Functional Nature of Electrogram Fractionation Demonstrated by Left Atrial High-Density Mapping

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Background—Complex fractionated atrial electrograms (CFAE) are targets of atrial fibrillation (AF) ablation. Serial high-density maps were evaluated to understand the impact of activation direction and rate on electrogram (EGM) fractionation.

Methods and Results—Eighteen patients (9 persistent) underwent high-density, 3-dimensional, left-atrial mapping (>400 points/map) during AF, sinus (SR), and CS-paced (CSp) rhythms. In SR and CSp, fractionation was defined as an EGM with ≥4 deflections, although, in AF, CFE-mean <80 ms was considered as continuous CFAE. The anatomic distribution of CFAE sites was assessed, quantified, and correlated between rhythms. Mechanisms underlying fractionation were investigated by analysis of voltage, activation, and propagation maps. A minority of continuous CFAE sites displayed EGM fractionation in SR (15+/−4%) and CSp (12+/−8%). EGM fractionation did not match between SR and CSp at 70+/−10% sites. Activation maps in SR and CSp showed that wave collision (71%) and regional slow conduction (24%) caused EGM fractionation. EGM voltage during AF (0.59+/−0.58 mV) was lower than during SR and CSp (>1.0 mV) at all sites. During AF, the EGM voltage was higher at continuous CFAE sites than at non-CFAE sites (0.53 mV (Q1, Q3: 0.33 to 0.83) versus 0.30 mV (Q1, Q3: 0.18 to 0.515), P<0.00001). Global LA voltage in AF was lower in patients with persistent AF versus patients with paroxysmal AF (0.6+/−0.59 mV versus 1.12+/−1.32 mV, P<0.01).

Conclusions—The distribution of fractionated EGMs is highly variable, depending on direction and rate of activation (SR versus CSp versus AF). Fractionation in SR and CSp rhythms mostly resulted from wave collision. All sites with continuous fractionation in AF displayed normal voltage in SR, suggesting absence of structural scar. Thus, many fractionated EGMs are functional in nature, and their sites dynamic. (Circ Arrhythm Electrophysiol. 2012;5:32-42.)

Key Words: atrial fibrillation ■ CFAE ■ fractionation ■ wave collision ■ slow conduction ■ sinus rhythm ■ paced rhythm

When combined with pulmonary vein (PV) isolation, ablation of complex fractionated atrial electrograms (CFAE) is associated with higher acute and long-term success rates in patients with persistent atrial fibrillation (PsAF).1,2 Different electrophysiological mechanisms may result in CFAE,3 and these complex electrograms (EGMs) can either actively contribute to AF perpetuation or alternatively be bystanders.4,5 Notably, the ablation of continuous CFAE sites is associated with a higher likelihood of AF cycle-length prolongation and AF termination than ablation of intermittent CFAE activity.6 Indeed, CFAE ablation does not always impact on AF cycle length, confirming that not all are appropriate targets for ablation.7 Despite this, we currently largely ignore how to distinguish bystander from active CFAE in AF.

Editorial see p 5

Clinical Perspective on p 42

The aim of the current study is therefore to investigate the impact of different heart rhythms (AF and sinus rhythm [SR] and coronary sinus pacing [CSp]) on left-atrial (LA) CFAE properties in patients with atrial fibrillation, independent of any catheter ablation. Consistent LA fractionation during all rhythms may differentiate a local fixed atrial/anatomic sub-
strate (structural remodeling) from wave collision or functional slow conduction. Moreover, acquisition of high-density activation maps during SR and CSp allows analysis of the underlying mechanisms of fractionation.

Methods
Twenty-one patients with symptomatic, drug-refractory AF were enrolled. All antiarrhythmic drugs except amiodarone were stopped at least 5 half-lives before the procedure. Six out of 9 patients with PsAF and 5 out of 9 in the paroxysmal AF (PAF) group were on amiodarone.

All patients gave written informed consent for the study, which was approved by the institutional clinical research and ethics committee.

Electrophysiological Study
All patients received oral anticoagulation (target international normalized ratio [INR], 2 to 3) for at least 1 month prior to the procedure and underwent transoesophageal echocardiography within 48 hours preceding the procedure to exclude the presence of thrombus. Electrophysiological study was performed in the fasted state using conscious sedation.

The following catheters were introduced via the right femoral vein: (1) a deflectable decapolar catheter (Extreme) was positioned within the coronary sinus (CS); (2) a 3.5-mm externally irrigated-tip catheter ( Biosense Webster) was used for ablation; (3) a 20-pole high-density double-loop mapping catheter (St Jude Medical) was used to create the LA geometry and also to map CFAE in the LA using a long sheath (St Jude Medical). LA access was gained through a single transapical puncture or via a patent foramen ovale. A single bolus of heparin (50 IU/kg) was administered after LA access had been achieved. Activated clotting time was subsequently measured every 45 minutes, and an activated clotting time range of 270 to 330 s was targeted.

Definition of CFAE During AF
Continuous CFAE was defined as a CFE-mean value of 0.05 mV ("low-VID").

In order to prevent far-field EGMs from being falsely counted as low voltage or fractionated,5 we reduced the accepted EGM projection distance to 4 mm (to LA geometry); i.e., EGMs with a distance exceeding 4 mm from NavX-created LA geometry were not included on the map.

Definition of CFAE During SR and CSp
CFAE during SR or CSp were defined as fractionated potentials exhibiting ≥4 deflections from the isoelectric line with continuous electric activity (without an isoelectric line).8

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CFAE Mapping During AF
During AF, the automatic “CFE-mean” detection algorithm of NavX (St Jude Medical) was applied to create the CFAE maps.10,23 To obtain accurate CFAE mapping during AF, we recorded at each LA site for 8 s. CFE-mean was calculated by NavX for the whole recording period of 8 s for each registered LA site. CFE-mean refers to a measure of fractionation derived from the mean interval between EGMs at each site. Continuous CFAE was defined as a CFE-mean value of ≤80 ms with a refractory period setting of 40 ms and detection of EGMs exceeding 0.05 mV ("low-VID").

In order to prevent far-field EGMs from being falsely counted as low voltage or fractionated,5 we reduced the accepted EGM projection distance to 4 mm (to LA geometry); i.e., EGMs with a distance exceeding 4 mm from NavX-created LA geometry were not included on the map.

CFAE Mapping in SR and CSp
In SR, a high-density activation map was created of the LA, comprising >400 points (Figure 1A). In order to assess number and distribution of fractionated EGMs during SR, we visually scrutinized all recorded EGMs and labeled them manually according to the number of deflections from baseline, using a linear scale on the NavX system (Figure 1B). LA EGMs with 4 deflections are represented as blue and ≥5 deflections as purple. The borders of areas of fractionation were outlined using the white surface markers.

For CSp, the mid-CS was paced at a rate 5 to 8 beats per minute faster than the intrinsic sinus rate. Attention was paid to exclude ectopic beats and to obtain a homogenous-paced activation map. The pacing rate was limited to slightly faster than the intrinsic rate to minimize any impact of heart rate on fractionation. The mid-CS was chosen as it was felt to be a reliable, reproducible site for pacing. It would also give a contrasting LA activation pattern to SR (with regard to the direction of the main activation front). The CFAE map was created as for SR. Regions of CFAE during CSp were outlined using the black surface markers (Figure 1D).

Quantification of CFAE Area
The NavX 3-dimensional electroanatomic system allows for measurement of distances and surfaces on the 3-dimensional cardiac shell, based on electrode size and interelectrode spacing of introduced catheters (“field-scaling”). The system enables accurate distance and surface measurements on the 3-dimensional LA geometry. To compare, quantitatively, the overlapping areas of CFAE during AF and SR, AF and CSp, and SR and CSp, the surfaces of overlapping CFAE regions between these rhythms were measured for each patient and each rhythm combination. Furthermore, the total LA endocardial surface (including the LA appendage and the first 1 cm of the PVs) on the NavX geometry was measured in each patient. Thus, the relation of the CFAE surface to the total LA surface could be calculated.

Analysis of Mechanism of Fractionation During SR and CSp
In order to analyze the prevalence of functional CFAE, isochronal activation maps were used to create propagation movies. Detailed analysis of LA isochronal maps and propagation maps during SR and CSp was performed to distinguish functional CFAE (eg, because of areas of wave collision) from fractionation because of regional slow conduction or structural remodeling (fixed fractionation during different rhythms).

Correlation of Voltage With Degree of Fractionation (CFE-Mean) During AF
For each point taken during CFAE mapping in AF, the NavX system calculated mean voltage measurement corresponding to the mean EGM voltage during the 8-s period and also a CFE-mean. Data were downloaded for each patient, allowing correlation of CFE-mean with mean bipolar voltage at each LA site.
Statistical Analysis

Continuous data are presented as mean±standard deviation. Groups were then compared. In absence of normal distribution of data, the nonparametric Mann-Whitney U test was used. The Wilcoxon signed-rank test was used for paired data. Categorical data were analyzed with Fisher exact test. The Pearson correlation coefficient was used to calculate correlation between CFAE and bipolar voltage. Exponential line fitting was chosen based on the equation y=ax^b.

The median with the first (Q1) and third (Q3) quartiles are reported for skewed data with asymmetrical distribution (Figure 5C).

A probability value <0.05 was considered statistically significant. SPSS (IBM) was used for statistical analysis.

Results

Three patients with PsAF failed to cardiovert electrically and were excluded from the study. Therefore, 18 patients completed the study protocol. Patient characteristics are outlined in Table 1. At the time of the procedure, 13 patients presented in AF.

LA High-Density Mapping

A total of 21 096 EGMs were analyzed in 18 patients during AF, SR, and CSp. This represented 479+/−208 sites per map and >1150 sites per patient. The number of points per map was comparable between the different rhythms (AF, 463+/−136; SR, 470+/−186; and CSp, 471+/−243 sites). The mean mapping point density per cm² was 4.31+/−1.0 points/cm² on the SR map, 4.61+/−0.96 points/cm² on the CSp map, and 4.79+/−1.53 points/cm² on the CFE-mean maps during AF.

After manual/visual assessment of each EGM, EGMs with <4 deflections were considered as nonfractionated and were removed from the map. Thereby, only the CFAEs with >3 deflections remained on the LA geometry. During SR and CSp, 8+/−3% and 8+/−2% of all recorded LA EGMs were found to be fractionated (>3 deflections), respectively.

Quantitative Assessment of CFAE Area in AF, SR, and CSp

PsAF Versus PAF

Quantification of continuous CFAE area during AF demonstrated that, in patients with PsAF, CFAE cover a significantly greater percentage of the LA surface com-
pared with patients with PAF (27±4% versus 19±9%, respectively, \(P=0.01\), Figure 2 and Table 2, upper section). In contrast, in SR and during CSp, there was no significant difference in the relative extent of fractionated LA sites between PAF and PsAF cases (SR, 19±6% versus 21±7%, respectively, \(P=0.55\); CSp, 21±12% versus 14±5%, respectively, \(P=0.16\)).

When analyzing the absolute surface areas of fractionated sites during SR or CSp, however, we observed significantly higher amount of fractionation (>3 deflections from zero line) in patients with PsAF versus PAF. The absolute surface area containing fractionated EGMs in SR was found to be 30.8±8.1 cm² versus 20.0±5.4 cm² (in patients with PsAF versus patients with PAF, \(P=0.019\)). The absolute surface area with fractionated EGMs in CSp was 29.1±16.6 cm² versus 14.7±4.6 cm² (patients with PsAF versus patients with PAF, \(P=0.047\)). Finally, the absolute surface area with continuous CFAE (CFE-mean, <80ms) during AF was measured at 37.6±5.8 versus 17.7±3.1 (in patients with PsAF versus patients with PAF, \(P=0.00003\)).

When these absolute areas of EGM fractionation were put into relation to patient’s total LA surface, the differences diminished because of higher LA size in patients with PsAF, so that the relative surface areas of EGM fractionation did not differ any more between the 2 groups during SR and CSp.

Comparison of CFAE Extent During AF, SR, and CSp

The area of the LA demonstrating continuous CFAE in patients with PsAF was 27±4% during AF, 21±7% in SR, and 21±12% during CSp (Table 2, upper section). In patients with PsAF, the area of continuous fractionation (during AF)
was significantly larger than fractionation in SR ($P=0.048$). There was no significant difference in fractionation in PsAF versus CSp ($27\% \pm 4\%$ during AF versus $21\% \pm 12\%$ during CSp, $P=0.12$). Patients with PAF demonstrated consistent levels of fractionation in all 3 rhythms (AF, $19\% \pm 9\%$; SR, $19\% \pm 6\%$; CSp, $14\% \pm 5\%$; AF versus SR, $P=0.9$; and AF versus CSp, $P=0.06$).

**Comparison of CFAE Distribution in AF, SR, and CSp**

In both patients with PAF and PsAF, little anatomic correlation (overlap) exists between the distribution of CFAE sites in different rhythms (Table 2, middle and lower section, Figure 3). We calculated the region of concomitant fractionation during 2 rhythms (ie, [a] AF and SR; [b] AF and CSp; and [c] SR and CSp) as the percentage of total fractionation during AF for (a) and (b) and as percentage of fractionated sites during CSp for (c).

In patients with PAF, the following amounts of overlap of CFAE sites were found: (a) AF and SR, $16\% \pm 4\%$; (b) AF and CSp, $6\% \pm 3\%$; and (c) SR and CSp, $31\% \pm 13\%$. Similarly, in patients with PsAF, overlap was (a) AF and SR, $15\% \pm 5\%$; (b) AF and CSp, $18\% \pm 7\%$; (c) SR and CSp, $29\% \pm 8\%$. The overall anatomic correlation in all patients was (a) AF and SR, $15\% \pm 4\%$; (b) AF and CSp, $12\% \pm 8\%$; and (c) SR and CSp, $30\% \pm 10\%$. Figure 3 highlights the poor anatomic correlation of CFAE seen in AF and SR or CSp in a patient with PsAF.

When examined as a fraction of the entire LA surface, $<5\%$ of the total surface area demonstrated fractionation during both AF and SR (in both PsAF and PAF patients, Table 2, middle section). A negligible amount of the LA appeared fractionated in all 3 rhythms (Figure 3D).

**Mechanism of CFAE in SR and CSp**

In patients with PsAF, $27\% \pm 9\%$ of fractionated LA sites were fractionated both during SR and CSp (similar result in patients with PAF and the total study population: $31\% \pm 13\%$ and $30\% \pm 10\%$, respectively). Analysis of activation maps and propagation animations performed during SR and CS pacing revealed local wave collision that could explain $71\%$ of fractionated electrograms (Figure 4A and 4C, online-only supplemental material: propagation movies of SR and CSP). Another putative mechanism identified was “dyssynchronous” activation around a zone of slow conduction, representing $24\%$ of fractionation in these cases (Figure 4B and 4D). Five percent of remaining fractionated sites could not be explained by these mechanisms.

**Correlation of Fractionation With Electrogram Bipolar Voltage in AF**

Correlation of the fractionation interval (as a surrogate for the degree of fractionation during AF) with the mean electrogram bipolar voltage in AF, demonstrated an inverse CFE-mean-voltage relationship during AF (Pearson correlation coefficient $r=-0.32$ for the whole study population, $P<0.0001$,
range: −0.28 to −0.50 for individual patients, Figure 5D). More fractionated LA sites showed higher bipolar voltages during AF. Although this correlation is low when including all mapped LA sites (Figure 5D), the inverse voltage relationship is more enhanced when comparing regions surrounding the CFAE sites with LA sites that locate within CFAE sites (Figure 5B).

A quantitative analysis of the mean EGM voltage from CFAE maps of patients with PsAF was undertaken. Therefore, a total of >2000 EGMs were exported from CFAE maps. The bipolar voltage at LA sites with continuous CFAE (CFE-mean <80 ms) is significantly higher than at sites without evidence of CFAE (CFE-mean >120 ms) (median: 0.53 mV [Q1, Q3: 0.33 to 0.83] versus 0.30 mV [Q1, Q3: 0.18 to 0.515], respectively, \(P<0.00001\); mean values: 0.65+/−0.48 mV versus 0.52+/−0.52 mV, respectively, \(P<0.0001\); Figure 5C).

**LA Overall Mean Bipolar Voltage During AF in Patients With PsAF Versus Patients With PAF**

Analysis of the overall global LA voltage during AF in patients with PsAF versus PAF revealed lower voltages in patients with PsAF than in patients with PAF: The global overall mean LA voltage in patients with PsAF versus patients with PAF is 0.66+/−0.59 mV versus 1.12+/−1.32 mV (\(P<0.01\)). In contrast, we did not find any regions of reduced bipolar voltage during SR or CSp (all mapped sites had a voltage >1.0 mV in SR or CSp). This shows the functional alterations in EGM voltage during AF. Continuous CFAE sites in AF did not display low voltage in SR. Moreover, continuous CFAE sites displayed higher voltages than non-CFAE sites during AF. It is interesting that the global LA voltage during AF is a discriminating factor between AF types (PsAF versus PAF).

These voltage differences, however, are present during AF only. Both the regions of reduced voltage occurring around CFAE sites and regions of higher voltage within the CFAE sites show normal voltage values (>1.0 mV) during SR or CSp.

**Discussion**

The key finding of the current study is that both the quantity and the distribution of CFAE within the atria of patients with AF are highly rhythm-dependent. EGM fractionation depends on both direction of activation (SR versus CSp) and rate of activation (SR versus AF).12 Less than 5% of the LA demonstrates fractionation in both AF and SR. Furthermore, in SR, the majority of CFAE arise passively as a result of “wavelet collision” at sites that display normal bipolar voltages, suggesting absence of myocardial fibrosis/scar. These sites of wave collision are unlikely to represent effective targets for ablation.
High Density Mapping of CFAE

Targeting of CFAE is a frequently used strategy during the catheter ablation of PsAF, however the exact role of CFAE in the pathogenesis of AF remains unclear. Indeed, not all CFAE ablation impacts on AF tachycardia cycle length, implying that not all CFAE play a role in AF perpetuation. Hence, unnecessary ablation is being performed. Greater comprehension of CFAE is required to improve the specificity of ablation techniques.

High-density mapping has increased the quality of CFAE mapping, allowing 400 points to be acquired per map and, hence, strengthening its use both clinically and as a research tool. Miyamoto and colleagues have previously assessed CFAE volume in SR and AF but with only 76 points per map. Figure 5. Correlation of degree of electrogram fractionation with mean bipolar voltage during atrial fibrillation (AF). A, Complex fractionated atrial electrograms (CFAE) and B, Voltage maps of the same left atrium taken during AF. Typically, areas without fractionation correspond to sites of reduced voltage (<0.5 mV) surrounding CFAE sites in 5A and 5B (red arrows; green arrow shows a representative low-voltage electrogram (EGM) surrounding the anterior CFAE site). Conversely, the large area of CFAE on the anterior wall demonstrated higher-voltage electrograms (>0.5 mV; large white arrow shows representative EGM). C, Quantitative analysis of >2800 EGs (CFAE maps in AF; recording time, 8 s) in the patients with persistent AF (PsAF). Continuous CFAE sites (CFAE-mean, <80 ms) display higher bipolar voltage during AF than non-CFAE sites (CFAE-mean, >120 ms) (median: 0.53 mV (interquartile range [IQR]: 0.33 to 0.83) versus 0.30 mV (IQR: 0.18 to 0.515, respectively, P<0.00001). D, Example of inverse correlation between CFE-mean interval (surrogate of fractionation in AF) and mean electrogram voltage in a patient with persistent AF (r = -0.49, P<0.0001).
AF map, using an 8-mm tip catheter with lower mapping resolution.\textsuperscript{19} Using these methods, they found CFAE in AF at 42\% of the LA surface. The discrepancy in percentage of the surface area demonstrating fractionation between that study and the current report (CFAE at 28\% of the LA surface in PsAF) reflects the high- density mapping used in the current study (reducing the interpolation resulting from using fewer points) and the cut-off value for CFE-mean used to \( \leq 80 \) ms (measuring more continuously fractionated signals compared with CFE-mean \( \leq 120 \) ms that includes sites of intermittent EGM fractionation during AF). Furthermore, the exclusion of points with an EGM projection distance of \( >4 \) mm to the LA geometry prevents registration of points with poor contact and/or farfield signals as fractionation previously recognized as a common cause of \textquotedblleft CFAE.\textquotedblright\textsuperscript{5,20} Therefore, the current study aimed to identify LA sites that remain persistently fractionated in different rhythms (AF, SR, and CSp).

**Extent of CFAE in PsAF Versus PAF**

High-density mapping confirms increased fractionation in the atria of patients with PsAF (28\%±4\%) than those with PAF (16\%±4\%). This observation has been described previously.\textsuperscript{11,21} Interestingly, PV isolation during the ablation of PsAF results in an altered distribution and a significant reduction in LA pre-ablation fractionation without termination,\textsuperscript{22} suggesting, in turn, that much of the pre-ablation fractionation in the LA may play a passive role. Furthermore, ablation of those continuous CFAE that persisted both before and after PV isolation has been associated with a higher rate of AF termination.\textsuperscript{23} Hence, persistence of CFAE in changing LA conditions may be a marker of CFAE, resulting from fixed or pathological tissue changes (scar). Therefore, the current study aimed to identify LA sites that remain persistently fractionated in different rhythms (AF, SR, and CSp).

**The Spatial Distribution of CFAE Sites in AF, SR, and CSp**

Figure 3C highlights areas of fractionation identified in a single atrium during SR (white markers) and CSp (black markers). Note the different patterns of fractionation but that, in both rhythms, fractionation tends to localize close to the PV ostia and, also, the interatrial septum. It is in direct contrast to CFAE maps taken in AF where fractionation is identified in the body of the atrium (red markers in Figure 2 and 3A and 3B). Quantification of areas of overlapping fractionation during AF, SR, and CSp identified only a very small amount of anatomic overlap between fractionated LA sites in SR and CFAE regions in AF. In total, <5\% of the LA surface demonstrated fractionation in both rhythms. Moreover, LA sites with persistent fractionation in all 3 rhythms are rare, implying that most of the fractionation in AF arises in areas that appear entirely normal in SR, in terms of bipolar voltage and degree of fractionation. This does not exclude an active role for these CFAE in propagating AF but does argue that the fractionation may be a function of the complex atrial electric activity during AF rather than an underlying atrial disease process that is associated with localized atrial scar.

We also describe that distribution of fractionation differs between SR and CSp (Figure 3C). Indeed, there is only a 30\% correlation between the 2 rhythms (again representing <5\% of the total LA surface area). This implies that, despite both being regular stable rhythms with comparable cycle lengths, it is the direction of activation within the atrium that defines location and volume of fractionation, rather than characteristics of the local LA myocardium.

**Mechanism of CFAE in SR and CSp**

Using epicardial recordings in patients without a history of AF, Konings and colleagues showed previously that fractionation of unipolar EGM during induced AF occurs at sites of (a) conduction slowing/block, (b) pivot points of wavelets, (c) asynchronous activation, and (d) at sites of wave collision.\textsuperscript{1} In addition, Rostock and colleagues revealed that bipolar electrogram fractionation depends on the local activation rate/ cycle length. The shorter the cycle length, the more fractionated the EGMs (so-called \textquotedblleft fibrillatory conduction\textquotedblright\textsuperscript{12}). Lellouche and colleagues found a link between some of the fractionated LA sites in SR and parasympathetic (vagal) responses during RF ablation at those sites.\textsuperscript{8} Currently, ablation of CFAE sites (in AF) constitutes part of the routine ablation strategy for PsAF; however, even when ablating continuous CFAE during AF, an impact on AF cycle length/termination is observed in only 50\% of ablated LA sites.\textsuperscript{6}

High-density mapping during SR and CSp provides detailed activation maps that, in turn, give insight into the mechanism of fractionation within atrial myocardium. Figure 4A (during SR) and 4C (during CSp) represent isochronal activation maps, demonstrating clear evidence of wave collision at an area of fractionation (71\% of fractionated sites in SR/CSp). The site of fractionation depends on the vector of the LA activation in SR and CSp that determines the region of wave collision. In Figure 4A (during SR), the wave of depolarization wraps around the LA, and the wavelets collide under the left inferior PV. In Figure 4C (during CSp), a long region of wavelet collision is identified at the roof of LA (between the right and left superior PVs). This long line of wave collision at the LA roof results in a long area of fractionated EGMs during CSp (black markers) that is not present during SR.

An alternative mechanism is seen in Figures 4B and 4D. \textquotedblleft Dyssynchronous\textquotedblright\ activation is noted around a zone of slow conduction that corresponds to a fractionated area (24\% of fractionated sites in SR/CSp). In contrast to the passive nature of wave collisions, anisotropic conduction and dyssynchronous activation may reflect electrophysiological properties of the local myocardium crucial to AF maintenance.

Not all fractionation identified during high-density mapping can be explained by these 2 mechanisms; however, they can be repeatedly identified, giving rise to a large proportion of fractionation during SR and CSp. Moreover, an unexpectedly low percentage of the LA was fractionated in both AF and SR. This suggests that (a) there is minimal fixed fractionation, (b) there is probably a high proportion of passively formed CFAE in AF, and (c) fractionation identi-
fied in SR is unlikely to represent a good target for ablation. Finally, it is noteworthy that common sites of overlap between AF and SR were located at the PV antrum and LA septum. Furthermore, areas of overlap in all 3 rhythms were rare, but, when present, they localized to PV ostia or septum. Such regions merit further examination and could represent critical targets in AF ablation.

Analysis of CFAE Areas in AF With Regard to EGM Voltages Both in AF and SR
During SR, bipolar voltage maps of the LA display normal voltages (≥1.0 mV) within the atrial body in all patients (data not shown). Regions of reduced bipolar voltage during SR were only found within the PVs.

Analysis of the bipolar voltage during the 8-s recording period for each recorded EGM in AF revealed a mean voltage of 0.596 mV for the total number of EGMs recorded during AF (in all patients). Interestingly, areas of functional lower voltage (<0.5 mV) were found during AF within the left atrial body (Figure 5B) and appeared to surround regions of continuous CFAE. When compared with CFAE maps during AF in the same chamber (Figure 5A), continuous CFAE regions (CFE-mean <80 ms) correlate with areas of higher voltage in AF. This image of lower voltage sites surrounding continuous CFAE sites was consistently found in all patients during AF. Furthermore, quantitative analysis of mean bipolar voltage during AF at continuous CFAE sites (CFE-mean <80 ms versus non-CFAE sites (CFE-mean >120 ms) showed a significantly higher voltage at CFAE than at non-CFAE sites with an inverse correlation between mean fractionation interval (CFE-mean) as a surrogate of “degree of fractionation” in AF and mean voltage in AF (Figures 5C and 5D). This result confirms that low voltage in AF is functional and that areas of continuous fractionation during AF do not correspond to low voltage and diseased atrial tissue. Moreover, continuous CFAE sites display higher voltage during AF than surrounding (nonfractionated) LA sites. This finding may be related to the fibrillatory wave dynamics/wave collisions during AF that result in globally reduced bipolar voltages during AF versus SR. Moreover, less fractionated LA sites that surround continuous CFAE sites display even lower voltage during AF.

LA Overall Mean Bipolar Voltage During AF in Patients With PsAF Versus PAF
Analysis of the overall global LA voltage during AF in patients with PsAF versus patients with PAF revealed lower voltages in patients with PsAF than in patients with PAF (0.6+/−0.59 mV versus 1.12+/−1.32 mV, P<0.01). It is interesting that the global LA voltage during AF is a discriminating factor between AF type (PsAF versus PAF); however, these voltage differences are present during AF only. Both the regions of reduced voltage occurring around CFAE sites, and regions of higher voltage within the CFAE sites show normal (>1.0 mV) voltage values during SR or CSp.

CFAE Mapping Using NavX Algorithm (CFE-Mean)
CFE-mean is a widely used algorithm that is integrated into the NavX system. The method has been used and evaluated by other authors with regard to the temporal stability of CFAE sites in AF.23 Aizer and colleagues24 demonstrated that a standardized and validated algorithm for the identification of fractionation, using an FI <120 ms, refractory window of 49 ms, and signal width of 10 ms could achieve a sensitivity of 0.75 and specificity of 0.80. Tsai WC and colleagues25 re-evaluated the automatic CFAE detection algorithm of the NavX with regard to Nademanee’s criteria: In their analysis, the automatic CFAE algorithm exhibited the highest combined sensitivity and specificity with a CFE-mean (fractionation interval, [FI]) of <60 ms for the sites within areas of low voltage in SR (<0.5 mV) and a CFE-mean <70 ms for the sites with a voltage value >0.5 mV.

Based on our experience with visual assessment of CFAE sites and higher probability of AF cycle-length prolongation when ablating continuous CFAE sites (displaying continuous activity during AF),8 we defined LA sites with CFE-mean values <80 ms as best corresponding to continuous CFAE sites with our reported refractory settings (refractory period: 41 ms).

If the refractory settings are changed from 41 to 49 ms and the CFE-mean is considered as up to 120-ms range, the extent of CFAE in AF will be larger (because also CFE-mean interval value between 80 and 120 ms are added to the map); however, the CFAE map still looks similar, with its original outer limits being little extended. When comparing these surfaces with fractionated sites during SR or CSp, the important discrepancy in the spatial distribution between the rhythms still remains.

The settings we used to detect continuous CFAE sites (CFE-mean, up to 80 ms; refractory window of 41 ms) highlight the core of CFAE sites with higher fractionated EGMs during AF, with an attenuation of surrounding intermittent fractionated sites (CFE-mean, 80 to 120 ms).

Nademanee and colleagues first described ablation of CFAE sites in AF as a electro-physiological substrate-based ablation of AF.1 They described regions <0.15 mV as low voltage during AF. However this was not the criterion that they used to guide ablation.1 Using high-density mapping with up to 900 mapped LA sites per rhythm (Figure 1, 5), we observed EGMs of reduced mean voltage during AF (<0.5 mV) that surround higher voltage EGMs at sites with continuous CFAE; however, both CFAE sites and sites of reduced voltage in AF (surrounding CFAE sites) showed normal voltage in SR and CSp (>1.0 mV), proving the functional nature of the dispersion in mean bipolar voltage during AF. Future studies, focusing on activation pattern and local activity rates during AF, may give explanation to these observations.

Limitations
The shape, voltage, and degree of fractionation of bipolar EGM recordings depend on the orientation of the recording bipolar with regard to the regional/local wave propagation. By using the 20-polar, double-loop catheter, we could reduce the probability that certain LA sites were only mapped in 1 bipolar orientation only (because similar LA regions were mapped through different catheter positions).
The absence of simultaneous, entire-LA-chamber mapping during AF does not allow determination of the instantaneous LA fractionation. Simultaneous recording of the AF over the entire LA (and right atrium) would be the best method to get deeper understanding of the fibrillatory mechanism and to characterize the instantaneous local cycle lengths and evaluate the extent of fractionated LA sites during AF; however, even the serial acquisition of CFAE maps, using point-by-point mapping technique with the ablation catheter, have shown a certain temporal consistency in the CFAE maps up to 78%.23 We applied high-density mapping using a circumferential 20-electrode catheter with a diameter of 20 mm that enables simultaneous EGM recording over the catheter surface area (5 to 7 cm²). Using this method, the high-density map could be generated in <10 minutes during AF. The mapping time did not exceed 10 minutes in case of SR and CSp.

Owing to the post-processing required to identify and map out areas of fractionation in the 3 rhythms, correlation of highly fractionated areas was not possible in real time. Hence, ablation could not be targeted at the <5% of the LA total surface area that demonstrated fractionation in both AF and SR. Such a strategy, examining for cycle-length prolongation, may represent a goal for future work.

Conclusions

This paper describes high-density mapping of the LA performed during AF, SR, and CSp. We observe that the distribution of fractionation is highly rhythm-dependent and that there is little overlap between areas that are fractionated in each rhythm. Most fractionated EGMs during SR or CSp result from wave collisions. Therefore, targeting fractionated LA sites during SR (or CSp) does not seem to present a more specific strategy in order to identify proarrhythogenic LA sites. The work provides evidence that CFAE areas that are presently targeted for AF ablation represent areas of atrial myocardium with normal voltage (>1.0 mV) and EGM morphology in SR, excluding structural scar as underlying substrate. Thus, a substantial part of CFAE sites in AF may correspond to regions of wave collision and represent passive CFAE that may play little role in the perpetuation of AF. Further studies are warranted to identify those CFAE sites that actively perpetuate AF.

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References


**CLINICAL PERSPECTIVE**

Complex fractionated atrial electrogram (CFAE) sites continue to be an enigma in atrial fibrillation (AF). We compared the distribution and voltage of CFAE sites during clinical AF, sinus (SR) and CS-paced (CSp) rhythm using high-density maps of the left atrium prior to ablation. CFAE distribution was found to be highly variable, depending on direction and rate of activation (SR versus CSp versus AF). Fractionation in SR and CSp occurred at sites of wave collision in 71% and at sites of slow conduction in 24%. All sites with continuous fractionation in AF displayed normal voltage (>1.0 mV) in SR, suggesting absence of structural scar; however, during AF, the electrogram voltage was higher at continuous CFAE sites than at non-CFAE sites (0.53 versus 0.30 mV, \(P<0.0001\)). These findings indicate that electrogram fractionation and voltage are predominantly functional in nature, and most CFAE sites occur at regions of wave collision. Further study is warranted to identify the atrial regions crucial for AF maintenance.
Functional Nature of Electrogram Fractionation Demonstrated by Left Atrial High-Density Mapping


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SUPPLEMENTAL MATERIAL

Movie Legends:

Movie 1: Sinus rhythm propagation map (AP and PA views). Regions of electrogram fractionation being outlined using blue markers. Notably, regions of wavelet splitting and wave collision correspond to left atrial sites with fractionated electrograms (blue markers).

Movie 2: Propagation map during coronary sinus paced rhythm (AP and PA views). Regions of electrogram fractionation are outlined using green markers. Note that the distribution of fractionated sites is distinct to fractionation during sinus rhythm (movie1). Again, most of outlined fractionated regions occur at left atrial sites of wave collision.