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ORIGINAL ARTICLE

Quantitative analysis of fractionated electrogram area of left atrium during right atrial pacing as an indicator of left atrial electrical remodeling in patients with atrial fibrillation

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Abstract

Background: The clinical significance of left atrial local electrogram fractionation after restoration of sinus rhythm in patients with atrial fibrillation (AF) has not been elucidated.

Methods: We evaluated ultrahigh-resolution maps of the left atrium (LA) during RA pacing acquired after pulmonary vein isolation in 40 patients with AF. The association between low-voltage area (LVA, <0.5 mV), fractionated electrogram area (FEA, the highlighted area with LUMIPOINT™ Complex Activation), the interval from onset of LA activation to wavefront collision at the mitral isthmus (LA activation time), and wave propagation velocity (WPV) was evaluated quantitatively.

Results: The total LVA, total FEA with ≥5.0 peaks or ≥7.0 peaks were $7.0 \pm 7.9\,cm^2$, $15.9 \pm 12.9\,cm^2$, and $5.2 \pm 7.5\,cm^2$, respectively. These areas were predominantly observed in the anteroseptal region. Total LVA, total FEA with ≥5.0 peaks, and total FEA with ≥5.0 peaks in the normal voltage area (NVA: ≥0.5 mV) correlated with LA activation time ($R = 0.69$, 0.75, and 0.71; each $p < .0001$). In the anterior wall, these areas correlated with regional mean WPV ($R = -0.75$, −0.83, and −0.55; each $p < .0001$) and the extent of slow conduction area (SCA) with WPV <0.3 m/s ($R = 0.89$, 0.84, 0.33; $p < .0001$ for LVA and FEA, $p < .05$ for FEA located in NVA). The anterior wall FEA with ≥7.0 peaks and that in the NVA showed a better correlation in predicting anterior wall SCA ($R = 0.92$ and 0.86, each $p < .0001$).

Conclusion: Quantitative analysis of FEA together with LVA may facilitate the assessment of LA electrical remodeling.

KEYWORDS
atrial fibrillation, atrial remodeling, atrial substrate, conduction velocity, ultrahigh-resolution mapping

1 | INTRODUCTION

Catheter ablation is the first-line therapy for atrial fibrillation (AF), with pulmonary vein isolation (PVI) as the established cornerstone procedure. The extent of left atrium (LA) remodeling is associated with AF recurrence after ablation.[1] Recently, low-voltage area (LVA) in the LA has been used as a marker of LA electrical remodeling, which correlates with poor-ablation outcomes.[2] However, LVA is not necessarily observed in all patients. Patients with paroxysmal AF usually present with smaller LVA than those with persistent AF.[3] Therefore, assessing the extent of LA electrical remodeling based solely on the presence of LVA might be challenging. The establishment of more sensitive indicators of LA remodeling is an unmet need.

In addition to LVA, local electrogram (EGM) fractionation during sinus rhythm (SR) has recently been proposed as a target for the non-PV substrate.[4] The areas with such EGMs, which we call fractionated EGM area (FEA) in the present investigation, have been proposed to reflect atrial electrical remodeling.[5] However, the theory has not been systematically and quantitatively investigated using an ultrahigh-resolution mapping system. In this study, we evaluated the prevalence of FEA during right atrial (RA) pacing using the LUMIPOINT™ Complex Activation of Rhythmia™ mapping system (Boston Scientific, Marlborough, MA, USA). The purpose of this study was to investigate the relationship between LVA, FEA, and LA electrical remodeling parameters using ultrahigh-resolution LA maps acquired from patients with AF.

2 | METHODS

2.1 | Study population

This prospective observational study included 40 patients who underwent initial or repeat AF ablation using Rhythmia™ mapping system from June 2022 to September 2023. Patients with a history of prior ablation for the LA body except for the posterior wall or open-heart surgery with left atriotomy were excluded. This study complied with the Declaration of Helsinki. The hospital's institutional review board approved the study protocol (opt-out method).

2.2 | AF ablation method

Ablation procedures were performed under general anesthesia or moderate sedation with dexmedetomidine hydrochloride, thiopental sodium, hydroxyzine hydrochloride, and pentazocine hydrochloride. Periprocedural oral anticoagulation was not interrupted. Activated clotting time was kept over 300 s during the procedure. All class I and III antiarrhythmic drugs were basically discontinued for 24 h before the procedure. Body surface electrocardiograms and bipolar intracardiac electrograms were continuously monitored and stored on a computer-based digital recording system (CardioLab; GE Healthcare, Chicago, IL, USA and LABSYSTEM™ PRO; Boston Scientific). For patients undergoing an initial session, we performed PVI with radiofrequency ablation (RF–PVI) or cryoballoon ablation (CB–PVI). RF–PVI was performed with an IntellaNav Stablepoint™ ablation catheter (Boston Scientific) using a power of 35–50 W (30 W near the esophagus). Target local impedance drop and contact force were set to 20–30 Ω and 5–20 g, respectively. CB–PVI was performed with a 28-mm Arctic Front Advance™ Pro with the Achieve™ mapping catheter (Medtronic, Minneapolis, MN, USA). A single 180-s freezing was applied to each PV except the left inferior pulmonary vein with 150-s freezing. After the PVI procedure, we proceeded with ultrahigh-resolution mapping of the left atrium during RA pacing. When AF rhythm was sustained after the completion of PVI, we restored SR via electrical cardioversion. During the repeat ablation session, ultrahigh-resolution LA mapping was performed at the start of the session or after PV re-isolation.

2.3 | Ultrahigh-resolution mapping of the left atrium

After PVI and SR restoration, study patients underwent LA activation mapping. To exclude the influence of cycle length oscillation during SR, we performed mapping during constant RA appendage pacing or high-RA pacing at a pacing cycle length (PCL) of 600 ms. Mapping was performed using the Rhythmia™ mapping system and the IntellaMap Orion™ catheter (Boston Scientific). PCL was modulated when Wenckebach atrioventricular conduction or frequent overlapping of ventricular electrocardiograms caused insufficient local activation time (LAT) stability due to overlapping ventricular electrocardiograms. Points within 3 mm of the surface of the LA shell were projected. All maps were acquired under strict beat acceptance criteria: cycle length, stability of reference LAT, catheter moving speed, and respiration gating. If areas with low-amplitude were observed, we increased the mapping density of the area and validated the presence of LVA.

2.4 | Area analysis of the LVA and FEA in the left atrium

We analyzed the bipolar voltage and activation map on the Rhythmia™ system. We segmented the LA body into four regions, excluding the posterior wall: anterior wall, septum, inferior wall, and lateral wall (Figure S1). The LA appendage was excluded from the analysis because we did not insert the Orion catheter deep inside the left atrial appendage for safety reasons. The posterior wall was also excluded from the analysis because some patients presented with small non-isolated posterior wall area due to wide PVI and this study included patients with posterior wall ablation (LA roof or bottom line). All analyses described below were performed on a region-by-region basis. First, we manually measured the prevalence of LVA with <0.5 mV amplitude. Next, we measured FEA, defined as the area with ≥5.0 or ≥7.0 peaks detected by the LUMIPOINT™ Complex

Activation tool at 85% strictness criteria. The tool can highlight the areas with EGMs that have peak deflections greater than the threshold named "Peak Slider"; applying a higher Peak Slider level selectively highlights the area with higher local EGM fractionation (Figure 1A–C). The other features of the LUMIPOINT™ software have been summarized in the previous publications.[6] Whether each FEA was located in the normal voltage area (NVA: ≥0.5 mV amplitude) or LVA was also identified. Extremely tiny LVAs or FEAs consisting of ≤2 highlighted points were excluded from the analysis. LA diameter (LAD)-adjusted LVA and FEA were calculated for multiple regression analysis by multiplying each area by the ratio of the mean LAD of the study to each patient's LAD.

2.5 | Measurement of LA activation time and wave propagation velocity

We calculated LA activation time, which has been reported to increase in parallel with AF disease progression.[3] In this study, we defined LA activation time as the interval from the earliest LA activation of the anterior wall or interatrial septum to the collision of the wavefronts from the anterior wall and inferior wall at the lateral mitral isthmus.

We also calculated the regional mean conduction velocity to evaluate local LA electrical remodeling. Quantitative analysis of 3D electroanatomical maps was performed using EPLab Research Works (www.pawelkuklik.com/eplabworks). Based on the imported mapping data from the Rhythmia™ system, the conduction velocity, called wave propagation velocity (WPV) in the software, was automatically calculated using the LATs with >0.1 mV bipolar amplitude. The algorithm of WPV calculation by the software was based on the geometry triangles method, as used in the previous report.[7] The regional mean WPV was automatically calculated by selecting any surface area of the LA shell. The slow conduction area (SCA) with <0.3 m/s WPV was also calculated.[8] Before calculating the WPV, the points with apparent outlier LAT were excluded, and each LAT value was adjusted to the mean of the points within a 3 mm radius. The difference in WPV was expressed by the color range, as shown

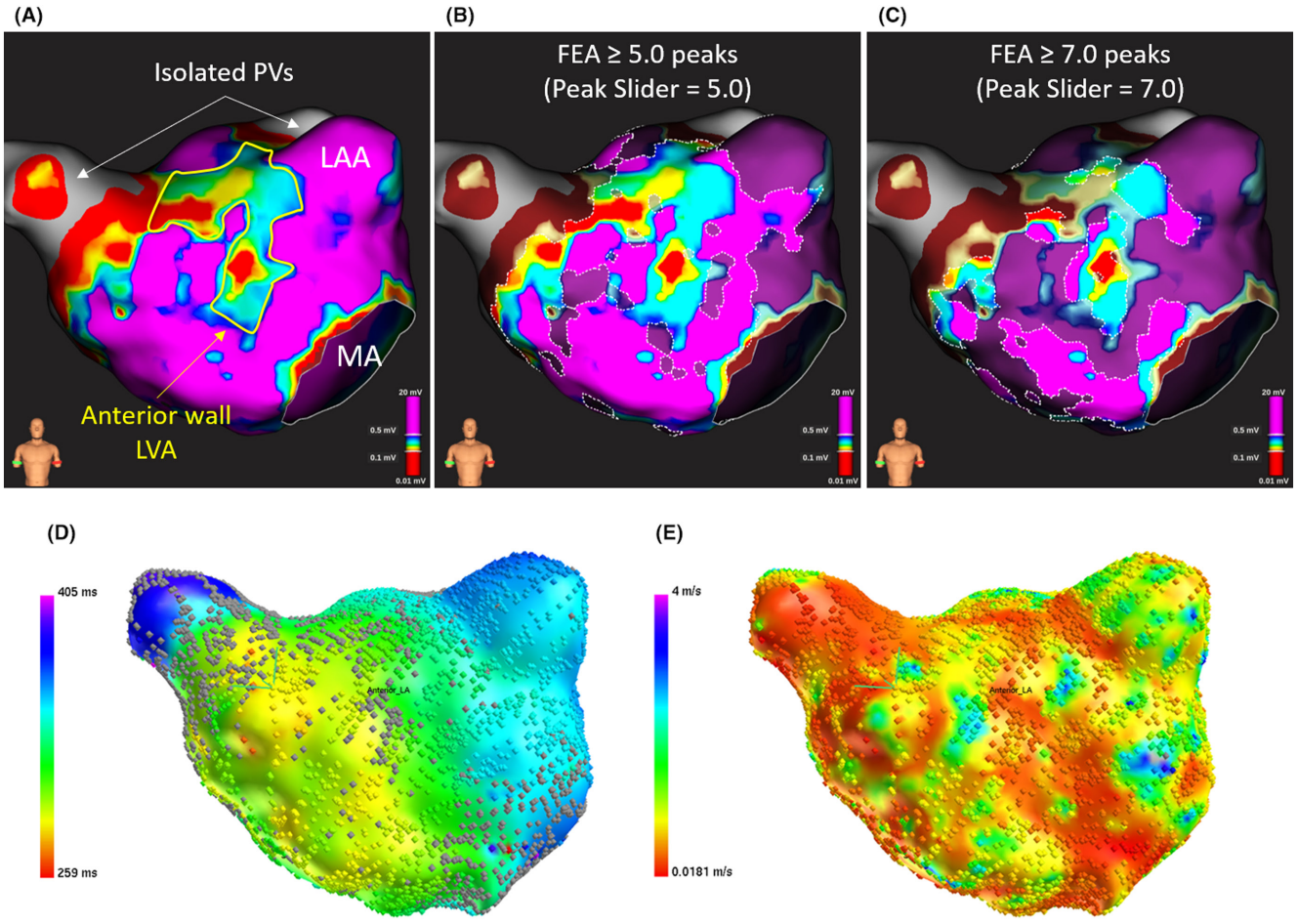

FIGURE 1 Representative case with LVA, FEA, and WPV measurements. (A) LVA measurement. (B, C) The highlighting of FEA ≥5.0 peaks and ≥7.0 peaks by LUMIPOINT™ Complex Activation. "5.0" and "7.0" indicate the Peak Slider of the LUMIPOINT™ module. These areas were calculated as the sum of each region. (D) The activation map on EPLab Research Works software after 3 mm spatial filtering. (E) The WPV map generated from map (D). FEA, fractionated electrogram area; LAA, left atrial appendage; LVA, low-voltage area; MA, mitral annulus; PV, pulmonary vein; WPV, wave propagation velocity.

in Figure 1(E). The lateral LA wall was excluded from this analysis because of the wavefront collision, which could lead to the overestimation of conduction velocity.

2.6 | Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median [interquartile range]. A value of $p < .05$ was considered statistically significant. The relationship between two continuous variables was evaluated using the correlation coefficient I. Pairs of values within each patient were compared using the paired *t*-test. Multiple regression analysis was performed using the least squares method. All the statistical analyses were performed using JMP software, version 14.2.0 (SAS Institute).

3 | RESULTS

3.1 | Patient characteristics

Baseline patient characteristics are shown in Table 1. The study patients ($N = 40$) had moderately dilated LAs and preserved left ventricular ejection fractions. Approximately half of the patients had non-paroxysmal AF. Classes I and III antiarrhythmic drugs were discontinued before the procedure, except for one patient taking 100 mg of amiodarone. In the other three patients, two patients, bepridil was administered until 2 or 4 days before the procedure or continued.

TABLE 1 Baseline patient characteristics and ablation procedure ($N = 40$).

Patient characteristics	
Age, year	66 ± 12
Female, *n* (%)	15 (38%)
Height, cm	163.8 ± 9
Body weight, kg	66 ± 11
Body mass index	24.6 ± 3.8
Hypertension	17 (43%)
Diabetes	5 (13%)
Chronic kidney disease (GFR < 60 ml/min/kg)	16 (40%)
History of stroke or TIA	4 (10%)
CHA_2DS_2-VASc score	2.3 ± 1.4
Echocardiographic findings	
LVEF, %	66 ± 11
LA diameter, mm	44 ± 8
LA volume, mL	91 ± 35
AF type, *n* (%)	
Paroxysmal AF	19 (48%)
Non-paroxysmal AF	21 (52%)
Number of AF ablation, *n* (%)	
Initial procedure	32
Repeated procedure (≥2)	8
Pulmonary vein isolation, *n* (%)	
Radiofrequency ablation[a]	37
Cryoballoon ablation	3
Additional LA lesions created before ultrahigh-resolution mapping	
LA roof line	5 (13%)
LA bottom line	1 (3%)

Note: Values are *n* (%), mean ± SD.

Abbreviations: AF, atrial fibrillation; LA, left atrium; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.

[a]Including six repeated procedure patients who underwent prior ablation with radiofrequency ablation with the CARTO® system.

3.2 | Prevalence of LVA and FEA of the left atrium

Ultrahigh-resolution LA maps were successfully acquired during the ablation procedure. Right atrial pacing was performed basically with 600 ms PCL, except for one patient with 660 ms, one with 666 ms, and two with 750 ms. The total number of mapping points was 8176 ± 1858, and the total mapping time was 14.7 ± 4.1 min. The distribution of LVA and FEA is shown in Figure 2(A). Both LVA and FEA were frequently observed in the anteroseptal region. Total FEA with ≥5.0 peaks was significantly larger than total LVA (15.9 ± 12.9 cm^2 vs. 7.0 ± 7.9 cm^2, $p < .0001$). Total FEA with ≥7.0 peaks (5.2 ± 7.5 cm^2) was significantly smaller than total FEA with ≥5.0 peaks ($p < .0001$). The relationship between FEA and local amplitude is shown in Figure 2(B). The FEA located in NVA was significantly larger than that in the LVA at each Peak Slider (≥5.0 peaks: 12.2 ± 8.5 cm^2 vs. 3.7 ± 5.5 cm^2, $p < .0001$, ≥ 7.0 peaks: 3.4 ± 4.4 cm^2 vs. 1.8 ± 3.4 cm^2, $p = .0003$). Total LVA correlated with total FEA and the FEA located in NVA (Figure 2C,D). In the multiple regression analysis, age, female sex, body weight, history of stroke or transient ischemic attack (TIA), and AF type were associated with LAD-adjusted FEA with ≥5.0 peaks (Table S1).

3.3 | Relationship between LVA or FEA and LA activation time

The relationship between the extent of LVA or FEA and global LA electrical remodeling was investigated using LA activation time. The mean LA activation time was 84.3 ± 14.1 ms. The extent of total LVA and FEA, with or without LAD adjustment, were significantly correlated with LA activation time (Figure 3; Figure S2). These areas in the anteroseptal region showed a stronger correlation than those in the inferolateral region (Figure S3). In the multiple regression analysis, LAD-adjusted total FEA with ≥5.0 peaks located in NVA was associated with LA activation time independently of LAD-adjusted total LVA and LAD (Table 2), whereas LAD-adjusted FEA with ≥7.0 peaks located in NVA was not. Total

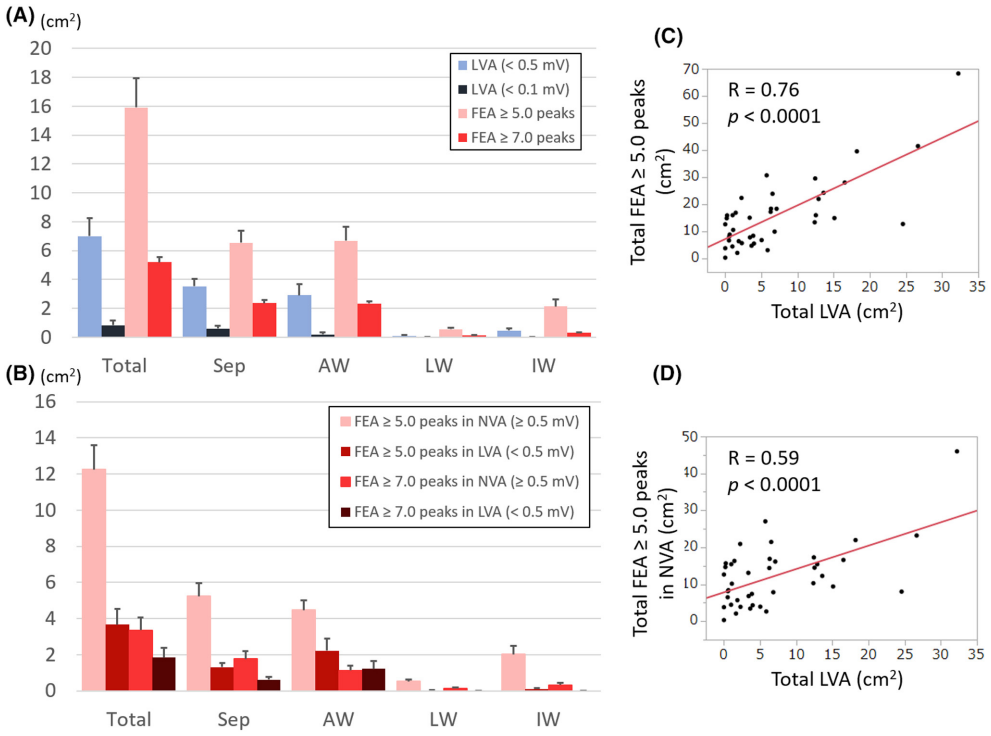

FIGURE 2 (A, B) Distributions of the LVA and FEA. "5.0" and "7.0" indicate the Peak Slider of LUMIPOINT™ Complex Activation. (C) The correlation between LVA and FEA ≥5.0 peaks. (D) The correlation between LVA and the FEA ≥5.0 peaks located in NVA (≥0.5 mV). Error bars indicate standard errors. AW, anterior wall; IW, inferior wall; LW, lateral wall; NVA, normal voltage area; Sep, septum.

FEA with ≥5.0 peaks located in NVA and total LVA were also independent predictors of LA activation time on the multiple regression model including age, sex, history of TIA or stroke, and AF type (Table S1).

3.4 | Relationship between LVA or FEA and regional mean WPV

The relationship between the extent of LVA or FEA and the regional mean WPV of each LA region was also evaluated. The regional mean WPV in the anterior wall, septum, and inferior wall were 0.94 ± 0.15 m/s, 0.90 ± 0.15 m/s, and 1.03 ± 0.11 m/s, respectively. The inferior wall presented significantly greater regional mean WPV than the anterior wall and septum ($p < .0001$, respectively). The prevalence of LVA and FEA in the anterior wall correlated significantly with regional mean WPV and the extent of SCA (Figures 4 and 5). Similar but weaker correlations were observed in the septum and inferior wall (Figures S4–S7). Multiple regression analysis for regional mean WPV and SCA in the anterior wall showed that LVA and FEA were independently associated with them (Table 3). The FEA with a higher peak threshold (≥7.0 peaks) showed a better correlation coefficient and standardized partial regression coefficient than that with a lower threshold (≥5.0 peaks) in the simple and multiple regression analysis for SCA in the anterior wall.

4 | DISCUSSION

Using an ultrahigh-resolution mapping system, we evaluated the characteristics of FEA in the LA during RA pacing and the relationship between LVA, FEA, and LA conduction properties. The main findings of this study are as follows. (i) FEA was associated with baseline patient characteristics, including many CHADS2–VASC score components. (ii) FEA was predominantly observed in the NVA (≥0.5 mV) and the anteroseptal LA region. (iii) The extent of FEA correlated with that of LVA but more broadly observed than LVA. (iv) The extent of FEA, especially in the anteroseptal LA region, correlated with LA activation time independent of LVA. (v) The extent of FEA correlated with decreased regional mean WPV and the extent of SCA in the anterior wall, independent of LVA. (vi) The suitable Peak Slider was different by the electrical remodeling indicators: ≥5.0 was for LA activation time and regional mean WPV prediction, and ≥7.0 was for SCA prediction. These results suggest that FEA, together with LVA, may be an indicator of LA electrical remodeling.

4.1 | FEA as an indicator of LA remodeling

The evaluation of AF substrates is one of the most important issues in current AF ablation, especially in patients with PVI-refractory AF. Recently, the presence of LVA has been considered an indicator of

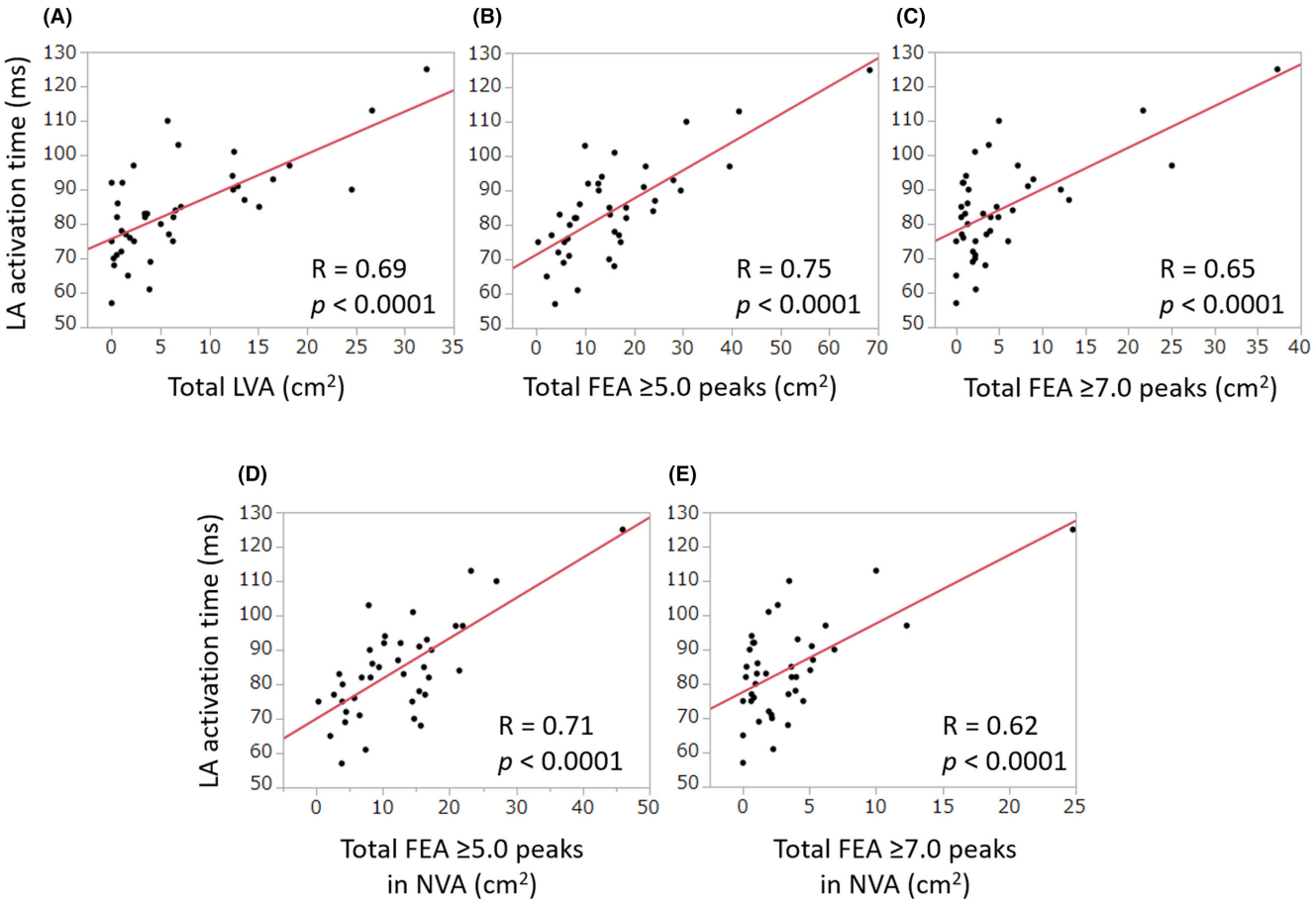

FIGURE 3 (A–E) Scatterplots of LVA, FEA, the FEA located in NVA, and LA activation time. R = correlation coefficient. Abbreviations are as in Figures 1 and 2.

TABLE 2 Multiple regression analysis of LA activation time with the electro-anatomical factors.

	Beta [95% CI]	Standard beta	*p*-value
Model 1: Adjusted R^2 = 0.62, p < .0001			
LAD-adjusted FEA (≥5.0 peaks) in NVA	0.62 [0.16, 1.08]	0.33	.0092
LAD-adjusted LVA	0.79 [0.34, 1.24]	0.42	.0011
LAD	0.60 [0.24, 0.96]	0.35	.0016
Model 2: Adjusted R^2 = 0.58, p < .0001			
LAD-adjusted FEA(≥ 7.0 peaks) in NVA	0.94 [−0.06, 1.94]	0.25	.065
LAD-adjusted LVA	0.82 [0.32, 1.32]	0.43	.0020
LAD	0.64 [0.27, 1.01]	0.37	.0013

Abbreviations: FEA, fractionated electrogram area; LAD, left atrial diameter; LVA, low voltage area (<0.5 mV); NVA, normal voltage area (≥0.5 mV); R^2, coefficient of determination.

poor AF ablation outcomes.[2,9] However, LVA is not necessarily observed in some patients with PVI-refractory AF. We hypothesized that fractionated EGMs during SR are associated with LA remodeling because Kuo et al. reported that fractionated EGMs were associated with late gadolinium enhancement on cardiac magnetic resonance imaging, even in patients without LVA.[5]

In this study, the relationships between LVA, FEA, and LA conduction properties during RA pacing were evaluated. The extent of FEA was greater than that of LVA in the study patients, whereas the distribution of these areas was similar; both areas were predominantly observed in the anteroseptal LA region. The extent of FEA correlated with LA activation time and regional mean WPV

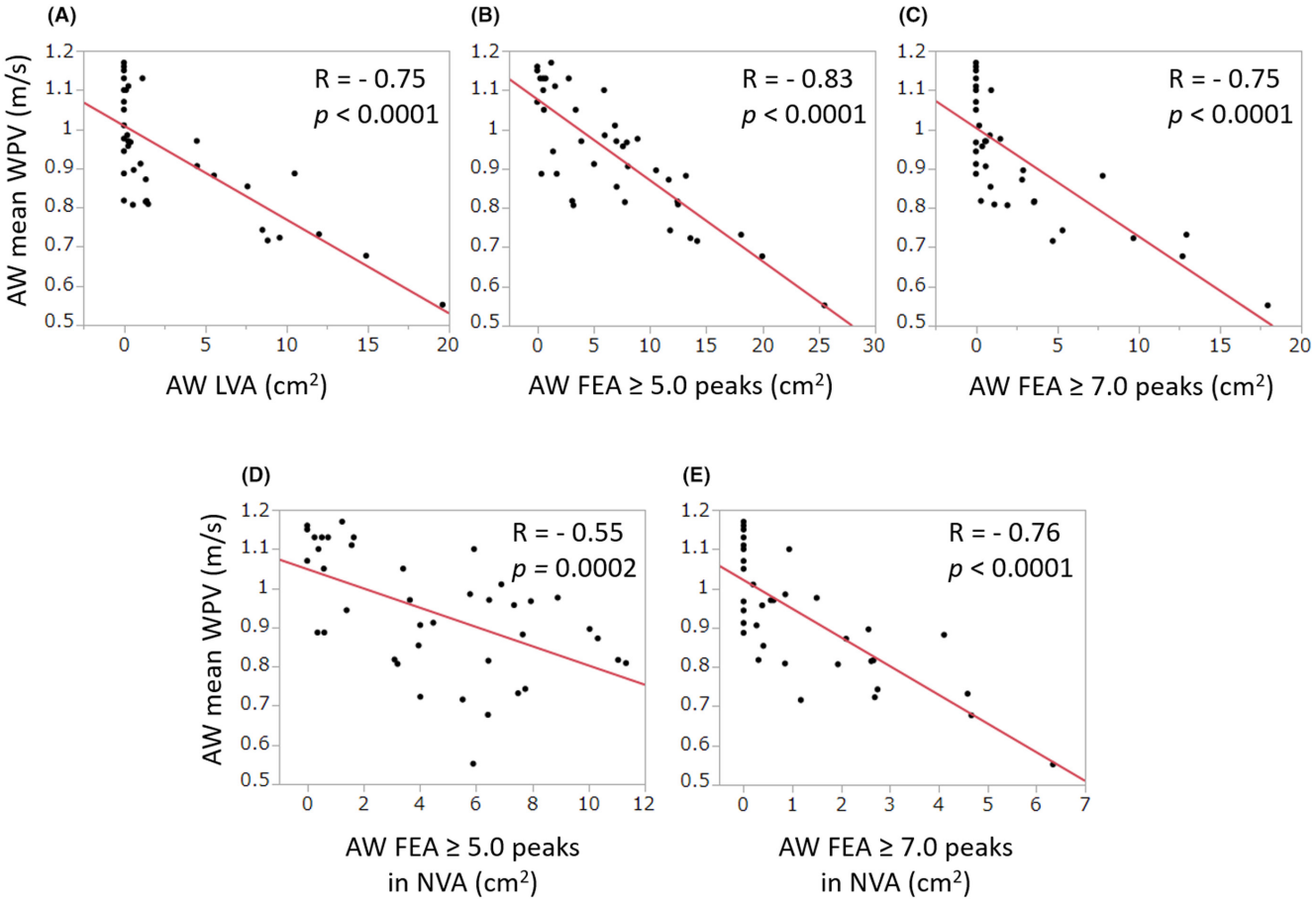

FIGURE 4 (A–E) Scatterplots of LVA, FEA, the FEA located in NVA, and regional mean WPV of the LA anterior wall. WPV, wave propagation velocity. *R* = correlation coefficient. Abbreviations are as in Figures 1 and 2.

and SCZ of the anterior wall. This relationship was maintained when analyzing FEA located in the NVA. These results suggested that FEA may be an indicator of LA electrical remodeling together with LVA.

Kishima et al. reported that conduction slowing in the LA is most commonly observed in the anterior wall, accompanied by a slight reduction in local amplitude.[10] Ohguchi et al. and Kurata et al. reported that the conduction velocity slowing in the anterior wall was a predictor of AF recurrence.[11,12] Takahashi et al. reported that fractionation of the local electrogram is associated with the expansion of the intercellular space, which they proposed as an interstitial change that occurs during the early structural atrial remodeling.[13] Considering these findings and the results of the current study, the emergence of FEA may precede that of LVA during the progression of LA electrical remodeling.

4.2 | Evaluation of EGM fractionation during AF and sinus rhythm

The evaluation of EGM fractionation during AF, as well as during sinus or paced rhythm, has also been studied. Among these, the complex fractionated atrial electrogram (CFAE) has been studied extensively.[14,15] CFAE was originally reported by Nademanee et al. as electrograms with continuous fractionation or very short cycle lengths of less than 120 ms over 10 s during AF.[14] Previous studies have reported the usefulness and clinical significance of CFAE. CFAE was associated with the site of AF or subsequent atrial tachycardia termination.[16,17] CFAE ablation also improved the SR maintenance rate in patients with non-paroxysmal AF.[18] However, the effect of CFAE ablation has been controversial. Subsequent randomized controlled trials failed to demonstrate the benefit of CFAE ablation.[19,20] The inconsistent efficacy of CFAE ablation may be due to the different methods used to measure CFAE. In addition, because CFAE is an EGM during AF, its measurement is essentially subject to reproducibility issues.[21]

Compared to CFAE, fractionation of EGMs during SR or atrial pacing is a presumably reproducible indicator of the atrial arrhythmogenic substrate. Current three-dimensional electroanatomical mapping systems can detect reproducible fractionated EGMs during SR or atrial pacing with the beat acceptance criteria as used in this study. Although we did not compare CFAE and FEA during RA pacing in this study, some studies have investigated the relationship in the era of low-resolution mapping systems. Saghy et al. reported that

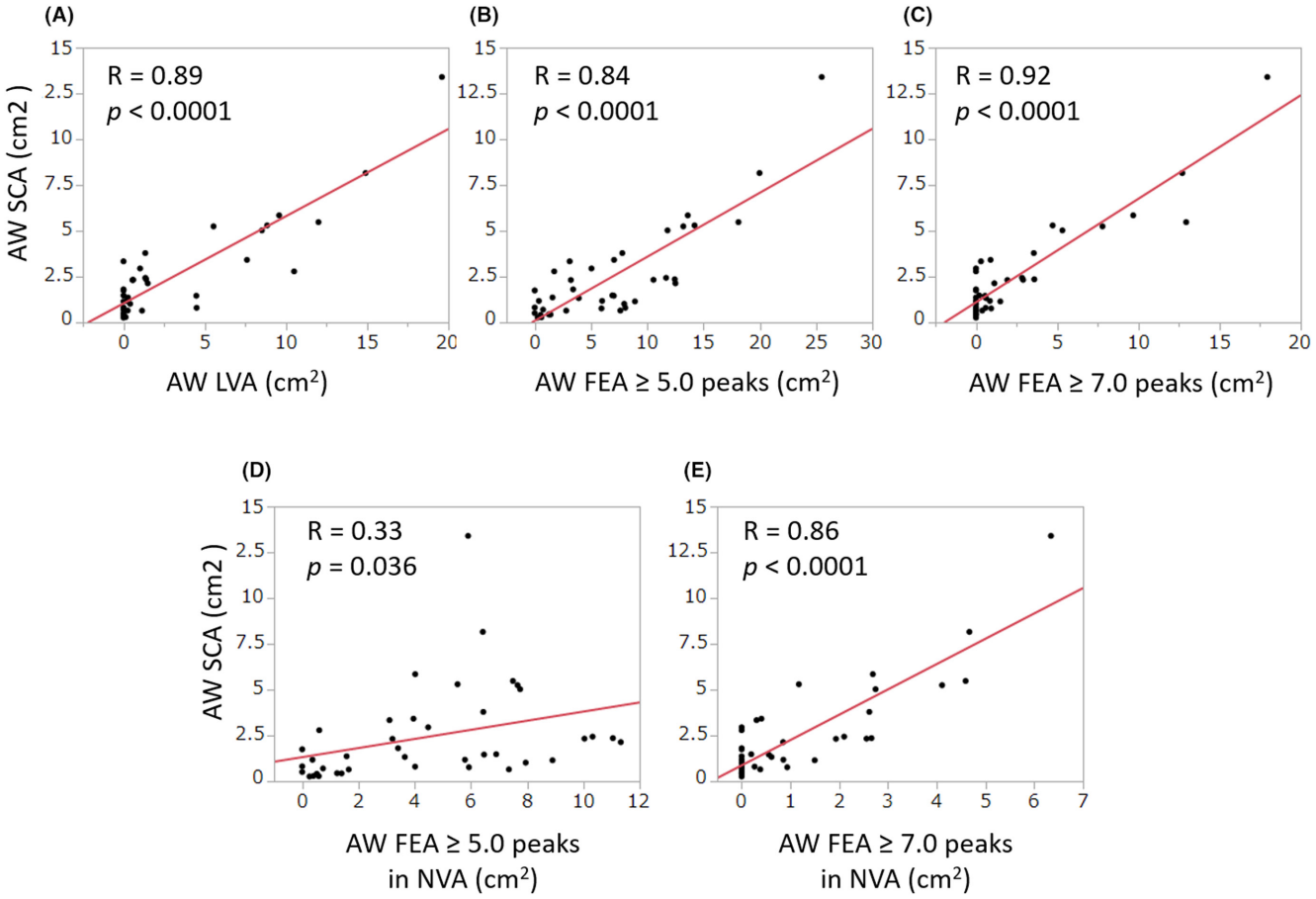

FIGURE 5 (A–E) Scatterplots of LVA, FEA, the FEA located in NVA, and SCA (<0.3 m/s) of the LA anterior wall. SCA, slow conduction area. *R* = correlation coefficient. Abbreviations are as in Figures 1 and 2.

TABLE 3 Multiple linear regression analysis of regional mean WPV and the extent of SCA of the LA anterior wall with the electro-anatomical factors.

	Beta [95% CI]	Standard beta	*p*-value
AW regional mean WPV model 1: Adjusted $R^2 = 0.70$, $p < .0001$			
FEA (≥ 5.0 peaks) in NVA	−0.018 [−0.026, −0.010]	−0.41	< .0001
LVA	−0.021 [−0.027, −0.015]	−0.66	< .0001
AW SCA model 1: Adjusted $R^2 = 0.80$, $p < 0.0001$			
FEA (≥5.0 peaks) in NVA	0.11 [0.0008, 0.22]	0.15	.049
LVA	0.46 [0.38, 0.54]	0.86	< .0001
AW regional mean WPV model 2: Adjusted $R^2 = 0.63$, $p < .0001$			
FEA (≥ 7.0 peaks) in NVA	−0.044 [−0.072, −0.016]	−0.45	.0031
LVA	−0.013 [−0.023, −0.004]	−0.41	.0064
AW SCA model 2: Adjusted $R^2 = 0.87$, $p < .0001$			
FEA (≥7.0 peaks) in NVA	0.72 [0.44, 0.99]	0.44	<.0001
LVA	0.30 [0.21, 0.39]	0.56	<.0001

Abbreviations: AW, anterior wall; LAD, left atrial diameter; LVA, low-voltage area (<0.5 mV); NVA, normal voltage area (≥0.5 mV); R2, coefficient of determination; SCA, slow conduction area (<0.3 m/s area); WPV, wave propagation velocity.

the CFAE and fractionated EGM areas showed similar distribution patterns: anteroseptal region dominant patterns similar to the FEA distribution in this study.[22] However, the exact locations of these areas were typically different. Another study also reported that CFAE areas did not overlap with LVA and that CFAE areas were not associated with slower conduction velocity.[23] The former finding was analogous to our present investigation of FEA: most of the FEA was not located in the LVA. The latter findings, which were inconsistent with our investigation, were likely due to the difference in the method of conduction velocity measurement. We measured the regional mean WPV based on the LAT data of all points in each region, including the points that were not in the FEA. Therefore, the regional mean WPV calculated by this measurement method may have reflected the remodeled areas that have not yet manifested as LVA or FEA. In addition, the CFAE area during AF may have included both intrinsically remodeled areas and functional conduction delay due to the rapid AF cycle length. Therefore, the degree of conduction delay in the CFAE area and the FEA may be different.

5 | STUDY LIMITATIONS

First, this study was a single-center analysis and included a small number of patients. Second, ablation of FEA and LVA was not mandatory in this study. Therefore, this study did not elucidate the prognosis of ablation of these areas and the clinical impact of FEA modification. Third, because ultrahigh-resolution mapping was performed after PVI, PVI may have affected the LA activation pattern near the PVI lines. To minimize the influence of PVI, we measured LA activation time, which reflects the conduction property of the LA body away from the PVs.

6 | CONCLUSION

In conclusion, our study demonstrated that FEA of the LA was frequently observed in AF patients during RA pacing, especially in the anteroseptal area. The extent of FEA was significantly correlated with LA activation time and regional mean WPV slowing of the anterior wall. FEA with a higher degree of fractionation was associated with the extent of SCA. Based on these results, the prevalence of FEA may be an indicator of LA electrical remodeling together with LVA; thus, it may help to identify the potential AF substrate or guide the strategy for additional ablation.

AUTHOR CONTRIBUTIONS

Takayuki Sekihara: Conceptualization, Methodology, Investigation, Original draft writing.

Takafumi Oka, Kentaro Ozu, Yasushi Sakata: Review and editing.

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FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Upon reasonable request.

ETHICS APPROVAL

The hospital's institutional review board approved the study protocol. The study complied with the Declaration of Helsinki.

PATIENT CONSENT

Under the opt-out method.

CLINICAL TRIAL REGISTRATION

None.

DECLARATIONS

Approval of research protocol: Approved by the institutional review board.

Informed consent: N/A (opt-out method).

Registry and the Registration No.: N/A.

Animal studies: N/A.

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REFERENCES

1. McGann C, Akoum N, Patel A, Kholmovski E, Revelo P, Damal K, et al. Atrial fibrillation ablation outcome is predicted by left atrial remodeling on MRI. Circ Arrhythm Electrophysiol. 2014;7(1):23–30.
2. Yamaguchi T, Tsuchiya T, Nagamoto Y, Miyamoto K, Murotani K, Okishige K, et al. Long-term results of pulmonary vein antrum isolation in patients with atrial fibrillation: an analysis in regards to substrates and pulmonary vein reconnections. Europace. 2014;16(4):511–20.
3. Lin Y, Yang B, Garcia FC, Ju W, Zhang F, Chen H, et al. Comparison of left atrial electrophysiologic abnormalities during sinus rhythm in patients with different type of atrial fibrillation. J Interv Card Electrophysiol. 2014;39(1):57–67.
4. Hirokami J, Hiroshima K, Yamaji K, Korai K, Nagashima M, Fukunaga M, et al. Relationship between fractionated signal areas in the atrial muscle during sinus rhythm and atrial pacing and non-pulmonary vein foci: novel mapping strategy. Circ Arrhythm Electrophysiol. 2020;13(8):e008667.
5. Kuo L, Zado E, Frankel DS, Santangeli P, Arkles J, Han Y, et al. Association of left atrial high-resolution late gadolinium Enhancement on cardiac magnetic resonance with electrogram abnormalities beyond voltage in patients with atrial fibrillation. Circ Arrhythm Electrophysiol. 2020;13(2):e007586.
6. Martin CA, Takigawa M, Martin R, Maury P, Meyer C, Wong T, et al. Use of novel electrogram "Lumipoint" algorithm to detect critical isthmus and abnormal potentials for ablation in ventricular tachycardia. JACC: Clin Electrophysiol. 2019;5(4):470–9.

7. Kojodjojo P, Kanagaratnam P, Markides V, Davies DW, Peters N. Age-related changes in human left and right atrial conduction. J Cardiovasc Electrophysiol. 2006;17(2):120–7.
8. Vicera JJB, Lin Y-J, Lee P-T, Chang SL, Lo LW, Hu YF, et al. Identification of critical isthmus using coherent mapping in patients with scar-related atrial tachycardia. J Cardiovasc Electrophysiol. 2020;31(6):1436–47.
9. Yang G, Zheng L, Jiang C, Fan J, Liu X, Zhan X, et al. Circumferential pulmonary vein isolation plus low-voltage area modification in persistent atrial fibrillation. JACC: ClinElectrophysiol. 2022;8(7):882–91.
10. Kishima H, Mine T, Fukuhara E, Takahashi S, Ishihara M. Is the abnormal conduction zone of the left atrium a precursor to a low voltage area in patients with atrial fibrillation? J Cardiovasc Electrophysiol. 2020;31(11):2874–82.
11. Ohguchi S, Inden Y, Yanagisawa S, Fujita R, Yasuda K, Katagiri K, et al. Regional left atrial conduction velocity in the anterior wall is associated with clinical recurrence of atrial fibrillation after catheter ablation: efficacy in combination with the ipsilateral low voltage area. BMC Cardiovasc Disord. 2022;22(1):457.
12. Kurata N, Masuda M, Kanda T, Asai M, Iida O, Okamoto S, et al. Left atrial localized low-voltage areas indicate whole left atrial electrophysiological degeneration in atrial fibrillation patients. Circ J. 2022;86(2):192–9.
13. Takahashi Y, Yamaguchi T, Otsubo T, Nakashima K, Shinzato K, Osako R, et al. Histological validation of atrial structural remodelling in patients with atrial fibrillation. Eur Heart J. 2023;44:ehad396.
14. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, et al. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol. 2004;43(11):2044–53.
15. Nademanee K, Schwab MC, Kosar EM, Karwecki M, Moran MD, Visessook N, et al. Clinical outcomes of catheter substrate ablation for high-risk patients with atrial fibrillation. J Am Coll Cardiol. 2008;51(8):843–9.
16. Seitz J, Bars C, Ferracci A, Maluski A, Penaranda G, Theodore G, et al. Electrogram fractionation-guided ablation in the left atrium decreases the frequency of activation in the pulmonary veins and leads to atrial fibrillation termination: pulmonary vein modulation rather than isolation. JACC Clin Electrophysiol. 2016;2(6):732–42.
17. Ban J-E, Chen Y-L, Park H-C, Lee HS, Lee DI, Choi JI, et al. Relationship between complex fractionated atrial Electrograms during atrial fibrillation and the critical site of atrial tachycardia that develops after catheter ablation for atrial fibrillation. J Cardiovasc Electrophysiol. 2014;25(2):146–53.
18. Li WJ, Bai YY, Zhang HY, Tang RB, Miao CL, Sang CH, et al. Additional ablation of complex fractionated atrial electrograms after pulmonary vein isolation in patients with atrial fibrillation. Circ Arrhythm Electrophysiol. 2011;4(2):143–8.
19. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015;372(19):1812–22.
20. Wong KC, Paisey JR, Sopher M, Balasubramaniam R, Jones M, Qureshi N, et al. No benefit of complex fractionated atrial electrogram ablation in addition to circumferential pulmonary vein ablation and linear ablation: benefit of complex ablation study. Circ Arrhythm Electrophysiol. 2015;8(6):1316–24.
21. Habel N, Znojkiewicz P, Thompson N, Müller JG, Mason B, Calame J, et al. The temporal variability of dominant frequency and complex fractionated atrial electrograms constrains the validity of sequential mapping in human atrial fibrillation. Heart Rhythm. 2010;7(5):586–93.
22. Saghy L, Callans DJ, Garcia F, Lin D, Marchlinski FE, Riley M, et al. Is there a relationship between complex fractionated atrial electrograms recorded during atrial fibrillation and sinus rhythm fractionation? Heart Rhythm. 2012;9(2):181–8.
23. Viles-Gonzalez JF, Gomes JA, Miller MA, Dukkipati SR, Koruth JS, Eggert C, et al. Areas with complex fractionated atrial electrograms recorded after pulmonary vein isolation represent normal voltage and conduction velocity in sinus rhythm. Europace. 2013;15(3):339–46.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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