Spatiotemporal organization during ablation of persistent atrial fibrillation

Shahriar Iravanian, MD, Jonathan J. Langberg, MD

From the Emory University, Atlanta, Georgia.

BACKGROUND Targeting complex fractionated atrial electrograms improves the outcome of ablation of persistent atrial fibrillation (AF); however, the mechanism(s) responsible for the generation of complex fractionated atrial electrogram signals and efficacy of ablation is not clear.

OBJECTIVE The aim of this study was to gain mechanistic insight into ablation of persistent AF by evaluating the spatiotemporal patterns of atrial organization during ablation.

METHODS Intracardiac recordings from 18 ablation procedures were analyzed. Signals recorded by right atrial/coronary sinus catheters were processed. We quantified atrial organization using recurrence maps and recurrence percentage (Rec%) methodology and generated temporally dense time series of cycle lengths and Rec%.

RESULTS A total of 162 intra-atrial recordings were categorized into type I (sudden jump in Rec%), type II (gradual increase), and type III (no increase). Type I was the most common form and was seen in 57% ± 4% of the recordings. A typical pattern was the initial appearance of local organization, which then expanded to adjacent channels in discrete jumps until eventually an organized atrial flutter emerged. This pattern is consistent with the atrial organization signature expected from ablation of a single spiral wave with fibrillatory conduction to the rest of atria.

CONCLUSION Temporally dense spatiotemporal assessment of atrial organization during the ablation of persistent AF is feasible and provides complementary information to cycle length measurements. Atrial organization starts locally and expands spatially in discrete jumps. The regularization of AF to atrial flutter exhibits characteristics of phase transition in complex systems.

KEYWORDS Atrial fibrillation; Ablation; Signal processing; Recurrence maps; Complex fractionated atrial electrograms

ABBREVIATIONS AF = atrial fibrillation; AFL = atrial flutter; CFAE = complex fractionated atrial electrogram; CL = cycle length; CS = coronary sinus; LA = left atrium/atrial; PVI = pulmonary vein isolation; RA = right atrium/atrial; Rec% = recurrence percentage

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with increased morbidity and mortality.1 Both pharmacological and catheter-based interventions are used for rhythm control in patients with AF. Pulmonary vein isolation (PVI) has proved to be successful in control of paroxysmal AF.2 However, as a stand-alone procedure, PVI is less successful in patients with persistent AF. Hence, a multitude of approaches have been developed for the ablation of persistent AF.3

The catheter ablation of persistent AF is based on the placement of lesions in the left atrium (LA) and occasionally in the right atrium (RA) in addition to PVI lesions. These additional lesions are either anatomical (eg, roof line or mitral isthmus line) or electrogram based. Complex fractionated atrial electrograms (CFAEs) are defined as fractionated short cycle length (CL) and low-amplitude atrial signals, which are a common target of ablation of persistent AF.4

A meta-analysis of the published clinical trials found that CFAE-targeted ablation improved the outcome of ablation in persistent, but not paroxysmal, AF.5 Nevertheless, the benefit of CFAE-targeted ablation procedures is modest, and long-term freedom from AF remains elusive in many patients with persistent AF. Newer techniques based on direct visualizations of rotors responsible for persistence of AF are under active development and herald an era of mechanistic approaches to ablation.6,7

Despite these advances, there is still debate about the exact mechanism(s) responsible for persistence of AF: a single spiral wave (mother rotor) with fibrillatory conduction to the rest of atria or multiple meandering rotors.8–10 Even less is known regarding the mechanism of ablation and how the resulting lesions disrupt fibrillation. Lessons learned from CFAE-targeted ablation procedures can enhance our knowledge and guide the planning of ablation.

In this article, our main goal is to study how ablation organizes atrial activity by assessing the spatiotemporal pattern of atrial organization during ablation procedures. We posit that this pattern depends on the underlying mechanism of AF.
In a computational modeling study of single spiral wave AF, Ashihara et al\textsuperscript{11} postulated that ablation works by stopping slow conduction through CFAE areas and allows spiral waves to anchor to the ablated region with local regularization of atrial activity. Further ablation eliminates shortcuts through these sites and expands areas of regular activity. The expected organizational signature is the initial local regularization (anchoring), followed by stepwise growth of the organized areas. In another in silico analysis, Spector et al\textsuperscript{12} studied the ablation of multiwavelet AF. They identified the requirement for a successful ablation procedure as placement of linear lesions from the edge of excitable tissue that expands the atrial boundary. Meandering waves collide with the expanded boundary and terminate. In this model, global atrial organization occurs in quantum steps associated with the elimination of each wavelet.

In order to distinguish between these 2 possibilities, we need a tool to quantify atrial organization. Multiple algorithms and methods have been proposed in this regard. In the frequency domain, the regularity index is defined as the ratio of the power under the dominant frequency peak to the total signal power.\textsuperscript{13} It is easy to calculate, but lacks sufficient sensitivity to detect subtle changes in atrial organization. Time-domain methods are more sensitive, but also more complex to calculate. The similarity index reflects distance between pairs of local activation waves (atrial complexes) and has been used to map the spatial distribution of atrial organization in AF.\textsuperscript{14,15} More recently, the related methodology of recurrence maps and recurrence percentages (Rec\%), which is also based on pairwise comparison of atrial complexes, is shown to be particularly useful in the quantification of regularity during AF and forms the basis of this article.\textsuperscript{16,17}

**Methods**

**Patient population and ablation procedure**

The procedural and data collection methods were previously described.\textsuperscript{18} The study protocol was approved by the Emory University Institutional Review Board. The data were collected retrospectively from catheter ablation procedures for persistent AF performed at the Emory University Hospital, Atlanta, GA.

After a written informed consent was obtained, patients were brought to the electrophysiology laboratory in the fasting state and sedated. If a patient had been on a class IC or III antiarrhythmic medication before ablation, it was continued throughout the periprocedural period. All patients had persistent AF at the time of ablation. A duodecapolar catheter (Livewire, St Jude Medical, Inc, St Paul, MN) was placed in the RA and advanced into the coronary sinus (CS). An ablation catheter (Blazer II, Boston Scientific Corporation, Marlborough, MA) and, in the case of patients undergoing initial ablation, a basket mapping catheter (Constellation, Boston Scientific) were positioned in the LA and pulmonary veins. PVI was performed in patients undergoing their first ablation for persistent AF. CFAE-targeted ablation was performed beginning in the LA. CFAEs were defined as low-amplitude continuous or short CL (<120 ms) atrial signals.\textsuperscript{19} RA lesions were delivered if there was reversal of the left-to-right frequency gradient during ablation. Only patients who transitioned to an organized atrial activity during ablation were selected for this study.

**Signal processing**

Electrophysiological studies were performed using the CardioLab System (GE Medical, XXXX, XX). All signals were filtered at 30–500 Hz, digitized with a resolution of 12 bits, and sampled at 977 Hz. After the procedure, 10 bipolar intracardiac channels recorded from the duodecapolar catheter in the RA/CS were downloaded for off-line analysis. Signal processing, statistical analysis, and visualization were performed using the Julia programming language.\textsuperscript{20}

The beginning of the recorded signals coincided with the placement of the first ablation lesion, and the end point was the time of either the last ablation, infusion of ibutilide, or cardioversion. Each channel was partitioned into 16.77-second segments. The first signal-processing step was the detection of spikes in each segment using a continuous wavelet transform–based peak detection algorithm.\textsuperscript{21} Peaks or spikes detected in this way corresponded to local atrial activation (Figure 1A). The CL was calculated as the median of interspike intervals.

Segments were split into 100-ms normalized windows centered at the spikes (Figure 1B). For each pair of spikes in a given segment, the corresponding windows were compared by overlaying them (Figure 1C) and finding the phase shift that maximized the cross-correlation between the windows. The goodness of the match was quantified as the correlation coefficient between the 2 windows. A value of 0 signifies lack of any similarity between the atrial signals in the 2 windows, and a value of 1 signifies identical signal complexes. The resulting correlation coefficients were listed in an N × N table, where N is the number of spikes in the segment (Figure 1D).

Recurrence maps are color-coded representations of these correlation coefficient tables (Figure 1E). The main power of recurrence maps is in the detection of subtle regularity and similarity among atrial complexes. For example, in Figure 2A the presence of a checkerboard pattern shows bursts of regular atrial activity in the midst of irregular AF.

To compare different recurrence maps, the information contained in each map is reduced into a Rec\%. For each column, we calculate the percentage of the correlation values above 0.8 (the cutoff value is adopted from Ng et al\textsuperscript{17}). The Rec\% for the whole map is defined as the maximum value among all the columns, ranging from 0% to 100%. A value near 100% signifies regular atrial activity (Figure 2D) in contrast to irregular AF (Figure 2B). Intuitively, Rec\% is equal to the fraction of atrial complexes that are similar to the predominant morphology. For the example in Figure 1, all the values in column 2 are above 0.8. Therefore, Rec\% for this column and thus for the whole map is 100%.

**CFAE**
Figure 1  Schematic describing the process of calculating the recurrence maps. A: One-second atrial electrogram. Dashed vertical lines point to the detected atrial complexes. B: The segment in panel A is split into five 100-ms normalized windows centered at the spikes. C: Overlay of windows 1 and 2. D: The correlation coefficient values between pairs of windows are tabulated. The numbers listed by the rows and columns refer to the atrial complexes in panel B. E: The recurrence map corresponding to the table in panel D.

Figure 2  Representative recurrence maps and 3-second segments of intracardiac electrograms during AF (A and B) and AFL (C and D). The element at the intersection of the ith row and the jth column of the recurrence maps depicts the correlation coefficient between the ith and jth atrial complexes. The checkerboard pattern seen in panel A suggests the presence of AF organization during ablation. The horizontal bar represents 100 ms. AF = atrial fibrillation; AFL = atrial flutter.
Statistical tests

One-way analysis of variance was used to compare the means of continuous variables among the groups, and the χ² test was used to compare frequencies. The Fisher exact test was used to analyze 2 × 2 contingency tables. Time series were compared by using Spearman rank correlation coefficients. Channel noise was determined as the median of the rectified point-to-point difference in Rec%. Values are reported as mean ± SD.

Results

Eighteen of the 37 screened ablation procedures of persistent AF (49%) exhibited transition to an organized atrial rhythm during ablation. Intracardiac recordings from these 18 ablation procedures were analyzed. Patients were 48–77 years old (mean age, 61 years; 14 men and 4 women). Five patients had undergone AF ablation. Thirteen patients were on a class IC or III antiarrhythmic medication at the time of ablation (4 patients on sotalol, 3 on dronedarone, 2 on flecainide, 2 on amiodarone, 1 on propafenone, and 1 on dofetilide).

Of the 180 recorded channels (10 for each procedure), 18 were excluded because of lack of sufficient signal or very low signal-to-noise ratio. The remaining 162 channels were categorized into 3 groups:

Type I: The Rec% time series exhibited at least 1 sudden jump, defined as an increase of > 4σ within a 5-minute interval, where σ is the root mean square of the baseline noise (Figure 3A).

Type II: The Rec% time series showed a gradual increase (the end point at least 4σ higher than the starting Rec%) without any discrete jump, which fulfilled the criteria for type I (Figure 3B).

Type III: The Rec% time series did not meet the criteria for either type I or type II (Figure 3C).

Sudden jumps (type I: n = 92 [57%]) were more frequent than were gradual increases (type II: n = 38 [23%] or type III: n = 32 [20%]) (P = .0001). All studies had at least 1 channel of type I. The ratio of the number of type I channels to all channels (type I ratio) was 0.57 ± 0.04. The opening Rec%, CL, and noise level for each group are given in Table 1. Type III channels had significantly higher noise and baseline Rec%.

There were 7 documented cases of recurrent atrial tachyarrhythmias within the first year of ablation. Six of the 7 cases exhibited atypical atrial tachycardia/atrial flutter (AT/AFL). Type I ratio was higher in the recurrent cases than in the rest (0.67 ± 0.06 vs 0.50 ± 0.05; P = .036). Antiarrhythmic medication use did not affect type I ratio (0.56 ± 0.05 vs 0.59 ± 0.07; P = .86).

Figure 4 shows recurrence maps before, at the time of, and after a jump. Specifically, the transitional map (Figure 4B) demonstrates that the transition from irregular AF to regular AFL occurred abruptly in the course of 4 beats covering less than a second.

Figure 3

Three representative Rec% time series for the 3 types of channels recognized in the Results section: (A) type I, when there is at least 1 jump in Rec% (at 65 min); (B) type II, when there is a gradual increase in Rec%, until it reaches ~100% (flatter); and (C) type III, Rec% fluctuates, but no general rising trend is apparent. Raw Rec% values are plotted in gray. The red curve is the smoothed version after the raw points were convoluted with a 9-point Savitzky-Golay quadratic smoothing kernel.29 Rec% = recurrence percentage.

In addition, we observed that channels in a given study may jump at different times. For example, 3 jumps are seen in Figure 5B, but only 2 of them are present in Figure 5A. Similarly, the 2 Rec% trends in Figures 5C and 5D exhibit jumps at different times.

In general, CL trends were only weakly correlated with Rec% trends. In Figures 5A, 5B, and 5D, transient slowing (increase in CL) occurs at the time of the jumps, but the one in Figure 5C is associated with a decrease in CL. The mean

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type I (n = 92)</th>
<th>Type II (n = 38)</th>
<th>Type III (n = 32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (ms)</td>
<td>149.3 ± 17.3</td>
<td>191.7 ± 14.4</td>
<td>157.2 ± 17.2</td>
<td>.074</td>
</tr>
<tr>
<td>DF (Hz)</td>
<td>6.7</td>
<td>6.5</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>SDCL (ms)</td>
<td>9.7 ± 5.4</td>
<td>10.5 ± 5.4</td>
<td>12.4 ± 6.6</td>
<td></td>
</tr>
<tr>
<td>Initial Rec%</td>
<td>48 ± 23</td>
<td>40 ± 18</td>
<td>57 ± 18</td>
<td>.0002</td>
</tr>
<tr>
<td>Noise (%)</td>
<td>5.2 ± 1.8</td>
<td>6.1 ± 1.3</td>
<td>6.5 ± 1.9</td>
<td>.0003</td>
</tr>
</tbody>
</table>

CL = cycle length; DF = dominant frequency; Initial Rec% = mean recurrence percentage at the beginning of ablation; SDCL = standard deviation of CL.
As mentioned above, different channels of a study could have different types of Rec% time series. In Figure 6, we compare 2 sets of Rec% trends. On both occasions, the less organized channel (green) jumps and reaches the more organized one (red) and then follows it closely for a period of time. This suggests that ablation enhances the linkage between adjacent channels.

The slope of Rec% trends after jumps has a bimodal distribution. Rec% plateaued in 58% of cases (such as in Figures 3A and 6A) and drifted down in the remaining 42% (Figures 3A and 6B) despite ongoing ablation.

In 6 cases, RA ablation (excluding cavotricuspid ablation) was also performed. Figure 7 provides a global view of an organization pattern in 4 cases: 2 with RA ablation and 2 without RA ablation. A common feature is the initial appearance of local organization, which then expands laterally to other channels in discrete jumps. In the 2 RA ablation cases, the initial organization was right sided, whereas for the 2 cases without RA ablation, organization was first seen in CS channels.

Discussion

In this article, we used a recurrence map methodology to study spatiotemporal patterns of atrial organization during the CFAE-targeted ablation of persistent AF.

We showed that temporally dense measurement of Rec% is feasible and provides complementary information to CL data. Specially, dense sampling with no gaps between consecutive segments allows us to capture the moments of transition from AF to AFL and to assess the transitional dynamics. This is in contrast to high-resolution spatial coverage with sparse temporal sampling performed in previous studies of similarity index and recurrence maps.

The most common pattern was type I, with at least 1 sudden jump in Rec% and which was more than twice as frequent as the type II pattern with a gradual increase in Rec%. In addition, jumps in different channels from a given study were not necessarily at the same time. We interpreted these findings as evidence that the process of atrial organization during ablation is usually dispersed in both time and space and occurs in discrete jumps.

There was a direct correlation between the number of channels with type I pattern and the risk of later recurrence in the form of AT/AFL, but not necessarily AF. This suggests that presence of type I is a marker for the presence of AFL substrates that may predispose to future recurrences.

The regularization of AF to AFL exhibits characteristics of phase transition in complex self-organizing systems. In this context, self-organization is defined as “the spontaneous emergence of global coherence out of local interactions.”

One critical feature of such systems is long-distance correlation among their components, allowing synchronization to emerge between the components. The process of ablation allows better synchronization between neighboring segments of atria that eventually coalesce into a single functional unit, exhibiting AFL.

This observed pattern is consistent with the atrial organization signature expected from the ablation of a single spiral wave with fibrillatory conduction, as described in the Introduction. In this model, the initial local regularization of atrial activity occurs because of anchoring of spiral waves to the ablated CFAE sites (local regularization). In addition, some of the CFAE sites are responsible for wave break and wavelet proliferation that promote fibrillatory conduction, whose suppression by ablation enables 1-to-1 conduction between neighboring areas and the subsequent merger and...
**Figure 5** Rec% time series (panels A and B) and CL trends (panels C and D) in type I channels. **A and B:** Two RA channels from the same study. **C and D:** Two LA channels from a different study. There are 3 jumps in panel B with the corresponding change in CL, but only 2 of the jumps are apparent in panel A. Similarly, there is a jump around 50 minutes seen in panel C, with the corresponding change in CL, but the jump in panel D occurs around 120 minutes. Raw values are plotted in gray. The red and blue curves show the smoothed trends. CL = cycle length; LA = left atrial; RA = right atrial; Rec% = recurrence percentage.

**Figure 6** Two sets of overlapped Rec% time series. **A:** The red and green curves represent type II and type I channels, respectively. Note that there are 2 clusters of jumps on the green graph: one between 40 and 50 minutes, which is transient, and one after 80 minutes. On both occasions, the green curve reaches the red curve before following it for a period of time. **B:** Similar to the curves shown in panel A, there is a jump on the green curve (type I) at 65 minutes and it then follows the red curve (type III) from 65 to 105 minutes. Panels A and B are from different studies. Raw Rec% values are plotted in gray. The red and green curves show the smoothed trends. Rec% = recurrence percentage.
growth of the organized areas. In contrast, multiwavelet reentry is disfavored by lack of global correlation in the timing of jumps and non-detection of a staircase pattern in Rec% time series, which is expected as a result of reduction in the total number of (global) rotors responsible for persistence of AF.12

If CFAE ablation works by enhancing the linkage between neighboring regions of atria, then there should be an optimal amount of ablation that results in maximal coherence. Not enough ablation leaves fibrillatory conduction intact, while too much ablation decouples atrial regions, reduces the linkage, and decreases atrial organization. The latter situation may be responsible for the observed downward drift in 42% of Rec% trends after the jumps and could explain why CFAE ablation has only a marginal benefit.

The methodology discussed in this article can be useful in guiding ablation of persistent AF. For example, one possible strategy is to stop ablation at a given site soon after a local jump in Rec% is detected.

Study limitations
The main limitation of the study is that the data were collected from the RA/CS catheter, which is usually some distance from LA ablation sites and covers only a limited portion of the atria. The degree of organization in this CS catheter only weakly reflects the true LA organization.

We have made the trade-off of using dense temporal sampling instead of dense spatial sampling to obtain complementary data. Of course, a combined dense temporal and spatial sampling using a stable multipolar basket catheter in the LA for the duration of ablation would be ideal. Nevertheless, its application is generally limited to special cases, such as during focal impulse and rotor modulation ablation, because of a higher risk of thromboembolism and patient’s safety considerations. Future prospective studies using combined dense spatiotemporal sampling are needed to confirm the findings of this study and test the applicability of the presented method in guiding ablation.

Rotors (either single or multiple) are the driving force behind persistent AF. In this study, we had no direct way of visualizing rotors and only indirectly studied and inferred their effects on atrial activity.

Different pathophysiological mechanisms result in fractionated signals that are classified as CFAE.24 Apparent CFAE signals may be bystanders because of wave collision or fiber orientation with no causal relationship to AF. This possibility is especially important in paroxysmal AF when CFAE ablation does not improve the outcome. Another possible mechanism for the generation of CFAE signals is the activity of ganglionated plexi.25 The evidence in support of this possibility is mixed, and ganglionated plexi are most likely responsible for only a subset of the observed CFAE areas.26,27

Furthermore, we have performed a subgroup analysis to evaluate the effect of different variables (such as antiarrhythmic medication use or RA ablation) on the derived parameters and patterns. The small sample size limits the power of these analyses.
Conclusion
Temporally dense spatiotemporal assessment of atrial organization during the ablation of persistent AF is feasible and provides complementary information to CL measurements. Atrial organization starts locally and expands in discrete jumps, which are dispersed in time and space, until the organized areas merge into a single functional unit, exhibiting AFL. This pattern favors, but does not prove, the presence of a mother rotor, with fibrillatory conduction as the underlying mechanism of persistent AF.

References

Clinical Perspectives
Ablation of persistent atrial fibrillation (AF) is challenging and not very effective. Traditionally, a combination of anatomical linear lesions and complex fractionated atrial electrogram (CFAE)–targeted ablation has been used to guide ablation. In this study, we characterized the spatiotemporal organizational pattern of atrial activity during CFAE-targeted ablation by using the recurrence map methodology. The goals were to elucidate the mechanisms of successful CFAE ablation procedures and to apply lessons learned to the newer ablation techniques based on the direct detection of the rotors responsible for persistence of AF. One major finding was that the ablation of persistent AF works by suppressing fibrillatory conduction and enhancing the linkage between the neighboring areas of atria. However, excessive ablation may decouple atria and reduce coherence. Therefore, we postulate that it is possible to improve the success rate by fine-tuning the amount of ablation at each site to achieve the maximum linkage. This hypothesis needs to be verified in future prospective studies.