Mechanisms of Fractionated Electrograms Formation in the Posterior Left Atrium During Paroxysmal Atrial Fibrillation in Humans

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Objectives The aim of this paper was to study mechanisms of formation of fractionated electrograms on the posterior left atrial wall (PLAW) in human paroxysmal atrial fibrillation (AF).

Background The mechanisms responsible for complex fractionated atrial electrogram formation during AF are poorly understood.

Methods In 24 patients, we induced sustained AF by pacing from a pulmonary vein. We analyzed transitions between organized patterns and changes in electrogram morphology leading to fractionation in relation to interbeat interval duration (systolic interval [SI]) and dominant frequency. Computer simulations of rotors helped in the interpretation of the results.

Results Organized patterns were recorded 31 ± 18% of the time. In 47% of organized patterns, the electrograms and PLAW activation sequence were similar to those of incoming waves during pulmonary vein stimulation that induced AF. Transitions to fractionation were preceded by significant increases in electrogram duration, spike number, and SI shortening (R² = 0.94). Similarly, adenosine infusion during organized patterns caused significant SI shortening leading to fractionated electrograms formation. Activation maps during organization showed incoming wave patterns, with earliest activation located closest to the highest dominant frequency site. Activation maps during transitions to fragmentation showed areas of slowed conduction and unidirectional block. Simulations predicted that SI abbreviation that heralds fractionated electrograms formation might result from a Doppler effect on wave fronts preceding an approaching rotor or by acceleration of a stationary or meandering, remotely located source.

Conclusions During induced AF, SI shortening after either drift or acceleration of a source results in intermittent fibrillatory conduction and formation of fractionated electrograms at the PLAW. (J Am Coll Cardiol 2011;57:1081–92) © 2011 by the American College of Cardiology Foundation

Paroxysmal atrial fibrillation (AF) is maintained by high-frequency sources most commonly located at pulmonary-vein-left atrial junctions (PV-LAJ) (1,2). Thus, catheter-based PV isolation has proved to cure AF in a significant proportion of AF patients (3). Recent studies have proposed targeting complex fractionated atrial electrograms (CFAEs) at a range of atrial sites as a means to increase AF ablation success, but results are controversial (4,5). Although some fractionated signals might represent critical zones related to AF maintenance (i.e., high-frequency sources “driving” AF), others might be passive and unrelated to the primary arrhythmia mechanism (i.e., wave front collision or overlapping) (6–8). In fact, the pathophysiological relationship between high-frequency PV discharges and CFAEs on the posterior left atrial wall (PLAW) is far from being understood. Previous studies suggested that there might be a relationship between fractionated electrograms and short AF cycle lengths, but AF initiation and transitions to...
fractionation were not analyzed, and no mechanistic explanations were proposed (6,9–11). By contrast, recent studies suggest that signal fractionation results from the dynamic interplay between high-frequency sources and the specific anatomic arrangements of the PV-LAJ (12–14). Because the PLAW plays a critical role in the initiation and maintenance of paroxysmal AF, we aimed to study the mechanisms of fractionation formation at the PLAW, after AF induction. We hypothesized that:

1) the fractionation of electrograms on the PLAW during AF is rate-dependent and secondary to fibrillatory conduction of waves emerging from high-frequency sources; and 2) adenosine infusion during organized phases triggers fractionation by accelerating the re-entrant sources that activate the PLAW.

Methods

Patients admitted for ablation of drug-refractory paroxysmal AF were included in this protocol, as approved by the Institutional Ethics Committee. All patients gave informed consent. Exclusion criteria were arriving in AF to the electrophysiology laboratory and induction of nonsustained AF (<5 min duration). All antiarrhythmic agents were withheld >5 half-lives before the study.

Electrophysiological study and recording protocol. The electrophysiological study used catheters positioned at high right atrium and distal coronary sinus and an ablation catheter at the PVs. The PLAW was mapped with a 20 pole-spiral catheter and analyzed offline. The 3-dimensional geometry of the left atrium (LA) was reconstructed with an electroanatomic navigation system (Online Appendix). We infused central venous boluses of 12 mg adenosine during AF, while catheters remained at fixed predefined positions (15).

Spatiotemporal analysis of PLAW recordings during PV stimulation and during AF. During AF, we defined “organized pattern” as a repetitive, uniform, and constant sequence of ≥4 consecutive electrograms with isoelectric line between them and identical sequence of activation (Fig. 1A) on the 10 bipoles of the PLAW catheter. “Fractionated electrograms” were defined as electrograms exhibiting multiple (≥2) deviations from baseline and/or continuous electrical activity without isoelectric line and duration >50 ms (4,9,10). The time course of organization during the first 5 min after AF induction was calculated as the duration of the sum of organized phases in seconds, divided by total recording period duration (300 s).

We analyzed the following patterns of activation: 1) “incoming wave pattern”: double-bracket sequence, with earliest activation consistently occurring in adjacent bipoles at the outer and inner loops of the spiral catheter; 2) “incomplete conduction block” along a line of functional block: wave front breaks occurring across the line at a point of slowed conduction; and 3) “re-entrant pattern” around a line of functional block: rotating wave not associated with an anatomic obstacle, with significant isochrone crowding and double potentials, not present during sinus rhythm (10). Activation patterns on the PLAW during PV stimulation before AF induction were compared with organized patterns that occurred during the first 5 min after AF induction in all patients. In a subset of patients (n = 5), offline PLAW activation and propagation maps during transitions from organized to fragmented electrograms were constructed with the NavX system (St. Jude Medical, Minneapolis, Minnesota) (Online Appendix).

Analysis of regional rate of activation. For interbeat interval analysis, the timing from the maximal rapid deflection of a bipolar electrogram to the next was considered to be the systolic interval (SI). During organized-to-fragmented electrogram transitions, we analyzed 10 consecutive electrograms before fragmentation and 5 consecutive organized beats immediately after fragmentation, as shown in Figure 1B. Intervals during fragmented phases were measured at the closest adjacent channel not showing fragmentation.

For stationary spectral analysis, dominant frequency (DF) was determined as previously described (Online Appendix) (7,8,12,13,15). Time courses of DF during the 5-min recording period were calculated from 5-s samples obtained at one-half of each 1-min interval after AF induction and averaged for all recordings at the PLAW. In a subset of patients (n = 10), real-time DF determination on the LA was obtained with NavX with embedded spectral analysis capabilities.

Computer simulations. We used a 5 × 5 cm² model of realistic human atrial kinetics with heterogeneous $F_{K,ACH}$ density in the presence of 0.1 μm acetylcholine (Online Appendix) (16).

Statistical analysis. Continuous variables are reported as mean ± SD or median and interquartile range, depending on data distribution. For details, including internal validation measurements, see the Online Appendix. Statistical significance was established at p < 0.05.

Results

Patients. Atrial fibrillation was induced with PV stimulation in 24 paroxysmal AF patients (53 ± 10 years; 73% male) arriving to the electrophysiology laboratory in sinus rhythm. Unless otherwise stated, all results correspond to the entire sample of 24 patients.

Time courses of organization and DF change. During the first 5 min after AF induction, both organized and fragmented electrograms were intermittently recorded at the PLAW (Fig. 1A). Organized patterns were recorded 31 ±
18% of the time. In Figure 2, the duration of organized phases decreased gradually from AF onset to the fifth minute of recording (solid bars; \( p = 0.007 \)), whereas PLAW DFs significantly increased (open bars; \( p < 0.001 \)). There was a highly significant inverse correlation between the duration of organized phases and PLAW DF (Pearson correlation \( r = -0.373; \ p < 0.001 \)).

**Transitions between organized and fragmented electrograms.**

Transitions from organized to fragmented phases were analyzed in episodes showing 10 consecutive intervals whereby the first 7 were not fragmented and the last 3 showed progressively more fragmentation (Fig. 1B). Overall, electrograms undergoing transition showed progressive disorganization, until no regular activation could be identified. As illustrated in Figures 3A to 3C, in channels showing fragmentation, the mean electrogram duration (Fig. 3A) and the number of spikes (Fig. 3B) increased gradually as the SI (Fig. 3C) decreased and the pattern changed from organized to fragmented. As summarized in Figure 3D, a bimodal behavior was observed for the SI as the pattern changed from organized to fragmented and back to organized. The average SI pre-fragmentation was significantly longer than during fragmentation \( (198.9 \pm 34.2 \text{ ms vs. } 177.6 \pm 25.6 \text{ ms}; \ p = 0.006) \). Similarly, the SI for 5 consecutive organized beats after fragmentation also was significantly longer \( (193 \pm 39.1 \text{ ms}; \ p = 0.038) \) than during fragmentation. No significant difference in SI was observed between organized pre-fragmentation and post-fragmentation phases on either side of the fragmented phase.

**Adenosine infusion increases DF and leads to fragmentation.**

Boluses of adenosine were infused in 9 patients. At peak adenosine effect, mean DF increased significantly at the PLAW compared with baseline \( (7.64 \pm 1.57 \text{ Hz vs. } 6.22 \pm 1.39 \text{ Hz}; \ p < 0.05) \). In 4 patients, adenosine was infused...
during a stable organized phase. At peak adenosine effect, there was a transition from organized to fragmented electrograms coincident with SI shortening (Fig. 4A). In fact, as shown in Figures 4B to 4D, there was a significant SI shortening, with increase in electrogram duration and number of spikes in all cases. As expected, a bimodal behavior was also observed in the SI when comparing the pre-fragmentation, fragmentation, and post-fragmentation phases occurring, respectively, before, during, and after the peak adenosine effect (Fig. 4E).

**Spatial patterns of activation and transitions to fragmentation.**

Overall, organized phases during AF were characterized by incoming wave patterns of activation recorded by the spiral catheter at the PLAW (Fig. 5A). The following incoming activation patterns were recorded: 1) concordant: incoming AF pattern identical to that generated by high-frequency stimulation from any PV; 2) ipsilateral: incoming AF pattern showing an activation sequence similar to that during pacing from either the superior or the inferior PV; and 3) discordant: activation pattern dissimilar to those during pacing from any PV (Online Appendix). As illustrated in Figure 5 (Figs. 5B and 5D), the incoming wave pattern of activation at the PLAW during organized AF mimicked that obtained during PV stimulation from which AF was induced (i.e., the pattern was concordant 46 ± 27% of the organized time). Moreover, as seen in Figures 5C and 5E, the incoming wave pattern mimicked that obtained during pacing from any of the ipsilateral PVs that induced AF 63 ± 24% of the organized time (p = 0.025).

In 10 patients, real-time LA DF maps revealed the presence of high DF sites close to the PV–LA junctions (Fig. 6A). In 7 such patients the location of the maximal DF site was the same as the earliest site of activation, which was concordant with the directionality of the predominant incoming wave front as recorded by the spiral catheter at the PLAW (Fig. 6B). In this group, the number of maximal DF sites and the number of organized patterns/patient were similar (2.1 ± 0.99 vs. 2.2 ± 0.78; p = 0.48).

In 5 cases we analyzed the patterns of activation at the PLAW for each beat during organized-to-fragmented electrogram transitions. The direction and propagation pattern of the incoming wave were similar for each of the 7 pre-fragmentation beats with earliest activation occurring at bipoles closest to the PV–LAJ (Fig. 6B, Online Video 1). However, several beat-to-beat changes were observed in the transition toward the fragmented phase. First, as the rate of the penetrating wave increased (i.e., SI shortened), the electrograms widened and double electrograms began to appear during the last 3 beats of the transition to fragmentation. The propagation pattern of the incoming wave changed, yielding 1 of 2 new outcomes: 1) re-entry pattern around a line of functional block, as in Figure 7A, in which the re-entrant excitation wave front circulated clockwise around a pivoting point located anatomically at the septo-pulmonary bundle (Online Video 2); and 2) activation breakthrough across a line of slow conduction (Fig. 7B, Online Video 3). Overall, these patterns appeared in 62% of the cases, of which 71% were re-entrant and 29% were breakthrough-like. Once fragmentation in all the PLAW electrograms ensued, interpretation became unreliable.

**Numerical simulations and possible mechanisms.** Figure 8A shows snapshots of activity in the model at different times along with bipolar electrograms from a spiral catheter simulating the one used in the patients. When broad waves from a distantly located main rotor approached the recording site, well-organized electrograms were inscribed at relatively long SIs. However, as the rotor drifted toward the catheter, the SI shortened monotonically (see bipoles 3–4 and 13–14; see also Online Appendix), and the electrograms widened. At approximately 0.8 s after onset, sudden SI prolongation ensued (vertical red line), revealing conduction impairment and wavebreak at the catheter area. This was followed by the creation of 2 short-lived rotors (middle top panel), one of which lingered briefly on the upper right corner, pivoting between bipoles 3–4 and 13–14 (red square). Once fragmentation in all the PLAW electrograms ensued, interpretation became unreliable.
accommodated with a briefer periodicity than the wave fronts behind the tip (Online Appendix) (17). In Figure 8C, we have plotted the SI at the electrogram location as a function of the distance between the tip and the recording site. As the drifting rotor approximated the bipoles, SI abbreviated, resulting in wavebreak (Fig. 8A).

**Discussion**

The major findings of the study are as follows. First, in induced, paroxysmal AF, electrogram fractionation at the PLAW is rate-dependent. Second, organized AF phases show a highly stable and recurrent pattern of incoming waves of activation emanating from high-frequency sites at the PV-LAJ area. Third, transitions from organized to fractionated electrograms are preceded by progressive cycle length shortening leading to beat-to-beat changes in wave front directionality, intermittent wavebreak, and re-entry around a line of functional block, most likely at the septo-pulmonary bundle. Finally, the results of adenosine infusions and of computer simulations reproduced the spontaneous organized-to-fractionated-to-organized transitions and strongly supported the idea that wave front acceleration ahead of drifting rotors on the PLAW and/or rotor meandering gives rise to intermittent local fractionation. The overall results suggest that, in paroxysmal AF, electrogram fractionation at the PLAW is a reflection of fibrillatory conduction and a consequence of the dynamic interaction between high-frequency re-entrant sources and the atrial anatomy.

![Figure 3](image_url)
Adenosine Infusion Effect on Electrogram Fractionation Characteristics and Systolic Interval

(A) Tracings during peak adenosine effect. Lead V1 and intracardiac electrograms recorded from spiral catheter at the posterior left atrial wall (PLAW). At peak adenosine effect (complete atrioventricular block), transition from organized to fragmented electrograms is observed, with simultaneous cycle length shortening. (B to D) Electrogram duration, number of spikes, and systolic interval during transitions from organized to fragmented electrograms (first 10 complexes). (E) Mean values of systolic interval before and during fragmentation and after resumption of organization.
Figure 5  Organized Patterns at the PLAW

(A) Left, activation patterns during sinus rhythm and during stimulation from the LSPV. Right, 2 activation patterns were observed during AF: pattern 1 resembled LSPV stimulation; pattern 2 was similar to sinus rhythm activation. (B and D) During AF, concordant patterns of activation resembling LSPV stimulation from which AF was induced (red arrow originating at the pacing catheter) accounted for 46 ± 27% of recording time when compared with discordant patterns (white arrows). (C and E) Organized patterns during AF resembling those obtained during pacing from any of the ipsilateral PVs (red arrows originating from the pacing PV side, superior and inferior) accounted for 63 ± 24% of the organized time (*p = 0.025). Abbreviations as in Figures 1 and 2.
Figure 6  Organized Activation Patterns in Relation to DF Sites Location

(A) Left atrial dominant frequency (DF) map (posterior view). White arrow points to highest DF site (10.8 Hz) at the left inferior pulmonary vein antrum. (B) Posterior left atrial wall activation map during organized phase before fragmentation (right) shows an incoming wave pattern of activation progressing from closest to the highest DF site at the left inferior pulmonary vein (left, white) to the right (purple-blue). Online Video 1, propagation map of the posterior left atrial wall during organized phase before fragmentation. ABL = ablation catheter at right superior pulmonary vein; CIR = spiral catheter; ECG = electrocardiogram; SC = coronary sinus.
Figure 7  Snapshots of Wave Propagation at the PLAW During Transitions to Fragmentation

Sequence 1 to 6: purple, unactivated regions; white, advancing activation. (A) Re-entrant circuit with a clockwise propagation around a pivoting point located to the right edge of the septo-pulmonary bundle (Online Video 2). (B) Activation breakthrough across a line of slow conduction, with activation of the posterior left atrial wall (PLAW) in both superior and inferior directions, and final convergence on the anterior aspect of the right superior pulmonary vein antrum (Online Video 3).
Figure 8  Simulation of a Drifting Rotor With Peripheral WB in an Atrial Model

(A) Snapshots of the model membrane voltage are at times indicated by the green markers. A 20-electrode catheter (D-20) shown on snapshots indicates locations of 10 pseudo-bipoles shown below maps. Red squares: pivoting sites of rotors (i.e., singularity point [SP]). Numbers on bipoles 3-4 and 13-14 indicate cycle length in milliseconds. Horizontal gray arrows indicate episodes with a single mother rotor (MR) (1 SP), additional 2 short living rotors after approximately 0.9 s (3 SPs), and their disappearance after approximately 1.5 s (1 SP). Red arrows: return of cycle length to pre-shortening phase.

(B) Trajectory of the tip of the drifting rotor (yellow trace and arrow) superimposed on a snapshot of voltage at time \( t \). Red square: starting point of the drift; green dots: the location of the tip at the completion of each of 9 initial rotations; blue square: location of bipoles 13-14; double-headed blue arrow: distance between 13-14 bipoles and a sample position of the tip of the rotor.

(C) Systolic interval (SI) at bipoles 13-14, as a function of distance between the tip of the rotor and the location of the bipoles. As the drifting rotor gets closer to the bipoles, SI abbreviates due to Doppler shift, particularly after the third rotation. After the seventh rotation, local conduction impairment at 13-14 increases SI with an eventual wavebreak (WB).
High level of organization of the PLAW during AF. Studies have demonstrated that AF is deterministic (7,8,11–13,17), despite the spatiotemporal complexity of wave propagation during AF. Using epicardial recordings, Wells et al. (11) found that the fibrillatory signal often increased or decreased its organization at different times. Here we have similarly demonstrated that—in human AF—organized and disorganized phases alternate, with the PLAW harboring regular, fast, and spatiotemporally organized activity during a significant proportion of time. As shown by our results, periodic impulses originating at the PV-LAJ propagate in highly recurrent directions repetitively toward the center of the PLAW. The high correlation between the location of maximal DF areas and the origin of incoming waves strongly suggests that during organized AF phases PLAW is passively activated from high-frequency sources located at the PV-LAJ.

**Activation frequency and fractionated electrograms.** The original definition of CFAEs includes 2 different features: electrogram fractionation and short electrogram cycle length (4). We considered both but analyzed them as separate variables to get mechanistic insight of their possible interaction. We found that the local frequency of activation is the main determinant of electrogram fragmentation at the PLAW, because the instantaneous atrial activation frequency (i.e., 1/cycle length) invariably increased before fragmentation and decreased upon organization. In other words, contrary to what may be implied in the definition by Nademanee (4), CFAEs and short electrogram cycle length are not independent of each other.

The relationship between activation rate and electrogram complexity has been previously documented; however, its pathophysiology remains unclear (6,11). Rostock et al. (9) found that the occurrence of fractionated electrograms anywhere in the atria was significantly associated with AF cycle length shortening. However, AF initiation and transitions to fractionation were not analyzed. Studies demonstrated that the atria respond to activation rate increments with progressive deterioration of stable directionality and electrogram fractionation (7,18). Moreover, high-density mapping has identified clusters of high DF sites with fractionation most likely observed adjacent to those sites (13,19). Thus, the transition to fractionation is not random and reflects functional deterioration in the atrial conduction properties in response to periodic input acceleration. Several of our findings support this idea. First, the lower degree of organization during the last 3 interbeat intervals before fragmentation was paralleled by an increase in AF activation rate (20). Second, adenosine infusion during the organized phase accelerated the maximal DF of the AF sources at the PV-LAJ and resulted in fragmentation (15). Finally, computer simulations showed that rotor drift toward the recording area yielded a similar increase (approximately 20%) in the local frequency of activation at the PLAW (17).

**Role of the atrial anatomy in fractionation.** In paroxysmal AF patients, Markides et al. (21) demonstrated the presence of a line of functional conduction block at the anatomical location of the septo-pulmonary bundle in the PLAW. At this site, conduction is markedly slowed when wave fronts propagate perpendicular to the septo-pulmonary bundle (12,14,21). Thus, this functional line of block creates the substrate for functional re-entry, causing wave fronts exiting the PV ostium to break.

We observed a change in the activation pattern as the rate increased during transitions from organized to fragmented patterns. Electrograms progressively widen, and double electrograms emerged, reflecting the formation of functional lines of block (10,14). In some cases, functional re-entry occurred around the line of functional block (Online Video 2). A breakthrough pattern across a line of slow conduction could also be observed in other cases at the same location (Online Video 3). In accordance with previous experimental work, most of the wavebreaks appeared at either edge of the septo-pulmonary bundle (12).

Of importance in our study was the transient nature of the fractionated signals at the PLAW. Although electrograms were narrow and discrete during organized AF phases, highly fractionated electrograms were recorded at the same location after local frequency acceleration (7). This observation is consistent with the finding that PV isolation reduces fractionated electrogram density by globally increasing AF organization (22). Our overall results suggest that a possible mechanism for transient electrogram fractionation is passive wavebreak around areas of functional block and unstable re-entrant circuit formation.

**Clinical implications.** The idea of targeting fractionated electrograms, either alone or in combination with other ablation strategies, remains controversial (4,5). Experimental and clinical studies have shown that fractionated signals might potentially represent zones critical to AF maintenance. Kalifa et al. (13) found that the periphery of high-frequency AF drivers is the area at which most fractionation occurs. Rotor meandering might also underlie, at least in part, the electrogram fractionation at close proximity of the source (8). This might explain the success of some CFAE ablation procedures that produce an anatomic obstacle around the highest DF site (4,13). However, other studies suggest that CFAEs might be unrelated to the primary arrhythmia mechanism and simply represent transient pivoting, wave front collision, or sink-to-source mismatch (6,7,10). Most importantly, fractionation is significantly reduced after PV isolation, with prolongation of AF cycle length underscoring its passive role (22). For all these reasons, CFAE ablation strategies have had a low impact on AF recurrence prevention in paroxysmal AF ablation and should not be recommended as a stand-alone strategy (5).

**Study limitations.** Higher density in a wider mapping area would be needed to better discriminate the possibility of other activation patterns, such as transient colliding waves. We only mapped the PLAW; therefore, the role played by sources originating outside the PV-LAJ is unknown. However, the importance of nonpulmonary vein sources seems
limited in paroxysmal AF maintenance (2). We cannot completely rule out the possibility that peak adenosine effect coincided with fractionation (15). In addition to the proposed Doppler Effect mechanism, acceleration of fixed sources could also explain our findings; however, these should involve external factors that are not likely to account for transitions that occur several times each minute. Finally, no correlation between fractionated electrograms and gan- glionated plexi location can be made on the basis of this study.

Conclusions

In paroxysmal human AF, electrogram fractionation at the PLAW is intermittent and is preceded by interbeat interval (SI) shortening. In this context, fractionation is a reflection of fibrillatory conduction consequence of the dynamic interaction between drifting high-frequency re-entrant sources originating at the PV-LAJ and the atrial anatomy. Thus, CFAE ablation should not be recommended as a stand-alone strategy to cure paroxysmal AF. Further studies are needed to elucidate the mechanisms of CFAE formation and the role of CFAE ablation in persistent AF patients.

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