overlapped with LVAs. Thirty-one (55%) of 56 high-DF sites overlapped with LVAs existing at border zones of LVAs (Figure 3). The overlap between the LVAs and high-DF sites were frequently identified at the inferior wall, anterior wall, and roof of the LA. There were no significant differences in the number of high-DF sites that overlapped with or were at border zones of LVAs in any LA segments between the two groups (Table 3).

A univariate Cox proportional hazard regression analysis including the LVA/LA surface area after the PVI, max-DF value in the LA and RA, LA diameter, AF termination, SR at the start of the procedure, age, AF duration, BNP, and CHA2DS2-VASc score indicated that the LVA/LA surface area after the PVI (hazard ratio (HR) 1.025; confidence interval (CI), 1.002-1.048, $P = .033$) and LA diameter (HR 1.097; CI, 1.007-1.196, $P = .035$) were significantly associated with AF recurrence. In a multivariate analysis, the LVA/LA surface area

TABLE 3 Overlapped high-DF sites in LA

	Total	AF-free group	AF-recurrent group	*P* value
LA anterior, n				
High-DF sites	17	13	4	.393
High-DF sites overlapped with LVAs	12	8	4	.857
High-DF sites at border zones of LVAs	5	3	2	.659
LA septum, n				
High-DF sites	12	8	4	.857
High-DF sites overlapped with LVAs	9	6	3	.881
High-DF sites at border zones of LVAs	2	2	0	.335
LA lateral, n				
High-DF sites	7	4	3	.473
High-DF sites overlapped with LVAs	6	3	3	.289
High-DF sites at border zones of LVAs	6	3	3	.295
LA posterior, n				
High-DF sites	6	4	2	.906
High-DF sites overlapped with LVAs	4	2	2	.398
High-DF sites at border zones of LVAs	1	0	1	.138
LA inferior, n				
High-DF sites	16	13	3	.186
High-DF sites overlapped with LVAs	15	10	5	.834
High-DF sites at border zones of LVAs	13	8	5	.516
LA roof, n				
High-DF sites	14	7	7	.072
High-DF sites overlapped with LVAs	10	5	5	.167
High-DF sites at border zones of LVAs	4	2	2	.398
LA LAA, n				
High-DF sites	6	5	1	.41
High-DF sites overlapped with LVAs	0	0	0	-
High-DF sites at border zones of LVAs	0	0	0	-
Total, n				
High-DF sites	78	54	24	.819
High-DF sites overlapped with LVAs	56	34	22	.243
High-DF sites at border zones of LVAs	31	18	13	.152

AF, atrial fibrillation; DF, dominant frequency; LAA, left atrial appendage; LVAs, low-voltage areas; PVI, pulmonary vein isolation; RA, right atrium; SR, sinus rhythm.

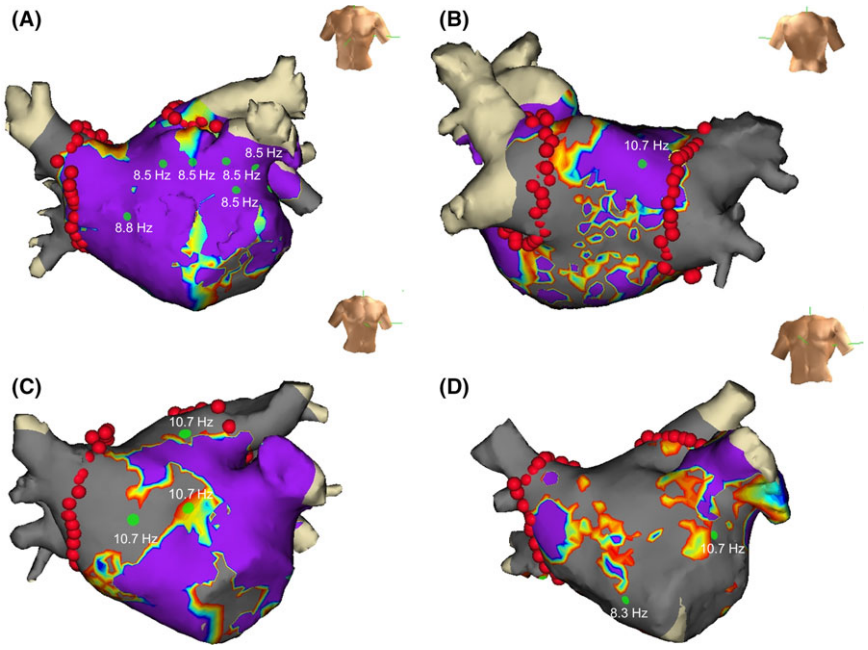

FIGURE 2 Distribution of the LVAs and high-DF sites in the LA after PVI. Voltage map with an LVA and high-DF sites in the LA are shown. In patients with fewer LVAs (LVA/LA surface area: 6%), only high-DF sites were found on the anterior wall (A). In the patients with LVAs on the posterior wall (LVA/LA surface area: 25%), a high-DF site was found in normal myocardium apart from the LVAs (B). The high-DF sites existed within and at LVA border zones on the anterior wall (LVA/LA surface area: 39%) (C). LVAs existed over a wide area of the LA. The high-DF sites existed within and at LVA border zones on the anterior and septum wall (LVA/LA surface area: 59%) (D). The red tags show the PVI ablation points. The green tags show the high-DF sites. Color coding is defined as follows: <0.1 mV = scar (gray), 0.1 to 0.5 mV = diseased atrial tissue, >0.5 mV = healthy atrial myocardium (purple). The high-DF site was determined as the frequency associated with the maximum peak power of the spectrum. DF = dominant frequency

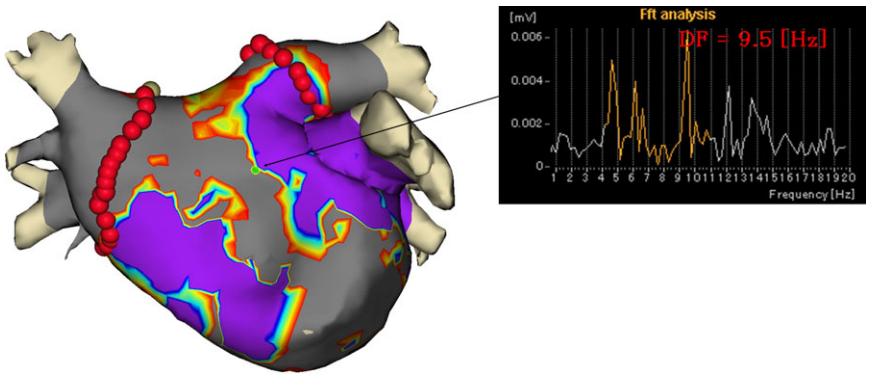

FIGURE 3 The high-DF sites at LVA border zones on the anterior wall. The red tags show the PVI ablation points. The green tags show a high-DF site. A regularity index = 0.25

after the PVI (HR 1.021; CI, 0.997-1.046, P = .087) and LA diameter (HR 1.078; CI, 0.992-1.173, P = .078) were not independent predictors of AF recurrence.

3.4 | LVAs and frequency analyses in persistent AF patients

LVA/LA surface area in the LA after the PVI did not differ between the AF-free and AF-recurrent groups in persistent AF patients (P = .576). However, in persistent AF patients, the LA max-DF value was significantly greater in the patients in the AF-recurrent groups than AF-free group (P = .008; Table 4). Twenty-four (77%) of 31 high-DF sites in the LA overlapped with LVAs. Twelve (50%) of 24 high-DF sites overlapped with LVAs existing at border zones of LVAs in the persistent AF patients.

4 | DISCUSSION

4.1 | Major findings

The major findings of the present study were as follows: (i) in non-paroxysmal AF patients, the LVA/LA surface area in the LA after the PVI had a significant difference between the AF-free and AF-recurrent groups; (ii) AF freedom after the PVI was significantly greater in

TABLE 4 Mapping and ablation results in persistent AF

	All (N = 41)	AF-free group (n = 30)	AF-recurrent group (n = 11)	*P* value
SR at procedure begin	8 (20%)	7 (23%)	1 (9%)	.495
AF termination	9/33 (27%)	4/23 (17%)	5/10 (50%)	.057
LA diameter (mm)	44 ± 5.1	43 ± 4.0	45 ± 6.3	.193
LVA area/LA surface area after PVI, median (Q1-Q3), %	15 (7-25)	15 (7-25)	16 (7-29)	.576
Max-DF value in LA, Hz	9.8 ± 1.1	10 ± 0.9	11 ± 0.2	.008
Max-DF value in RA, Hz	9.6 ± 1.0	9.6 ± 1.0	10 ± 1.0	.369
Inducibility after PVI	10/38 (26%)	7 (33%)	3/8 (38%)	.425

AF, atrial fibrillation; DF, dominant frequency; LA, left atrium; LAA, left atrial appendage; LVAs, low-voltage areas; PVI, pulmonary vein isolation; RA, right atrium; SR, sinus rhythm.

those with LVAs of ≤24% than in those with LVAs of >24% after 1 procedure during 12 months of follow-up; (iii) AF freedom after the PVI in nonparoxysmal AF patients with no LVAs was 92%; (iv) many high-DF sites overlapped with LVAs, and about half of the high-DF sites overlapped with LVAs existing at border zones of LVAs; and (v) in persistent AF patients, the LA max-DF value, not LVAs, exhibited a significant difference between the two groups.

4.2 | Previous reports of LVAs

LVAs were defined as areas with bipolar peak-to-peak voltage amplitudes of <0.5 mV. The definition of the value was based on the minimum grade of LA fibrosis evaluated by delayed-enhancement magnetic resonance imaging (MRI).[9] An increased amount of fibrosis as detected by LA voltage mapping has been shown to be a predictor of atrial tachycardia and AF recurrence after AF ablation.[9–13] LVAs have the electrophysiological effects of altered conduction, heterogeneous refractoriness, and rapid repetitive activity.[18,19] In addition, LVAs have a regional distribution of the septum, anterior, inferior, and posterior wall of the LA as we described in this study, which may be related to contact from external structures, including the aorta and vertebrae.[20]

4.3 | Optimal size of LVAs for substrate modification

The relationship between the size of the LVAs and AF recurrence has not been fully evaluated. In the previous report using delayed-enhancement MRI, according to the extent of enhancement, atrial remodeling of the LA wall was divided into 3 types; mild enhancement of <15%, moderate enhancement between 15% and 35%, and extensive enhancement of >35%.[9] However, the optimal LVA size required for an additional substrate modification remains unclear. In this study, a cut-off of 24% for the LVA was determined for the freedom from AF recurrence after the PVI. AF freedom had a good result of 78.6% in those with LVAs of ≤24% after a PVI alone. In addition, AF freedom in patients with no LVAs had a good result (92%), indicating that substrate modification is unnecessary in nonparoxysmal patients without LVAs. The LVAs at the anterior, lateral, and posterior wall of the LA could be found more frequently in the AF-recurrent group. Although various additional LVA-based substrate modifications after the PVI have been reported in nonparoxysmal AF patients with LVAs, the outcome and approaches vary widely due to the size and distribution of the LVAs.[11–13] In many AF patients, individually located sites and/or patchy fibrotic areas that may be specifically targeted for ablation have been found. However, some AF patients present with diffuse, massive fibrosis without an apparent curative ablation approach. Intrinsically, all LVAs may not always be ablated for the modification. This study also indicated that the LVAs after the PVI were not an independent predictor for AF recurrence as described previously.[21] Excessive lesion sets for substrate modification may lead to totally new atrial arrhythmias.[22] Therefore, an optimal LVA size may be helpful for deciding the need for additional substrate modification in nonparoxysmal AF patients after PVI.

4.4 | Relationship between LVAs and High-DF sites

Atrial sites that represent local electrograms with high-DFs may be associated with AF maintenance.[5,6,15] In a previous report, high-DF sites were mainly observed on the septum and bottom of the LA. High-DF sites after PVI were observed at an average of 6.0 ± 3.3 sites (3.8 ± 2.3 in the LA and 2.3 ± 1.8 in the RA) per patient in nonparoxysmal AF.[23] However, the relationship between LVAs and high-DF sites has not been evaluated yet. In the present study, 72% of high-DF sites overlapped with LVAs. In addition, about half of the high-DF sites overlapped with LVAs at border zones of LVAs. Therefore, the high-DF sites were closely related to LVAs in nonparoxysmal AF. LVAs are known to be associated with the electrophysiological effects of an altered conduction velocity, heterogeneous refractoriness, and rapid repetitive activity.[18–20] Ablation of sites harboring distinct regional electrogram characteristics within/in the vicinity of low-voltage areas in addition to PVI is more effective than conventional PVI only strategy for persistent AF.[24] Therefore, fractionated activity, rotational activity, or discrete rapid local activity during AF may contribute to the formation of high-DFs.[24] Although the high-DF area changed spatiotemporally, virtual ablation for high-DF areas remained effective in the defragmentation of AF, including AF termination or changing into AT in silico human AF models.[25]

A high-DF site ablation may modify the atrial substrate necessary to maintain AF in LVAs. However, in this study, there were no significant differences in the max-DF value and number of high-DF sites overlapping with LVAs in the LA between the two groups. That may be because the relationship between LVAs and sites without high-DFs was not evaluated. In patients with advanced atrial remodeling, the max- and mean DF values in AF were lower and the number of high-DF sites remained small.[5]

4.5 | LVAs in persistent AF

In persistent AF patients, the LA max-DF value, not the LVA/LA surface area, had significant differences between the AF-free and AF-recurrent groups, which differed from the findings including long-standing persistent AF. This may support that a high-DF site ablation following PVI is effective in persistent AF patients as described in a previous report.[5] Therefore, in patients with a lesser amount of LVAs, high-DF sites may be a potential target for sustaining AF.

4.6 | Study limitations

The present study was limited in several ways. First, the number of patients included in the present study was too small to draw definite conclusions. Second, we did not evaluate the relationship between LVAs and the max-DF value of <8 Hz sites. In many patients with a severe AF burden, high-DF sites often could not be found. Therefore, the effect of LVAs overlapping with DF sites of <8 Hz for AF recurrence is unclear. Third, AF recurrence was evaluated using surface ECGs and 24-h Holter monitoring. Accordingly, asymptomatic AF recurrences may have been overlooked in the present study. An implantable loop recorder may reveal a more accurate AF recurrence rate.[26] Fourth, LVAs mapping in RA could not be performed due to a long procedure. Therefore, we could not investigate the relationship between LVAs and DF in RA. Fifth, there may be possibility that voltage mapping was not adequately performed with sufficient catheter contact with atrial tissue because we did not use a contact force sensing catheter in mapping. Finally, the overlap between LVAs and high-DF sites was not ablated after the PVI in the present study. Accordingly, it is unclear whether RF applications at the overlap between the LVAs and high-DF sites were actually effective for AF freedom. This strategy may avoid atrial arrhythmias caused by excessive RF applications as compared with an additional LVA-based substrate modification as described previously. To draw definite conclusions, further prospective study is needed with additional RF applications performed at overlaps between LVAs and high-DF sites as compared to PVI alone.

5 | CONCLUSIONS

LVAs were associated with AF recurrences after PVI in nonparoxysmal AF patients and overlapped with many high-DF sites. PVI alone may be enough to treat patients with mild-to-moderate extent (≤24%) of LVAs.

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CONFLICT OF INTERESTS

Authors declare no conflict of interests for this article.

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