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Hierarchical Schema for Identifying Focal Electrical Sources During Human Atrial Fibrillation

Implications for Catheter-Based Atrial Substrate Ablation

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ABSTRACT

OBJECTIVES The study sought to localize focal sources (FS) during atrial fibrillation (AF) using periodic component analysis (PiCA) and QS unipolar electrogram (EGM) morphology based on the assumption that periodic activation with centrifugal propagation is inherent to a FS.

BACKGROUND The localization of FS maintaining AF remains challenging, due to limitations in conventional time-frequency domain analysis. This is relevant to identifying targets for AF substrate ablation.

METHODS In 41 patients (age 56 ± 9 years, 76% persistent AF), bipolar EGMs were recorded in the left atrium (LA) during AF with a roving 20-pole catheter. Bipolar EGMs with periodicity were determined using PiCA. FS were defined as periodic sites with predominantly QS unipolar EGM morphology.

RESULTS For each patient, 456 ± 109 bipolar EGMs were recorded, of which 261 ± 15 (60%) demonstrated periodicity. FS were identified in 63% of patients (pulmonary vein [PV] 1.5 ± 1.5, extra-PV 2.6 ± 2.3). After PV antral ablation and follow-up of 14 ± 9 months, 37% of patients had symptomatic AF recurrence. Mean global LA periodicity cycle length was shorter in patients with AF recurrence compared to those without (143 ± 20 ms vs. 154 ± 9 ms, $p = 0.02$). Among 12 (29%) patients with FS exclusively in the PV, only 1 (8%) had AF recurrence. AF recurrence was significantly higher (50%, $p = 0.01$) in 14 (34%) patients with extra-PV FS.

CONCLUSIONS Our novel hierarchical analysis schema, incorporating PiCA and unipolar EGM morphology, detected a small number of FS in patients with predominantly persistent AF. FS in the PV was associated with successful PV antral ablation. Further prospective studies are required to determine whether these FS maintain AF and represent ablation targets. (J Am Coll Cardiol EP 2016;■:■–■) © 2016 by the American College of Cardiology Foundation.

Although the initiation of atrial fibrillation (AF) by ectopic beats, primarily from the pulmonary veins (PV), has been well described (1), the mechanisms sustaining AF remain poorly understood in humans. AF drivers may include focal sources (FS) (2) or rotor-like activation (3), which have been shown to maintain AF in experimental studies. Intraoperative mapping in patients with persistent AF has identified a few FS in the right atrium, which exhibit high frequency activity with centrifugal propagation (4). However, the existence of FS has not been clearly demonstrated in patients undergoing catheter ablation. In this clinical arena, detecting FS is hampered by low spatial resolution mapping and the inherent inaccuracy of processing complex electrograms (EGM) using conventional complex fractionated atrial electrogram (CFAE) analysis, dominant frequency (DF) analysis, or phase

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CFAE = complex fractionated atrial electrograms

CL = curve length

DF = dominant frequency

EGM = electrogram

FS = focal source

LA = left atrium

PiCA = periodic component analysis

PV = pulmonary vein

mapping (5-7). These techniques also do not consider the direction of wave propagation, which is critical in defining FS.

Based on the assumption that periodic activation with centrifugal propagation is inherent to an FS, we propose a novel hierarchical signal processing approach to identify FS during AF using periodic component analysis (PiCA) and the evaluation of QS unipolar EGM morphology. In this proof-of-principle study, our objective was to determine the presence and location of FS during AF in the left atrium (LA) of patients undergoing pulmonary vein (PV) antral catheter ablation. We also sought to determine whether the presence of extra-PV FS, which were not ablated, were associated with AF recurrence.

METHODS

STUDY POPULATION. Patients undergoing their first catheter ablation procedure for symptomatic drug refractory persistent or high-burden paroxysmal AF were prospectively included. High-burden paroxysmal AF was defined as >4 self-terminating episodes of AF within the last 6 months with 2 episodes lasting at least 6 h within the last year. Given the long duration AF episodes in these patients that could invoke AF drivers, they were felt to be a relevant study group. Patients were excluded if sinus rhythm was present at the commencement of mapping. The study was approved by the University Health Network Research Ethics Board and all patients provided written informed research consent.

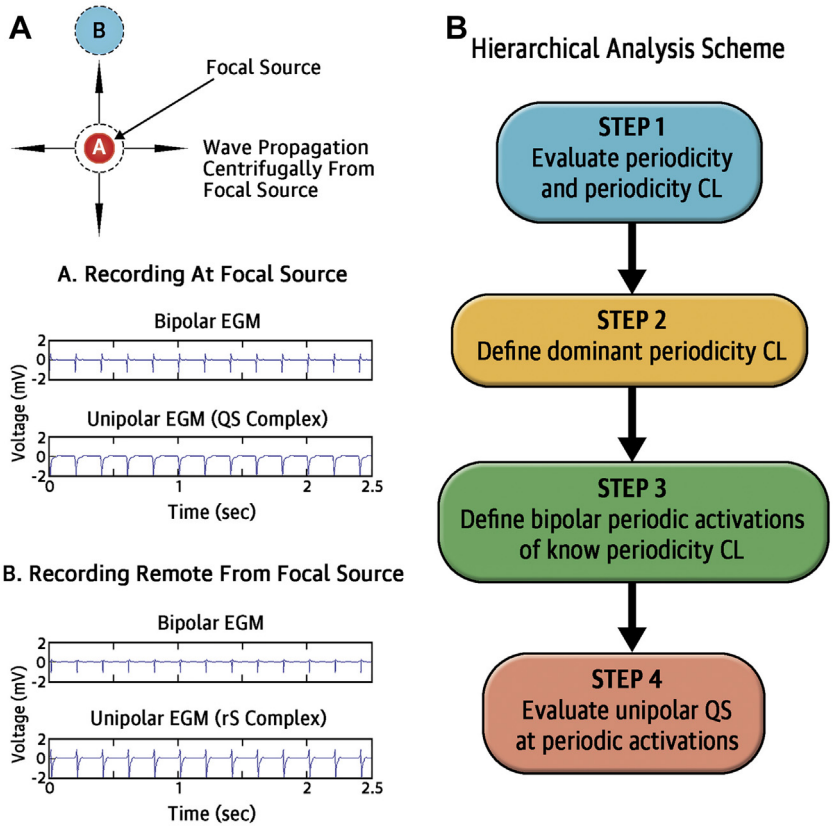
MAPPING PROTOCOL AND CATHETER ABLATION. Patients underwent AF ablation after overnight fasting and all anti-arrhythmic drugs were discontinued for 5 half-lives, with the exception of amiodarone, which was continued. A variable loop (15 to 25 mm) circular 20-pole mapping catheter (Lasso NAV, Biosense Webster, Diamond Bar, California) was placed in the LA through a guide sheath. This catheter was maintained at maximum diameter when possible and maneuvered throughout the LA. After achieving catheter stability at each location, 10 bipolar electrograms (EGMs) (30 to 500 Hz) and 20 unipolar EGMs (0.05 to 500 Hz) were simultaneously recorded for 2.5 s at 1 kHz.

Following LA mapping, circumferential PV antral ablation was performed using a 3.5 mm irrigated tip ablation catheter (Navistar SF, Biosense Webster). Contiguous lesions (25 to 30 W) were deployed around the PV antra until the procedural endpoint of PV entrance block was achieved. After ablation, those patients still in AF or atrial tachycardia/flutter were electrically cardioverted. Patients were maintained on antiarrhythmic drugs and anticoagulation for 2 months following ablation. Clinical follow-up included 48-h Holter recordings at 2, 6, and 12 months post-ablation. AF recurrence was defined as symptomatic AF episodes >30 s after a 2-month blanking period.

PERIODICITY AND FOCAL SOURCE ANALYSIS. After ablation, electroanatomic data were analyzed using custom software written in Matlab (The MathWorks Inc., Natick, Massachusetts). Data points were excluded if circular catheter stability was poor or if far-field ventricular activity was only present. LA and PV anatomy was reconstructed based on the 3D coordinates of each data point. Total LA surface area was derived from the anatomic mesh by summating the area of all triangles comprising the mesh. Among the remaining data points, hierarchical analysis of bipolar and unipolar EGMs was performed to identify FS as outlined in **Figure 1**. First, bipolar EGMs were evaluated for periodicity using PiCA which generates a periodicity strength or cost for a given cycle length (CL) (Online Appendix) (8,9). **Figure 2** illustrates the cost function derived from PiCA analysis of an AF bipolar EGM with simulated aperiodic signal (**Figure 2A**), simulated periodic signal of CL 125 ms (**Figure 2B**), and A+B combined (**Figure 2C**). PiCA confirmed the presence of periodicity with CL 125 ms in **Figures 2B and 2C**, but not **Figure 2A**. We evaluated periodicity within a CL range of 50 to 200 ms and periodicity was deemed present when the cost function minimum was less than the mean cost minus 2 standard deviations. The minimum periodicity of 50 ms was chosen to approximate a physiologic atrial refractory period or atrial blanking period. The maximum periodicity of 200 ms was considered sufficiently long that FS of clinical relevance would be captured. Our heuristic cutpoint of mean cost minus 2 standard deviations provided confidence that the cost function minimum was significant. Periodicity CL was determined from the cost function minimum for those bipolar EGMs with periodicity within the defined CL range.

Second, a histogram plot of all periodicity CLs in the LA was generated. The most prevalent periodicity CL was chosen as an indicator of a putative FS. This dominant periodicity CL was defined as the mode (±5 ms) of the periodicity CL histogram. Variability in periodicity CL in the LA was assessed from the SD of the same periodicity CL distribution. The location of periodic sites was displayed on the patient's LA

FIGURE 1 Hierarchical Analysis Steps to Define FS



(A) Focal source (FS) is depicted as a discrete site generating periodic electrical impulses with centrifugal wave propagation. The lower panels show bipolar and unipolar electrograms (EGMs) recorded from sites A (at FS) and B (remote from FS). At each site, the bipolar EGM has regular periodic activity. However, the unipolar EGM shows QS morphology at site A and rS morphology at site B. **(B)** Hierarchical analysis identifies FS during atrial fibrillation based on dominant periodic activity in the bipolar EGM and unipolar QS morphology. CL = cycle length.

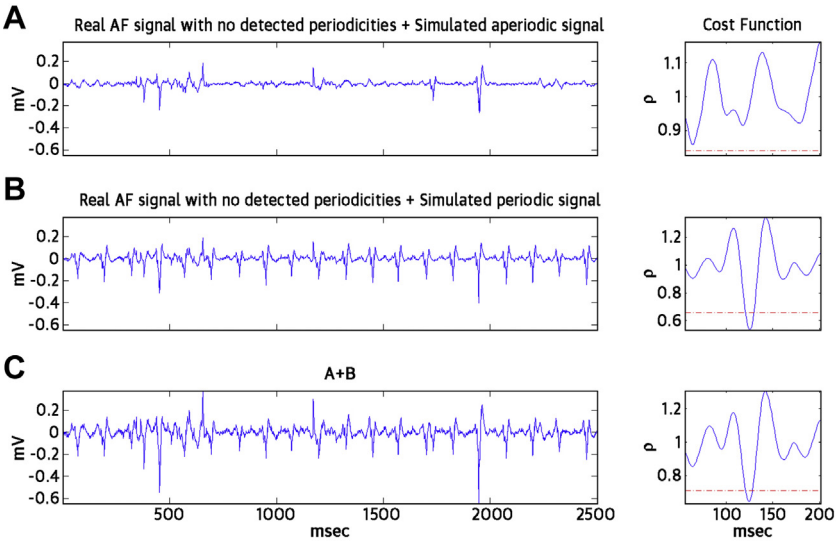
anatomic map and the area of periodicity was derived from the sum of all nonoverlapping 3 mm interpolated periodic sites.

Third, once dominant periodicity CL was determined, local activations in the bipolar and unipolar EGM corresponding to this periodicity were annotated. For this purpose, a graph search method was used to find the best candidate local activations in the bipolar EGM (Online Appendix). We have previously validated this method for detecting bipolar EGM activations with predefined periodicity CL contaminated by nonperiodic signal (10).

Fourth, all activations defined in the bipolar EGM were then transposed to the corresponding unipolar EGM in order to determine unipolar EGM onset and morphology. FS were identified based on unipolar EGMs with predominantly QS morphology, defined as an R/S ratio <0.1 in over 90% of activations. Anatomically distinct FS (>7 mm apart) were projected onto the patient's LA anatomic map in order to determine their number and location (PV [ostial or antral] vs. extra-PV) blinded to the patient's ablation outcome.

STATISTICAL ANALYSIS. Continuous variables were assessed for normal distribution using the Shapiro-Wilk test. Normally distributed data were presented as mean ± SD. Data that were not normally distributed were presented as median and interquartile range (interquartile range). Comparison between patient groups was performed using the unpaired *t* test or Mann-Whitney *U* test where appropriate. Proportions were compared using chi-square or Fisher exact test. Post hoc multiple comparisons were corrected with the Bonferroni adjustment when appropriate. Correlation between variables was assessed

FIGURE 2 PiCA of Simulated Bipolar EGMs



Representative bipolar EGM recorded during atrial fibrillation (AF) is shown with no periodic signal as confirmed by periodic component analysis (PiCA). To this EGM, we added either **(A)** simulated aperiodic signal or **(B)** simulated periodic signal with CL 125 ms. The PiCA cost function **(right)** confirmed the absence of periodicity in **A** and presence of periodicity with CL 125 ms in **B**. **(C)** The bipolar EGMs from **A** and **B** were combined, such that there was no visually apparent periodicity. The PiCA cost function identified periodicity with CL 125 ms. Abbreviations as in Figure 1.

using Pearson or Spearman rank correlation test. Agreement between periodicity CL assessed by PiCA versus visual measurement was determined using correlation and Bland Altman plots with 95% confidence intervals. All tests were 2-sided and a 2-tailed $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 20 (IBM, Armonk, New York).

RESULTS

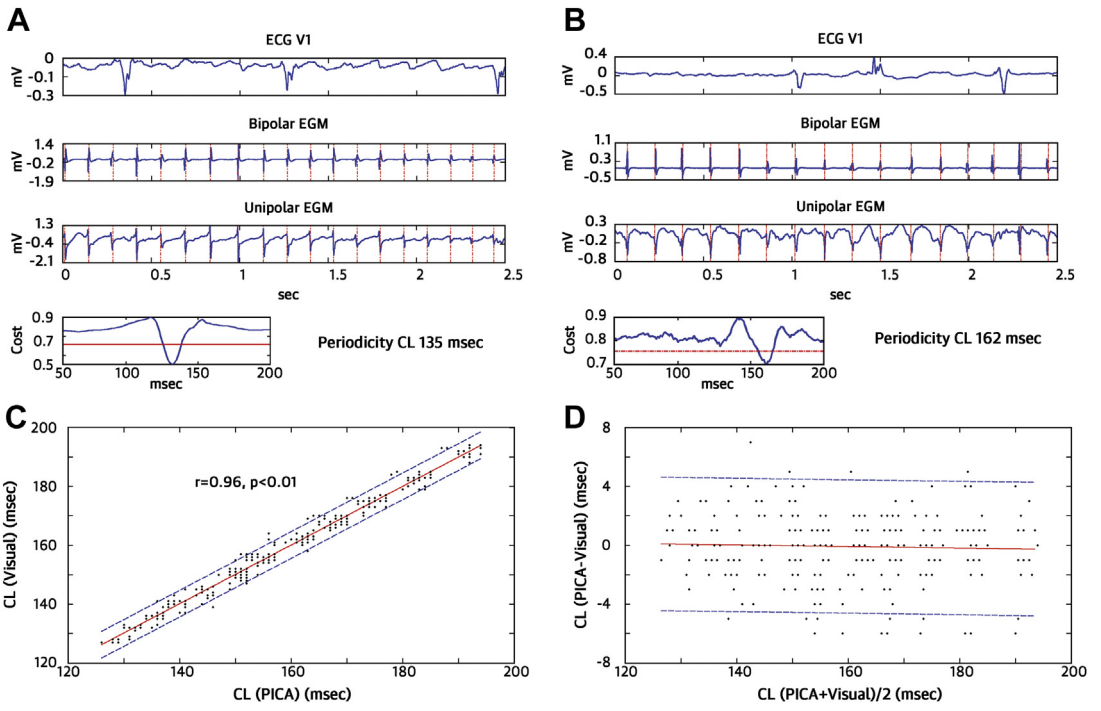
PATIENT CHARACTERISTICS. Forty-one consecutive patients were enrolled (56 ± 9 years of age, 71% male). AF symptom duration was 5.4 ± 4.0 years and the proportion with high-burden paroxysmal and persistent AF was 24% and 76%, respectively. LA size measured 43 ± 5 mm and LV ejection fraction was 58 ± 8%. A modest proportion of patients had AF risk factors, including hypertension (37%), diabetes (7%), thyroid disease (12%), obstructive sleep apnea (42%), and obesity (body mass index >30 kg/m^2, 39%). Patients on amiodarone (n = 12) had similar clinical characteristics to those taking no antiarrhythmic drugs at the time of ablation (Online Appendix, Online Table 1).

VALIDATION OF PERIODICITY CL AND UNIPOLAR EGM MORPHOLOGY CLASSIFICATION. To evaluate the accuracy of PiCA-derived periodicity CL, all bipolar EGMs with visually apparent stable periodicity and no fractionation were selected (n = 2,500) as shown in Figure 3. Periodicity CL was determined visually using digital calipers, and defined as the mean of consecutive peak-to-peak activations over 2.5 s. Figure 3C shows high correlation between periodicity CL derived with PiCA versus visual assessment ($r = 0.96$, $p < 0.01$). The Bland-Altman plot in Figure 3D also shows excellent agreement between the 2 methods (mean error 0.3 ± 2.2 ms). Furthermore, PiCA was accurate in detecting simulated periodicity in CFAE and under low periodic signal-to-noise conditions (Online Appendix, Online Figure 1).

Once PiCA identified periodicity, our graph search method annotated local activations in the bipolar EGM based on their periodicity CL. In Figure 3 for example, local activations are automatically defined in the bipolar and unipolar EGM, allowing classification of the unipolar EGM as non-QS (Figure 3A) versus QS (Figure 3B).

PERIODICITY AND FOCAL SOURCE MAPPING. Most bipolar EGMs (n = 16,120) manifested complex signal features, and four examples are provided in Figure 4 along with their corresponding periodicity CL and local activations. In each example, the unipolar EGM has a dominant QS morphology. Figure 5 illustrates

FIGURE 3 Validation of Periodity Detection

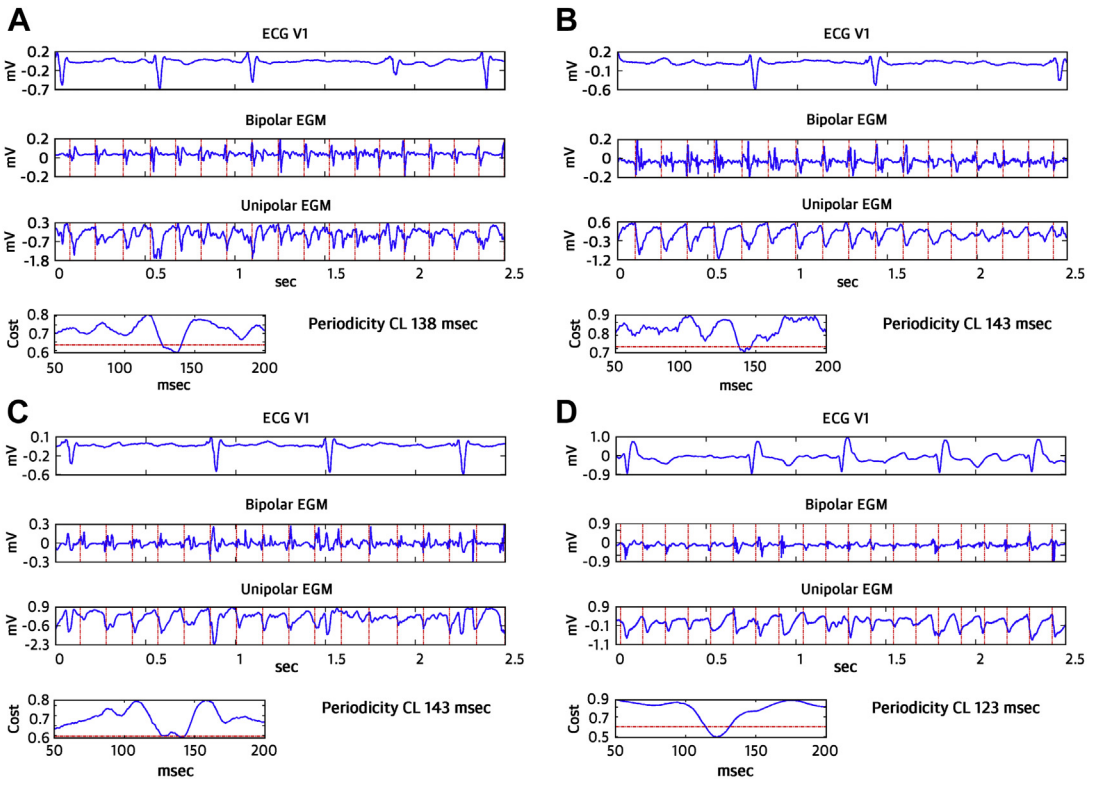


Visually apparent periodic bipolar EGMs are shown from 2 different sites in the left atrium. **(A)** The PiCA cost function of the bipolar EGM has a local minimum **(below red threshold)** at a periodicity CL 135 ms. Local activations with the same periodicity CL are annotated in the bipolar and unipolar EGM using our graph search algorithm **(red dotted lines)**. The unipolar EGMs have RS complexes. **(B)** The PiCA cost function has a local minimum at a periodicity CL 169 ms. Local activations are annotated showing QS unipolar EGM morphology. **(C)** PiCA-derived periodicity CL was validated against visually derived CL among bipolar EGMs with visually apparent periodic activity ($r = 0.96$, $p < 0.01$). **(D)** Bland-Altman plot showed excellent agreement (mean error 0.3 ± 2.2 ms) between the two. Abbreviations as in Figure 1.

the histogram plot of the periodicity CLs in the LA of 2 patients, which identified a dominant periodicity CL. FS with dominant periodicity CL and QS unipolar EGM were defined in the PV (Figure 5A) and extra-PV (Figure 5C) in these 2 patients. Figure 5B shows another patient with FS in the left superior PV antrum where spontaneous AF was initiated by repetitive high-frequency atrial bursts. These bursts were also evident during sustained AF when FS mapping was performed, suggesting that the PV FS was also maintaining AF.

The yield of each step in our hierarchical analysis is illustrated in Figures 6A and 6B for all bipolar EGMs and bipolar EGMs per patient, respectively. LA activation maps were comprised of 456 ± 109 bipolar EGMs per patient, representing a sampling density of 2.0 ± 0.6 bipolar EGM/cm^2. Bipolar EGMs demonstrating periodicity were present in all patients, and 60% of the bipolar EGMs had periodic activity (261 ± 15 per patient). The area of periodicity per patient was $18 \pm 9\%$ of the total LA surface and the mean periodicity CL was 150 ± 15 ms. Areas of periodicity often clustered in the LA, defined as >5% of total periodicity area. The number of periodicity clusters per patient was 2.6 ± 1.2, each with an area of $3.1 \pm 2.4\%$ (as a proportion of LA area). Periodicity CLs had a single-peak distribution in 34 (83%) patients, which permitted reliable assessment of dominant periodicity. Among all bipolar EGMs with dominant periodicity ($n = 4{,}510$, 110 ± 82 per patient), only 167 (3.7%) had QS unipolar EGM morphology, identifying them as FS. Wave propagation away from each FS was assessed using bipolar local activation times and unipolar EGM morphology in adjacent recording electrodes as detailed in the Online Appendix and Online Figure 2. The reproducibility of FS detection was evaluated in regions of the LA sampled more than once (Online Appendix). The prevalence of multiple periodicities in a given bipolar EGM and its relationship to the number of FS is also presented in the Online Appendix.

FIGURE 4 Detecting Periodicity and Local Activation in Complex EGMs



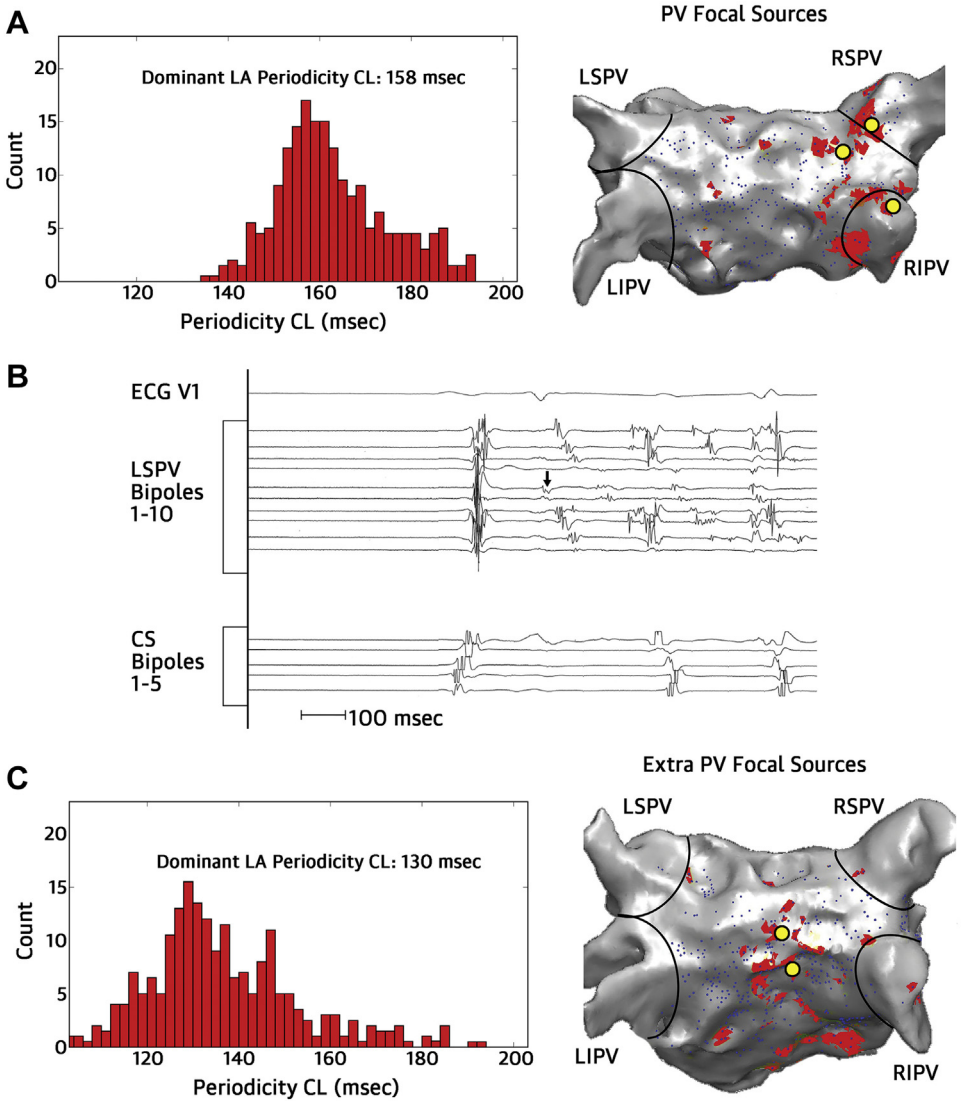
Bipolar EGMs without visually apparent periodicity are shown from 4 different sites in the left atrium. In each example, the PiCA cost function shows a local minimum (below red threshold) that corresponds to the periodicity CL. Each example also shows a unipolar EGM with QS morphology. ECG = electrocardiogram; other abbreviations as in Figure 1.

PREVALENCE AND SPATIAL DISTRIBUTION OF FOCAL SOURCES. FS were present in 26 (63%) patients (4.1 ± 3.2 FS per patient) and their clinical characteristics were similar to those without FS (Online Table 2). With respect to LA substrate, patients with FS had longer mean LA periodicity CL (154 ± 10 ms vs. 143 ± 20 ms, p = 0.03) and greater area of periodicity (as a proportion of LA area) (22 ± 7% vs. 10 ± 8%, p < 0.01) compared to those without FS. Among patients with FS, the prevalence of FS was no different between those with high-burden paroxysmal versus persistent AF (50% vs. 64%, p = 0.47) or those taking amiodarone versus no amiodarone (58% vs. 70%, p = 0.7).

Sixty-one (36%) FS were located in the PV (1.5 ± 1.5 per patient), as follows: left superior PV 10%, left inferior PV 5%, right superior PV 10%, right inferior PV 11%. The remaining 106 (64%) FS were extra-PV (2.6 ± 2.3 per patient), as follows: posterior wall (23%), roof (15%), septum (10%), anterior wall (8%), appendage (7%). The spatial distribution of extra-PV FS is illustrated in Figure 7. There was no difference in the prevalence of extra-PV FS between those with high-burden paroxysmal versus persistent AF (2.2 ± 2.7 per patient vs. 2.7 ± 2.2 per patient, p = 0.5). The periodicity CL of PV FS was similar to that of extra-PV FS (170 ± 4 ms vs. 167 ± 4 ms, p = 0.54). As a measure of the LA electrical substrate, mean LA periodicity CL was longer in patients with extra-PV FS compared to those without any FS (149 ± 16 ms vs. 136 ± 22 ms, p = 0.05).

RELATIONSHIP OF FOCAL SOURCES TO CLINICAL OUTCOMES AFTER ABLATION. Circumferential PV antral ablation with PV isolation was achieved in all patients. Ablation time was 58 ± 17 min and 5 (12%) patients converted to sinus rhythm during ablation, while another 2 (5%) organized to atrial tachycardia/flutter. Among the 5 patients with AF termination to sinus rhythm, 3 had FS in the PVs that were being isolated, while the remaining 2 patients had no FS. In these 2 patients, the PVs were not yet isolated at the

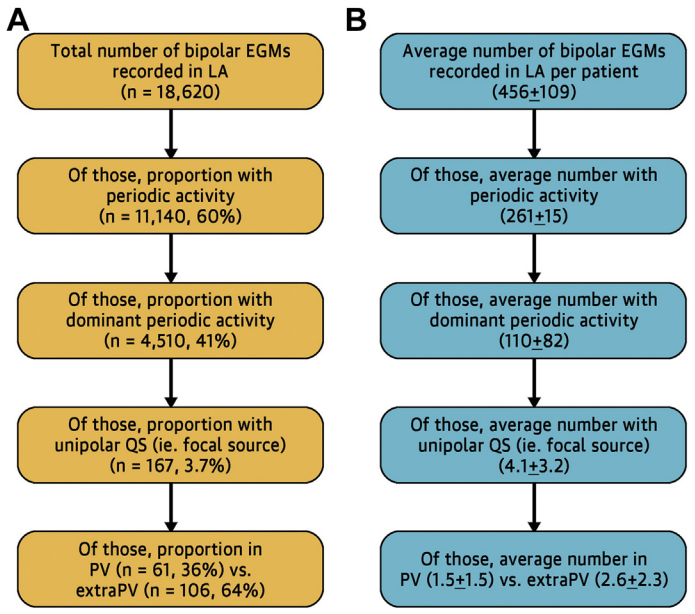
FIGURE 5 PV and Extra-PV FS



(A) In a patient with pulmonary vein (PV) FS, the histogram plot **(right)** of all periodicity CLs in the left atrium (LA) identifies a dominant periodicity CL of 158 ms, which corresponds to the mode of the distribution. The LA anatomic map (posteroanterior view, **left**) shows regions of periodic bipolar EGMs **(red)** with a range of periodicity CL according to the histogram. Three FS in the right PV **(yellow dots)** are also shown, whose periodicity CLs are all equal to the dominant periodicity CL. **Blue dots** indicate sampled bipolar EGMs. **(B)** In another patient with FS identified in the left superior PV (LSPV), spontaneous atrial fibrillation (AF) is initiated by repetitive high-frequency atrial bursts **(arrow)** from the same PV as recorded by a circular catheter (LSPV bipoles 1 to 10). Some atrial bursts do not conduct to the coronary sinus (CS bipoles 1 to 5). These bursts were also evident during AF when FS mapping was performed. **(C)** In another patient with extra-PV FS, the histogram plot **(right)** shows a shorter dominant periodicity CL of 130 ms. The LA anatomic map (posteroanterior view, **left**) shows regions of periodic bipolar EGMs **(red)** and 2 FS in the posterior wall **(yellow dots)**. CS = coronary sinus; ECG = electrocardiogram; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; other abbreviations as in Figure 1.

time of AF termination. After a follow up of 14 ± 9 months, 15 (37%) patients had symptomatic AF recurrences and their characteristics are presented in Table 1. Among those with FS exclusively in the PV (n = 12, 29%), only 1 (8%) had AF recurrence in follow-up. In the 14 (34%) patients with extra-PV FS, the rate of AF recurrence was significantly greater (50%, p = 0.01) (Figure 7C). Patients with no FS (n = 15, 36%) also had a higher rate of AF recurrence (47%) compared to those with only PV FS (p = 0.04).

FIGURE 6 Hierarchical Analysis of FS



The prevalence (among all recorded EGMs) and mean distribution (per patient) at each level of the analysis are shown in **A** and **B**, respectively. LA = left atrium; PV = pulmonary vein; other abbreviations as in Figure 1.

Patients experiencing AF recurrence had evidence of more structural and electrical remodeling compared to those remaining in sinus rhythm based on larger LA diameter (45 ± 6 mm vs. 42 ± 4 mm, $p < 0.05$) and shorter mean LA periodicity CL (143 ± 20 ms vs. 154 ± 9 ms, $p = 0.02$) (Figure 7D). However, the area of periodicity (as a proportion of LA area) did not differ between patients with and without AF recurrence (15 ± 11% vs. 19 ± 8%, $p = 0.18$).

DISCUSSION

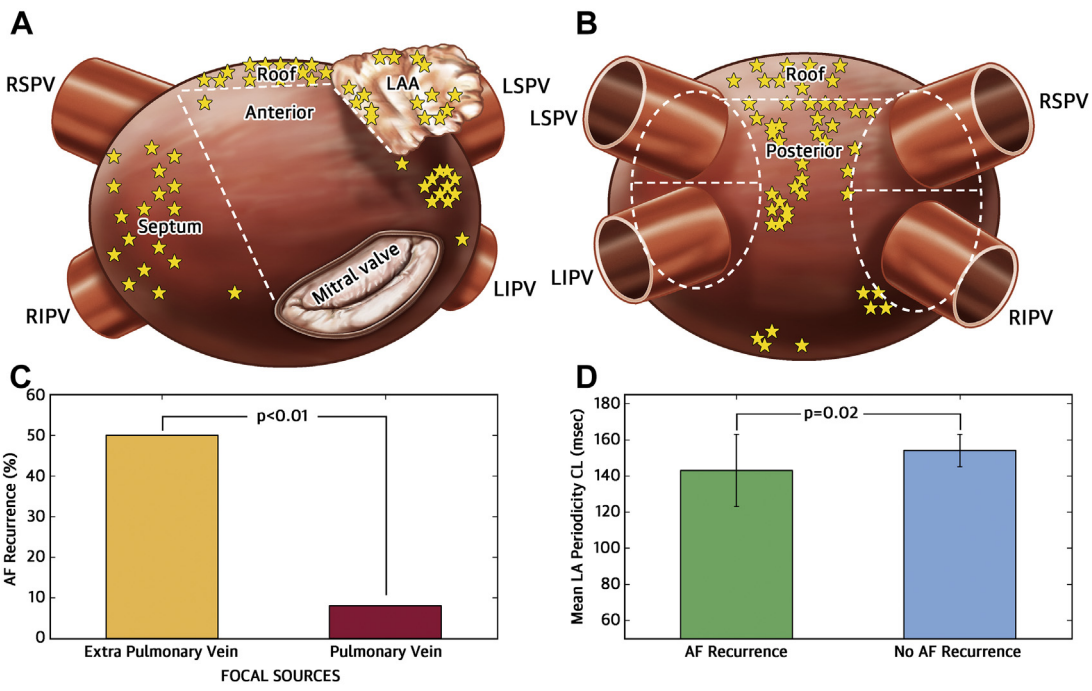
In this proof of principle study, we defined FS during AF using a novel signal processing algorithm, which incorporated a hierarchical evaluation of bipolar EGM periodicity, dominant periodicity CL, and unipolar EGM morphology. From high spatial resolution maps, a small number of FS were identified in the LA of more than half of patients with predominantly persistent AF. AF recurrence was significantly lower after PV antral catheter ablation in those with exclusively PV FS compared to those with extra-PV FS or no FS. AF recurrence was also associated with shorter mean LA periodicity CL reflecting more extensive electrical remodeling.

Although the presence of focal or rotor-like AF drivers maintaining AF has been shown in experimental studies involving structurally normal atria (2,3), their detection has been challenging in patients undergoing catheter ablation for persistent AF (11). Owing to complex local EGM morphology and signal nonstationarity, activation mapping during AF and conventional time- or frequency-domain analyses, such as CFAE and DF, may be prone to inaccuracy. To address these complexities, we first employed PiCA to evaluate periodicity CL, which identified the presence of periodic bipolar EGMs with similar morphology. Then, our graph search algorithm annotated local activations of known periodic CL to furnish classification of unipolar EGM morphology. Our study highlights the utility of electrogram morphology analysis in AF, as also demonstrated by Ng et al. (12), where the presence of highly repetitive morphology patterns was associated with AF recurrence post-ablation. We adopted a conservative definition of unipolar QS, with an R/S ratio <0.1, to improve the specificity of discerning centrifugal wave propagation. Eckstein et al. (13) demonstrated a similar unipolar EGM morphology with simultaneous endocardial-epicardial multielectrode LA mapping during AF in open-chest goats, which provided evidence for midmyocardial FS. However, dominant unipolar S waves during AF may not necessarily indicate FS, but may also arise from endocardial-epicardial breakthrough, and in theory, the stationary core of a rotor. These alterative mechanisms require confirmation with higher resolution panoramic atrial recordings, such as with optical mapping.

Our study also demonstrated a significant relationship between bipolar EGM periodicity and outcomes. Patients without FS and those with AF recurrences post-ablation consistently had lower mean LA periodicity CL and/or smaller areas of periodicity. Shorter LA appendage CL has also been associated with a lower likelihood of sinus rhythm conversion during substrate ablation (14). However, unlike LA appendage CL, LA periodicity CL is a composite of the entire LA and may therefore provide a more robust measure of LA electrical modeling.

COMPARISON WITH PREVIOUS STUDIES EVALUATING FS. Conventional CFAE analysis quantifies bipolar EGM fractionation in the time domain when CL is typically <120 ms. However, the specificity of CFAEs in identifying FS may be poor (15). Indeed, intraoperative mapping has implicated multiple mechanisms in the genesis of CFAEs, including wave pivoting, slow conduction and wave collision (5). Furthermore, the clinical benefit of adjunctive CFAE

FIGURE 7 Spatial Distribution of Extra-PV FS and PV Antral Ablation Outcomes



Spatial distribution of extra-PV FS in LA are shown in **(A)** anteroposterior and **(B)** posteroanterior views. **(C)** AF recurrence was significantly less among patients with only PV FS compared to those with extra-PV FS. **(D)** Among patients without AF recurrence, mean LA periodicity CL was significantly greater than those with AF recurrence. LAA = left atrial appendage; other abbreviations as in Figures 1 and 5.

ablation in persistent AF has not been shown in recent randomized trials (16,17). We evaluated periodicity CLs between 50 and 200 ms, and virtually all bipolar EGMs with periodicity had CL greater than 120 ms. Based on this CL cutpoint, CFAEs did not colocalize with periodic sites or FS in our patients.

In the case of DF analysis, activation frequency is evaluated, but EGM morphology and the direction of wave propagation is not considered. For bipolar EGMs with alternating potentials, the activation frequency may be overestimated with DF, but less so with PiCA, which evaluates periodicity of EGMs having similar morphology. The DF of highly complex bipolar EGMs may also be overestimated (i.e., DF >8 Hz) when no periodicity is detected by PiCA, as evident in 7% of our bipolar EGMs (Online Appendix, Online Figure 3). While the presence of DF gradients may imply propagation away from a region of high DF (>8 Hz) (18), fibrillatory conduction remote from a source can also produce higher DF in surrounding regions. Therefore, DF gradients may not be concordant with the direction of wave propagation, which may affect FS detection. These issues may contribute to the limited clinical benefit of adjunctive high-frequency DF ablation in persistent AF (19).

Recently, phase mapping of multiple unipolar EGMs recorded from a basket catheter has demonstrated the existence of FS in patients with persistent AF undergoing catheter ablation (20). However, the accuracy of this approach may be compromised when non-sinusoidal complex EGMs are present (21). Although the evaluation of centrifugal wave propagation is ideally achieved with simultaneous multielectrode mapping, conventional 64-electrode basket catheters may not have sufficient spatial resolution. A more practical alternative is to consider the QS unipolar EGM (2) recorded from a single electrode as an indicator of an FS, once periodic activity is detected.

CLINICAL IMPLICATIONS. Although PV isolation remains the cornerstone of paroxysmal AF ablation when PV ectopic beats represent important triggers, contemporary ablation targets to modify atrial substrate in persistent AF have not resulted in durable rhythm control in most patients (22). Increasing the specificity of substrate ablation by targeting AF drivers, such as FS, may improve long-term sinus

TABLE 1 Patient Characteristics and AF Recurrence Post-Ablation

	AF Recurrence (n = 15)	No AF Recurrence (n = 26)	p Value
Age, yrs	57 ± 10	57 ± 10	0.99
Type of AF			0.72
Paroxysmal AF	3 (30)	7 (70)	
Persistent AF	12 (39)	19 (61)	
AF symptom duration, yrs	6.4 ± 4.5	5.1 ± 3.8	0.36
Hypertension	4 (27)	11 (42)	0.50
Diabetes	1 (7)	2 (11)	1.00
Thyroid dysfunction	2 (13)	3 (13)	1.00
Obstructive sleep apnea	5 (37)	8 (44)	0.62
BMI, kg/m^2	29 ± 6	28 ± 7	0.93
FS Characteristics			
Number of FS per patient	1.5 ± 1.7	1.2 ± 1.1	0.48
Patients with only PV FS	1 (7)	11 (42)	**0.01**
Patients with extra-PV FS	7 (47)	7 (27)	0.20
Patients without any FS	7 (47)	8 (31)	0.31
FS periodicity CL	163 ± 15	162 ± 17	0.84
Structural and electrical characteristics			
LV ejection fraction, %	58 ± 8	58 ± 8	0.63
LA size, mm	45 ± 6	42 ± 4	**0.04**
Mean LA periodicity CL (ms)	143 ± 20	154 ± 9	**0.02**
Mean periodicity area (% of LA surface)	15 ± 11	19 ± 8	0.18
Ablation time (min)	57 ± 20	61 ± 23	0.42

Values are mean ± SD or n (%). **Bold** values of $p < 0.05$ are considered statistically significant.

AF = atrial fibrillation; BMI = body mass index; CL = cycle length; FS = focal sources; LA = left atrium; LV = left ventricular; PV = pulmonary vein.

rhythm maintenance. In our study, subjects with FS only in the PVs had lower rates of AF recurrence after PV antral ablation than those with extra-PV FS that were not ablated, or those without FS. It is therefore possible that FS or other AF sustaining mechanisms, such as rotors, outside the PV may be relevant to AF maintenance, and future work is required to determine the clinical response to ablation of such FS.

STUDY LIMITATIONS. First, the sample size was modest and included mostly patients with persistent AF rather than long-lasting persistent AF. Second, FS evaluation was performed offline after PV antral ablation. The role of FS identified by our algorithm in sustaining AF requires prospective study with real-time FS mapping and ablation, which is the intention of an ongoing randomized control trial. Third, the stability of FS beyond 2.5 s was not evaluated due to the recording constraints of the commercial mapping system. However, a 2.5-s recording window has been used to assess CFAE and DF (23); hence a similar window was applied for PiCA. Although longer sampling times have theoretical advantages, the stability of the recording catheter may be compromised. Finally, only high resolution mapping of the LA was performed and characterization of FS in the right atrium, coronary sinus, and the superior caval vein warrants further study.

CONCLUSIONS

A small number of FS can be identified in the LA of patients with predominantly persistent AF using our hierarchical analysis schema that includes PiCA, dominant periodicity CL and unipolar EGM morphology. Among patients with FS localized in the PV only, their rates of AF recurrence were lower post-PV antral ablation when compared to those with extra-PV FS or those with no FS. Although our algorithm provides a conceptual framework for identifying putative FS during AF, further prospective studies are needed to determine if these FS are relevant to sustaining AF and whether real-time FS ablation improves outcomes over PV antral ablation in patients with persistent AF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Hierarchical analysis of bipolar and unipolar EGMs can provide a conceptual framework for identifying putative FS during AF.

TRANSLATIONAL OUTLOOK: Real-time mapping and ablation of FS identified by our algorithm requires further study to determine whether this strategy improves PV antral ablation outcomes in patients with persistent AF.

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KEY WORDS atrial fibrillation, catheter ablation, electrogram, periodicity, signal analysis

APPENDIX For expanded Methods and Results sections as well as supplemental tables and figures, please see the online version of this article.