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NEW RESEARCH PAPERS

Spatial Relationships of Complex Fractionated Atrial Electrograms and Continuous Electrical Activity to Focal Electrical Sources

Implications for Substrate Ablation in Human Atrial Fibrillation

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ABSTRACT

OBJECTIVES This study sought to evaluate the spatial relationships of focal electrical sources (FSs) to complex fractionated atrial electrograms (CFAE) and continuous electrical activity (CEA).

BACKGROUND Fractionated atrial electrograms have been associated with atrial fibrillation (AF) drivers in computational studies and represent ablation targets in the management of persistent AF.

METHODS We included a subset of 66 patients (age: 63 [56, 67] years, 69% persistent AF) with electroanatomic data from the SELECT AF (Selective complex fractionated atrial electrograms targeting for atrial fibrillation) randomized control trial that compared the efficacy of CFAE with CEA ablation in AF patients undergoing pulmonary vein antral ablation. Focal sources were identified based on bipolar electrogram periodicity and QS unipolar electrogram morphology.

RESULTS A total of 77 FSs (median: 1 [1st quartile, 3rd quartile: 1, 2] per patient) were identified most commonly in the pulmonary vein antrum and left atrial appendage. The proportions of FSs inside CFAE and CEA regions were similar (13% vs. 1.3%, respectively; $p = 0.13$). Focal sources were more likely to be on the border zone of CFAEs than in CEAs (49% vs. 7.8%, respectively; $p = 0.012$). Following ablation, 53% of patients had ≥1 unablated extrapulmonary vein FS. The median number of unablated FS was higher in patients with AF recurrence post ablation than in patients without (median: 1 [0, 1] vs. 0 [0, 1], respectively; $p = 0.026$).

CONCLUSIONS One-half of the FSs detected during AF localized to the border of CFAE areas, whereas most of the FSs were found outside CEA areas. CFAE or CEA ablation leaves a number of FS unablated, which is associated with AF recurrence. These findings suggest that many CFAEs may arise from passive wave propagation, remote from FS, which may limit their therapeutic efficacy in AF substrate modification. (J Am Coll Cardiol EP 2017;3:1220–8)

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Catheter ablation of persistent atrial fibrillation (AF) is associated with high AF recurrence after pulmonary vein (PV) isolation alone. The incremental benefit of atrial substrate modification and ablation targets themselves have not been well defined. Complex fractionated atrial electrograms (CFAEs) may represent crucial sites for AF perpetuation (1); however, rhythm control has not been shown to consistently improve compared to PV isolation alone (2,3). In an attempt to improve the specificity of fractionated electrogram targets and reduce the extent of CFAE ablation, the ablation of more selective continuous electrical activity (CEA) has been proposed, which appears to slow or terminate human AF (4).

SEE PAGE 1229

The pathogenesis of CFAE and CEA can invoke multiple mechanisms, some of which are active to AF maintenance, such as localized AF drivers from rotors, focal sources (FSs), or autonomic ganglia (5). However, other mechanisms are clearly passive to AF maintenance and include wave collision, scar propagation (6), and far-field activity (7). In a computational study, Kalifa et al. (8) demonstrated that fractionation was the result of wave collisions from focal high-frequency AF drivers that were in proximity to these fractionated potentials. In that case, some CFAEs and CEAs, although passive to AF maintenance, were adjacent to AF drivers. The spatial relationship between electrogram fractionation and AF drivers has not been well defined in human AF, which depends in large part on the method of AF driver detection (9,10).

The presence of temporally stable FSs has been demonstrated in patients with persistent AF according to Lee et al. (11), who used long-duration, high-resolution intraoperative mapping of both atria, showing centrifugal wave propagation from a unipolar QS recording site. In contrast, other studies (12,13) found no FS or very transient FSs by using similar intraoperative recording techniques, but all their patients had long-standing persistent AF, and a smaller region of the atria was sampled for less time. We have developed a novel algorithm to identify FS, which uses bipolar electrogram periodicity analysis and the evaluation of QS unipolar electrography, based on the premise that a FS will demonstrate regular electrical activity with centrifugal wave propagation (14).

Using this algorithm, our objective was to evaluate the spatial relationship of FS to CFAE and CEA in AF patients from the SELECT AF (Selective complex fractionated atrial electrograms targeting for atrial fibrillation) trial (15) who were randomized to CFAE or CEA ablation following PV isolation. We also sought to determine whether AF recurrence was predicted by coincidental ablation of FS independent of CFAE or CEA ablation.

ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug
AF = atrial fibrillation
CEA = continuous electrical activity
CFAE = complex fractionated atrial electrogram
FS = focal source
LA = left atrium
PV = pulmonary vein

METHODS

STUDY POPULATION AND PROTOCOL. The SELECT AF trial included 86 patients with drug-refractory persistent or high-burden paroxysmal AF from 6 centers. Clinical follow-up was completed in 77 patients who comprised the cohort for the present study. The SELECT AF protocol has been described elsewhere (15) and is summarized in the Online Methods. Details of CFAE and CEA mapping and ablation are also presented in the Online Methods.

FOCAL SOURCE MAPPING. The recorded bipolar (bandpass filter of 30 to 400 Hz) and unipolar electrograms (EGM) (bandpass filter of 0.05 to 400 Hz) from the left atrium (LA) (sampling rate of 1,024 Hz) were exported after the ablation procedure for offline analysis of FS, using customized software written in Matlab (Mathworks, Inc., Natick, Massachusetts). Wilson central terminal provided an indifferent reference for unipolar recordings. Only EGMs recorded before ablation were analyzed. The details of our validated algorithm for FS detection

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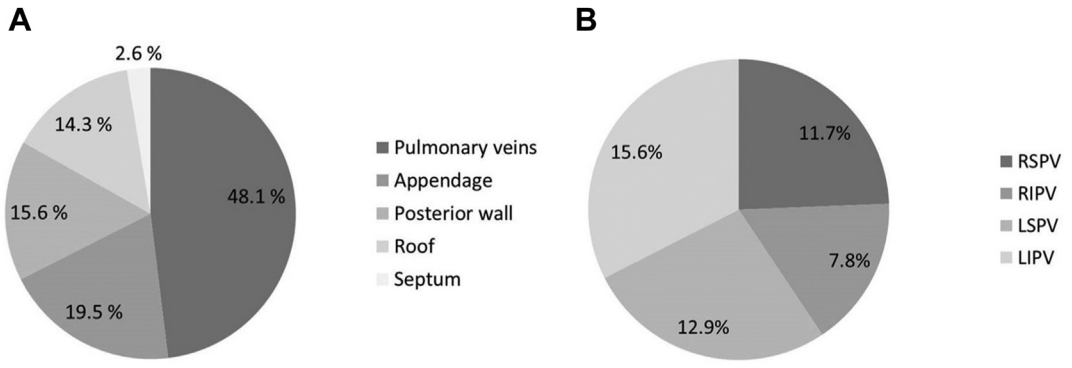
FIGURE 1 Focal Source Distribution in LA and PV



(A) Distribution of FS in the left atrium. **(B)** Distribution of FS in the PV. FS = focal source; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.

have been previously described (14). Briefly, periodicity in the bipolar EGM was evaluated using periodic component analysis. Local activations in the bipolar EGM with known periodicity cycle length were annotated using a graph search function as previously reported (16). These activations were transposed to the unipolar EGM in order to assess morphology features. Focal sources were defined as periodic bipolar EGMs with QS unipolar EGM (R-wave to S-wave ratio <0.1 in more than 90% of activations).

DEFINING SPATIAL RELATION TO CFAE AND CEA. Focal sources were tagged on the patient's respective electroanatomic maps in order to evaluate their spatial relationships to any CFAE and CEA areas. Accordingly, FSs were categorized as either inside, outside, or on the border zone of CFAE or CEA. The last location was defined as FS within 5 mm of the border of a coherent area of significant CFAE (interval confidence level [ICL] >7) or CEA (>75% CEA). Focal sources were considered ablated if they colocalized with ablation sites, whether they were PV antral or extra-PV antral. Focal sources inside the PV or at the PV ostium were not ablated but were considered "treated" because all patients had successful PV antral isolation. Treated FSs also included those that were considered ablated.

STATISTICAL ANALYSIS. Statistical calculations were performed using SPSS version 22.0 software (SPSS; IBM, Corp., Armonk, New York) and SAS version 9.4 software (SAS Inc., Cary, North Carolina). Distribution of normality in continuous variables was tested with the Shapiro-Wilks test. Continuous parametric variables were expressed as mean ± SD or median (1st quartile, 3rd quartile) in the case of non-normal distribution. A chi-square or Fisher exact test was used for comparison of categorical variables with extension of the Mantel-Haenszel test when center-specific effects had to be excluded. The Mann-Whitney *U* test was used for comparison of continuous nonparametric variables. In order to evaluate predictors of AF recurrence, univariate binary logistic regression was performed for all baseline clinical parameters, all FS-related parameters, and the randomized ablation strategy. Multivariate modeling included variables that were significant predictors ($p < 0.05$) of AF recurrence in the univariate regression. Multivariate binary models were also used to exclude center-specific effects on binary outcome variables. Model results are presented as odds ratios (OR) (95% confidence intervals [CI]). Cross-correlation of model variables was excluded using the Spearman-Rho test. A p value <0.05 was considered statistically significant for all tests results.

RESULTS

PATIENT CHARACTERISTICS. Among the 77 patients who completed follow-up in SELECT AF trial, 66 patients had EGM waveform data exportable from Carto XP (Biosense Webster Inc., Diamond Bar, California) to allow offline analysis of FS. Those 66 patients comprised the study cohort, and their clinical characteristics were no different from those of the 77 patients (Online Table S1). Among the 66 patients, 34 (52%)

underwent CEA ablation, and the remaining 32 (49%) had CFAE ablation with the endpoint of complete elimination of local bipolar electrograms. After 1-year follow-up, 42 patients (64%) had AF recurrence while the remaining 24 (36%) remained free of AF. There were no differences in baseline characteristics between these 2 groups (Online Table S2).

FOCAL SOURCE CHARACTERISTICS IN RELATION TO CFAE AND CEA. A median number of 101 [93, 111] anatomically distinct LA electrograms were analyzed per patient. A total of 77 FSs were found in 51 patients (77%), which represented a median of 1 [1, 2] per patient. The mean periodicity cycle length of these FSs was 162 ± 17 ms. Focal sources were most commonly found in the PV ostium/antrum (48%) as well as the LA appendage (19%) (**Figure 1A**). The distributions of FSs in the left and right PV are shown in **Figure 1B**.

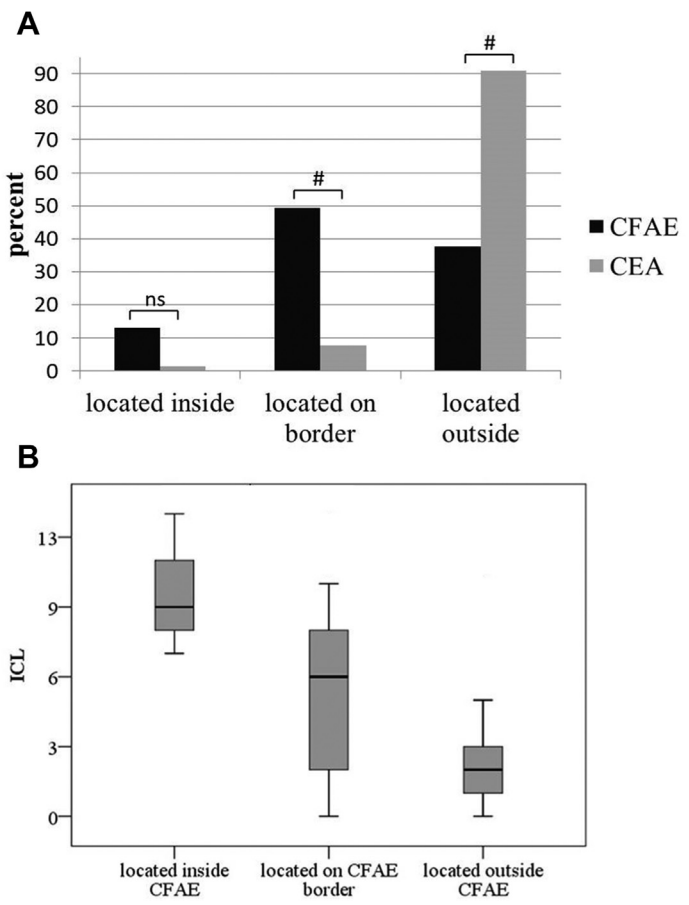
The spatial relationship of FS to CFAE and CEA is presented in **Figure 2A**. The proportion of FSs inside or bordering CFAE and CEA regions was 13% and 49%, respectively. The remaining FSs (38%) were outside the CFAE and CEA. When comparisons were made between CFAE and CEA, the proportions of FS inside CFAE and CEA were similar (13% vs. 1.3%, respectively; $p = 0.13$). Focal sources were more likely to be on the border zone of CFAEs than in CEAs (49% vs. 7.8%, respectively; $p = 0.012$). The proportion of FSs outside CFAE was significantly less than that of CEA (38% vs. 91%, respectively; $p = 0.031$). An overlap between CFAE and CEA regions was rare and had no relationship to FS location.

Focal sources inside CFAE regions showed a higher degree of fractionation with a higher median ICL than those on the border and outside CFAE regions (median 8.5 [7.8, 11.0] vs. 6 [1st quartile, 3rd quartile: 2.0, 8.3] vs. 2.0 [1st quartile, 3rd quartile: 1.0, 3.5], respectively). Mixed model analysis correcting for repeat intra-patient measurements showed a significant effect of the FS location on ICL ($p < 0.0001$) (**Figure 2B**). **Figures 3A and 3C** show 2 patients with FS bordering on a CFAE region and the electrograms of the respective FSs. The FSs for the 2 patients in **Figures 3A and 3B** localize well outside their CEA regions.

FOCAL SOURCE ABLATION IN RELATION TO CFAE AND CEA ABLATION. There were no differences in FS characteristics in relation to CFAE versus CEA ablation (Online Table S3). CFAE ablation led to significantly less AF recurrence than CEA ablation (38% vs. 62%, respectively; $p = 0.025$) after a mean follow-up of 328 ± 42 days. The total number of electroanatomic points analyzed per patients (median: 101 [93, 109] vs. 101 [94, 118], respectively; $p = 0.69$) as well as the number of FSs per patient (median: 1 [0.25, 1] vs. 1 [1, 2], respectively; $p = 0.29$) were not different between patients who underwent CFAE versus those who underwent CEA ablation. In addition, the number of unablated FSs (median: 0 [0, 1] vs. 1 [0, 1], respectively; $p = 0.31$) and the number of patients with unablated FSs (43% vs. 57%, respectively; $p = 0.33$) were similar between the two groups.

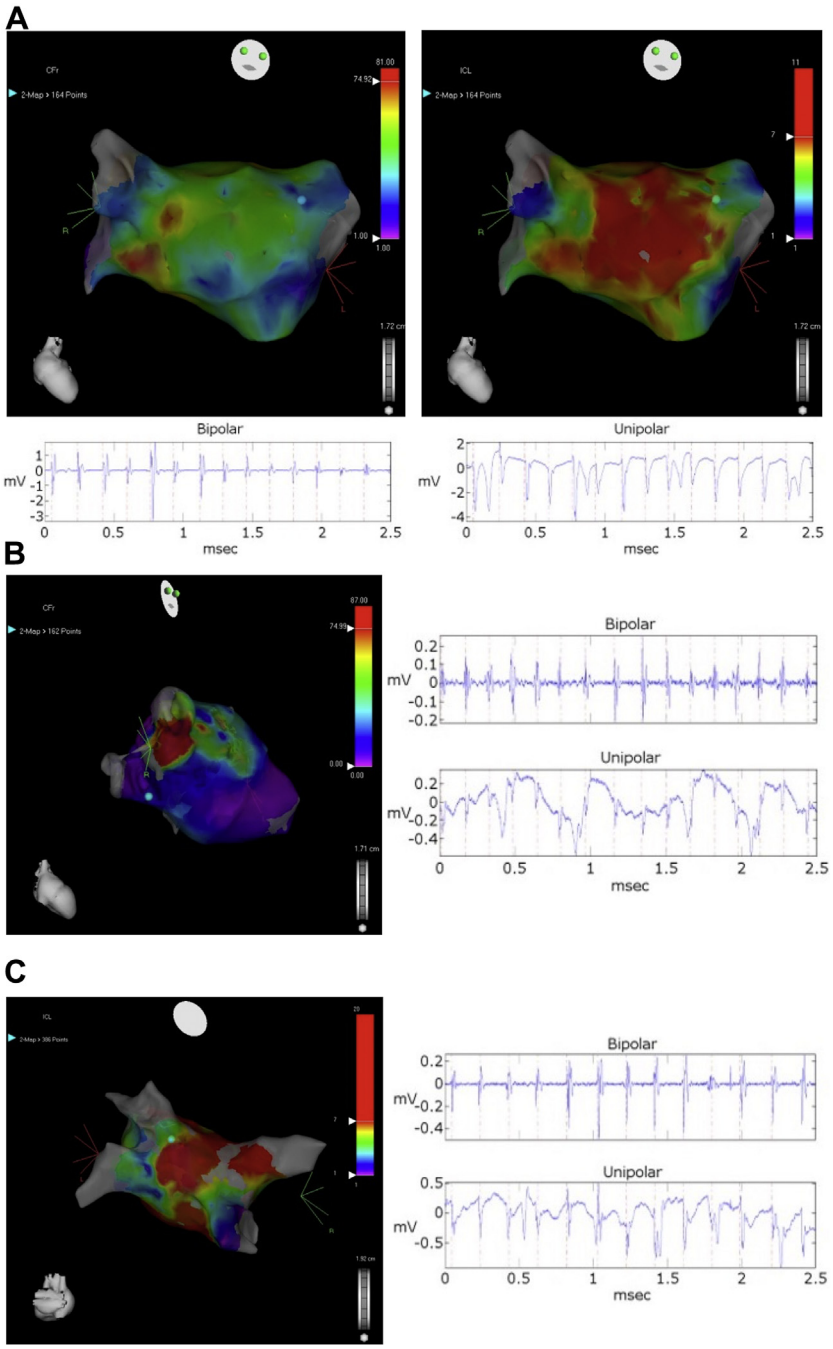
FOCAL SOURCE ABLATION AND AF RECURRENCE. The effect of FS ablation on AF recurrence is shown in **Table 1**. The median numbers of FSs found per

FIGURE 2 Spatial Relationship of Focal Sources to CFAE and CEA



(A) Proportion of FS located inside, bordering, and outside CFAE versus that in CEA areas; #$p < 0.05$. **(B)** Boxplot of the degree of fractionation depending on colocalization with CFAE. $p < 0.0001$ for influence of FS location on ICL in a mixed model analysis correcting for repeated intra-patient measurements. CEA = continuous electrical activity; CFAE = complex fractionated atrial electrograms; ICL = interval confidence level; ns = not significant.

FIGURE 3 Focal Sources Localize to CFAE Border Zone in 3 Patients



(A) Red indicates areas of significant CEA (>75% CEA) and significant CFAE (ICL >7) in the LA. Focal source **(blue tag)** at the base of the LA appendage is remote from CEA **(left)** but borders CFAE **(right)**. Bipolar and unipolar EGM of the FS are shown below CEA and CFAE maps. **(B)** Focal source **(blue tag)** in another patient is identified anterior to right inferior PV, which is remote from significant CEA **(red)**. Bipolar and unipolar EGM of the FS are shown beside CEA map. **(C)** Focal source **(blue tag)** in a third patient is present posterior to left superior PV, which borders the region of significant CFAE **(red)**. Bipolar and unipolar EGMs of the FS are shown beside the CFAE map. EGM = electrogram; LA = left atrium; other abbreviations as in Figures 1 and 2.

TABLE 1 Focal Source Characteristics Sorted by AF Recurrence

	All (n = 66)	AF Recurrences (n = 42)	No AF Recurrences (n = 24)	Hazard Ratio (95% CI)	p Value
Median points analyzed	101 (93, 111)	100 (93, 109)	101 (90, 115)	0.99 (0.97-1.02)	0.62
Median FS/patient	1 (1, 2)	1 (1, 2)	1 (0.25, 1.75)	1.00 (0.55-1.84)	0.97
Median ablated FS	1 (0, 1)	0 (0, 1)	1 (0, 1)	0.44 (0.20-1.01)	0.052
Median unablated FS	1 (0, 1)	1 (0, 1)	0 (0, 1)	2.96 (1.14-7.73)	0.026
Patients with unablated FS	35 (53%)	26 (74%)	9 (25%)		0.051
Median untreated FS	0 (0, 1)	1 (0, 1)	0 (0, 1)	1.31 (0.54-3.16)	0.55
Patients with untreated FS	23 (35%)	16 (69%)	7 (30%)		0.47

Values are median (1st quartile, 3rd quartile) or n (%), unless otherwise indicated. Hazard ratios for multivariate binary logistic regression are shown with center as covariate. The p values are shown for logistic regression or Mantel-Haenszel test, as applicable.

CI = confidence interval; FS = focal source.

patient were similar between those with and those without AF recurrence (median: 1 [1, 2] vs. 1 [0.25, 1.75], respectively; p = 0.97). The median number of unablated FS was significantly higher among patients with AF recurrence (1 [0, 1] vs. 0 [0, 1], respectively; p = 0.026). Approximately half of all patients (53%) had at least 1 unablated FS. The proportion of patients with at least 1 unablated FS was greater in those with AF recurrence than in those without (74% vs. 25%, respectively; p = 0.051), but this difference did not quite reach statistical significance (**Figure 4**).

In contrast to unablated FS, the median number of untreated FS was not significantly different between patients with and without recurrence (1 [0, 1] vs. 0 [0, 1], respectively; p = 0.55). Furthermore, the proportion of patients with at least 1 untreated FS was not significantly higher among patients with AF recurrence than among those without (69% vs. 30%, respectively; p = 0.47).

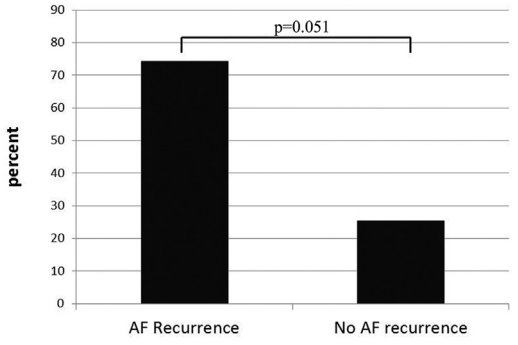
PREDICTORS OF AF RECURRENCE. In our univariate analysis, the number of unablated FS (OR: 2.37 [95% CI: 1.04 to 5.4]; p = 0.04) and the CEA ablation approach (OR: 3.25 [95% CI: 1.13 to 9.31]; p = 0.028) significantly predicted AF recurrence. The presence of at least one unablated FS (OR: 2.71 [95% CI: 0.96 to 7.62]; p = 0.059) and higher age (OR: 1.06 [95% CI: 0.995 to 1.13]; p = 0.07) were not significant predictors (**Table 2**). When CEA ablation approach and the number of unablated FS were included in a multivariate model, the former (OR: 3.06 [95% CI: 1.02 to 8.93]; p = 0.046) remained a significantly independent predictor of AF recurrence, whereas the number of unablated FSs (OR: 2.27 [95% CI: 0.96 to 5.36]; p = 0.061) did not quite reach the level of significance for predicting AF recurrence.

DISCUSSION

This study is the first to investigate the spatial relationship of fractionated EGMs to FS in the LA of patients with persistent or a high burden of paroxysmal AF. Focal sources detected with our previously described hierarchical schema (14), which evaluates bipolar EGM periodicity and unipolar EGM morphology, showed a high spatial relationship to CFAE border zones. In contrast, most FSs were found remote from CEA areas. We also demonstrated that the number of unablated FS was associated with greater AF recurrence; although in multivariate modeling, CEA ablation was the only independent predictor of AF recurrence.

To date, CFAE ablation has been widely applied in the management of persistent AF; however, CFAEs can cover large regions of the atria, and ablation of all CFAEs may increase the risk of collateral injury and flutter pro-arrhythmia. In order to refine the selection of fractionated electrograms as ablation targets, Takahashi et al. (4), in a study of 40 patients, suggested that ablating regions displaying an electrogram fractionation >80% (i.e., CEA) was associated with AF slowing or termination. Two prospective, randomized trials have evaluated the clinical efficacy of more selective CEA ablation and shown similar results. The SELECT AF trial (15) found a significantly higher rate of AF recurrence after CEA ablation than after CFAE ablation after PV isolation. Lin et al. (17) investigated 90 patients who underwent limited versus extensive CFAE ablation following PV isolation. The authors used an automated CFAE detection algorithm (NavX, St. Jude Medical, Inc., St. Paul, Minnesota) based on a fractionation index (FI) which represents the average time between electrogram deflections over a fixed recording period. For the limited ablation, only areas with FI ≤60 ms were

FIGURE 4 Focal Source Ablation and AF Recurrence



Proportion of patients with at least 1 unablated FS in relation to AF recurrence. AF = atrial fibrillation.

TABLE 2 Univariate, Binary Regression Model for the Prediction of AF Recurrences

	OR	95% CI	p Value
CEA ablation approach	3.25	1.13–9.31	0.028
No. of unablated FS	2.37	1.04–5.40	0.040
Not all FS ablated	2.71	0.96–7.62	0.059
Age, yrs	1.06	1.00–1.13	0.073
Male	0.50	0.14–1.77	0.28
TIA/stroke	0.95	0.20–4.36	0.94
Coronary artery disease	0.56	0.03–9.40	0.69
Valvular heart disease	1.77	0.17–18.02	0.63
Hypertension	1.50	0.52–4.35	0.46
Diabetes	2.20	0.42–11.56	0.35
Number of failed AADs	1.003	0.70–1.45	0.99
Ejection fraction, %	1.007	0.96–1.06	0.80
LA diameter, mm	0.96	0.88–1.05	0.35
Persistent AF	1.69	0.58–4.96	0.34

AAD = antiarrhythmic drugs; AF = atrial fibrillation; CEA = continuous electrical activity; OR = odds ratio; TIA = transient ischemic attack; other abbreviations as in Table 1.

targeted, whereas for the extensive approach, all areas with FI ≤120 ms were ablated. After a mean follow-up of 15 months post ablation, the rate of AF recurrence after multiple procedures was higher with the limited approach, but there was also a higher rate of post-procedural atrial flutter with the extensive approach (18).

The spatial relationship between CFAE or CEA and FS has been investigated in a few studies with contradictory results. In 1 report of 36 patients, Narayan et al. (10) found stable rotors and FS during AF in 97% of patients, using a 64-electrode basket catheter and a proprietary algorithm based on phase mapping. Ablation of these AF sources resulted in AF termination (55%) or organization (31%) to flutter. In that study, FS did not show different mean voltages, voltage ranges, or a different fractionation grades compared to the surrounding tissue, and only 13 of 31 FSs were surrounded by CFAE by more than 180° (10). The proximity of FS to CFAE was not investigated, unlike our study. In contrast, another report, applying dominant-frequency (DF) mapping in 50 patients with nonparoxysmal AF found distinct spatial patterns between the site of highest DF and highest fractionation (19). In patients with predominantly persistent AF and smaller LA, the area with the highest fractionation was most likely to be found in the boundary (5 to 15 mm) of the highest DF site, whereas in patients with larger LA and predominantly long-standing persistent AF, the highest fractionation was often found at the center (<5 mm) of the site of highest DF.

Lin et al. (9) applied DF and CFAE mapping in 72 patients before and after PV isolation (9). The authors investigated the spatial relationship between CEA and the highest DF site in a subset of 45 patients in whom AF did not terminate during PV isolation and found CEA close (<2 cm) to the highest DF in 24 of these patients. Ablation of the CEA areas in proximity to the highest DF significantly more often terminated AF than ablation of CEA remote from the highest DF.

In contrast to these reports, our novel signal processing algorithm identified FS by defining periodic bipolar EGMs with QS unipolar EGM features based on the premise that FS will manifest regular, pulse-like activity with centrifugal wave propagation. The number of FS identified by this algorithm is similar to that in previous reports, using conventional (20) or phase mapping and multielectrode basket catheter recordings in the atria (21). We found a large number of FS colocalizing with the border of CFAE areas. In contrast to the studies by Lin et al. (9,19), FSs detected by using our algorithm did not show a spatial relationship to areas of CEA. These findings suggest that most CFAEs may be passive to AF perpetuation, as they do not encompass FS. Rather, wave collision remote from FS may produce CFAE, as demonstrated by Kalifa et al. (8), who used a 2-dimensional computational model of atrial tissue to investigate signal fractionation in the presence of a high-frequency driver simulating FS activity. In their simulation, signals were organized in areas surrounding the high frequency driver and showed greatest fractionation in a narrow band on the border of the area with highest frequency (8).

We found that the number of unablated FS was significantly higher in patients with AF recurrence

and predicted AF recurrence in univariate analysis. Although not quite statistically significant, patients in whom at least 1 FS was not ablated were more likely to experience AF recurrence. These results suggest that FS may play a role in AF maintenance, which requires confirmation in larger, prospective studies. In contrast, there was no significant relationship with AF recurrence when FS inside the PVs were also considered treated with PV isolation rather than directly ablated. This may be explained by PV reconnection post PVI (22), which could allow unablated FS within the PV isolation segment to promote AF recurrence.

An important finding in our study was the lack of relationship between the number of FSs ablated and the applied ablation approach. In other words, a similar number of FSs were ablated despite more extensive ablation with CFAE than with the CEA approach. A plausible explanation is that the majority of CFAE-associated FS were localized to CFAE borders and therefore were not captured by the ablations targeting CFAEs themselves. Thus, FS may represent ablation targets distinct from CFAE or CEA.

CLINICAL IMPLICATIONS. CFAE and CEA ablations have been proposed as adjunctive therapeutic strategies in the management of persistent AF, particularly since PV isolation alone has limited long-term success. Our finding that FSs frequently localize outside CFAE and CEA areas suggests that most CFAE and CEAs may be passive to AF maintenance. Instead of eliminating CFAE and CEAs completely, bipolar EGMs with less fractionation may represent more suitable targets as they are more likely to be FS. The role of real-time FS mapping and ablation using our algorithm in persistent AF is currently being evaluated in a prospective, randomized trial.

STUDY LIMITATIONS. First, this was a retrospective analysis of electroanatomical mapping data collected from the SELECT AF trial, and the definitions of CFAE and CEA used by Carto XP. Although the results are primarily applicable to the population of the original study, the patients are representative of those with persistent or high-burden paroxysmal AF. Second, LA maps were acquired with high spatial resolution, but it is still possible that CFAE, CEAs, and FSs were not detected due to undersampling. Sampling density would also affect interpolation of CFAE and CEA areas and the definition of border zones, but this was fairly consistent between patients. Third, all FS were not directly ablated, which was not the intention of SELECT-AF trial. Rather, ablated FS were identified based on the anatomic location of ablation tags added to the LA anatomic map during CFAE and CEA ablation. Fourth, whether unablated FSs were solely responsible for AF recurrence is unclear, as other mechanism may exist such as PV reconnection. Focal source mapping from repeat AF ablation procedures would better define the role of unablated FS in AF recurrence, but EGM data from redo ablations were not available for analysis. Fifth, the unipolar QS pattern was a key signal feature used to detect FS, but it may arise from other mechanisms such as tissue discontinuities (i.e., small bundle inserting into a broad one), propagation perpendicular to fiber direction, or epi-to-endocardial breakthrough where wall thickness is small (11). Because we included a small R-wave in the unipolar EGM (R-to-S ratio <0.1) as part of our detection criteria, it is possible that epicardial-to-endocardial breakthrough was detected by our algorithm as a FS. Sixth, bipolar EGMs were recorded with a 3.5-mm ablation catheter tip, which may diminish the R-wave amplitude in the unipolar EGM and potentially reduce the specificity of FS detection, using our algorithm. Notwithstanding these potential limitations in algorithm specificity, only 1 to 2 FSs were detected per patient. Seventh, electrogram analysis was performed only in the LA, but the relationships of CFAE and CEA to FS in the right atrium or coronary sinus is anticipated to be similar to that of the LA. We were also not able to identify epicardial FS using endocardial EGM recordings, and this will require dedicated epicardial mapping.

CONCLUSIONS

One-half of the FSs detected during AF are found at the border of CFAE areas, whereas most of the FSs are found outside CEA areas. CFAE or CEA ablation leaves a number of FSs unablated, which is associated with AF recurrence. These findings suggest that many CFAEs may represent passive wave propagation remote from FSs, which may limit their therapeutic efficacy in AF substrate modification.

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PERSPECTIVES

COMPETENCY MEDICAL KNOWLEDGE: CFAE and CEA ablations have been proposed as adjunctive therapeutic strategies in persistent AF, presuming that these sites represent AF drivers. However, FSs frequently border CFAE and lie remote from CEA areas, suggesting that most CFAEs and CEA may actually be passive to AF maintenance.

TRANSLATIONAL OUTLOOK: Instead of eliminating CFAE/CEAs completely, bipolar EGMs with less fractionation may represent more suitable targets as they are more likely to be FSs. The role of real-time FS mapping and ablation using our algorithm in persistent AF is currently being evaluated in a prospective, randomized trial.

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KEY WORDS atrial fibrillation, ablation, CFAE, focal electrical sources

APPENDIX For an expanded Methods section and supplemental tables, please see the online version of this article.