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Electrogram Morphology Recurrence Patterns during Atrial Fibrillation

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Abstract

Background—Traditional mapping of atrial fibrillation (AF) is limited by changing electrogram morphologies and variable cycle lengths.

Objective—We tested the hypothesis that morphology recurrence plot analysis would identify sites of stable and repeatable electrogram morphology patterns.

Methods—AF electrograms recorded from left atrial (LA) and right atrial (RA) sites in 19 patients (10 male, 59±10 years old) prior to AF ablation were analyzed. Morphology recurrence plots for each electrogram recording were created by cross-correlation of each automatically detected activation with every other activation in the recording. A recurrence percentage, the percentage of the most common morphology, and the mean cycle length of activations with the most common morphology (CL_R) were computed.

Results—The morphology recurrence plots commonly showed checkerboard patterns of alternating high and low cross correlation values indicating periodic recurrences in morphologies. The mean recurrence percentage for all sites and all patients was 38±25%. The highest recurrence percentage per patient averaged 83±17%. The highest recurrence percentage was located in the RA in 5 patients and in the LA in 14 patients. Patients with sites of shortest CL_R in the LA and RA had ablation failure rates of 25% and 100%, respectively (HR=4.95; p=0.05).

Conclusions—A new technique to characterize electrogram morphology recurrence demonstrated that there is a distribution of sites with high and low repeatability of electrogram morphologies. Sites with rapid activation of highly repetitive morphology patterns may be critical to sustaining AF. Further testing of this approach to map and ablate AF sources is warranted.

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Conflicts of interest:

Drs. Ng, Gordon, Arora, and Goldberger were funded by the American Heart Association (AHA 12GRNT12070241) for this study

Drs. Ng, Gordon and Goldberger are inventors in a patent application for electrogram morphology recurrence analysis

Drs. Passman and Knight have no conflicts of interest

Keywords

atrial fibrillation; electrograms; mapping; non-linear analysis; signal processing

A successful ablation strategy tailored to the specific mechanism of a patient's atrial fibrillation (AF) is considered one of the “holy grails” of AF treatment. Because of the complexity of the electrical activity of the atria during AF and the limitations of the technology available to identify electrograms for “mapping” the atria, the ability to characterize the activation patterns during electrophysiologic testing in patients with AF is extremely difficult. AF has been traditionally thought to be maintained by either rapid firing foci^{1, 2}, reentrant wavefronts³⁻⁵, or rotors^{6, 7}. The pulmonary veins (PVs) have been shown to be a common location for AF triggers and drivers⁸. However, ablation strategies that isolate the veins are effective in only a subset of patients with AF⁹. The rapid and seemingly chaotic electrogram activity that is characteristic of AF cannot currently be used to determine whether AF in a particular patient has a PV origin or is maintained by other foci/mechanisms.

Attempts have been made to utilize catheter-based electrogram recordings in ablation procedures. Frequency domain measures have been used to estimate the rate and regularity of AF electrograms^{10, 11}. It has been hypothesized that high frequency sources could represent drivers of AF. However, the difficulty in using this technique is that the variability of these measurements may be almost as great as the difference between recording sites¹². Sanders et al showed that sites of high frequency activation could be located and ablated in paroxysmal AF patients^{11, 13}. However, mapping of activation rates in persistent AF could not identify the culprit sources^{11, 13}. Complex fractionated atrial electrograms (CFAEs)¹⁴ and focal impulse and rotor modulation (FIRM) mapping have also been proposed as strategies for mapping foci or sources of AF that can be targeted by ablation¹⁵.

In arrhythmias with regular activation patterns, the bipolar electrogram at a particular site is determined by the direction of activation and remains relatively constant during each activation. In AF, we hypothesized that similar activations from beat to beat, as would be expected to occur near the arrhythmia source, can be quantified by examining the repeatability of electrogram morphologies from beat to beat. In this study, we report a modified recurrence plot analysis to observe the nonlinear dynamics of AF electrogram morphologies that may offer new insights to the dynamics of AF and may provide a new clinical technique to mapping AF.

METHODS

Patient population

Electrograms from patients who were in AF at the time of their ablation procedure were collected prior to ablation. Patients had no prior ablation or surgical interventions in their atria. All patients provided written informed consent. The study was approved by the Institutional Review Board of Northwestern University.

Mapping and electrogram recordings

Bipolar electrograms were sequentially obtained from multiple sites in the right and left atria (RA and LA) and stored on the Prucka CardioLab EP System (GE Healthcare, Waukesha, WI) at a sample rate of 977 Hz. The majority of the signals were collected with a Navistar catheter (Biosense Webster, Inc., Diamond Bar, CA, USA) but diagnostic catheters were used for coronary sinus recordings and were also used for multisite recordings in some patients. At least 15 seconds of electrograms were recorded at each site. Recording sites were documented using an electroanatomical mapping system (NavX, St. Jude Medical; or CartoXP, Biosense Webster). Electrograms were obtained from distributed RA (appendage, lateral wall, superior and inferior vena cava junctions, posterior wall, and septum) and LA (septum, roof, posterior wall, appendage, and the ostia of the four PVs) locations. In addition, we analyzed 36 electrograms from seven patients with typical atrial flutter recorded from multiple sites in the RA to compare recurrence analysis during AF with a non-fibrillatory arrhythmia where stable activation patterns were expected.

Electrogram morphology recurrence analysis

MATLAB (Mathworks, Natick, MA) was used for all aspects of the signal processing performed in this study. Electrogram morphology recurrence plots of each AF electrogram recording were created by first performing activation detections of the electrogram signal using an iterative technique developed and validated by our laboratory¹⁶. The same algorithm was used for the detection of complex activations and in the setting of continuously fractionated sites. Additional details are in the Data Supplement.

Recurrence analysis was then performed on the original signal after 40 Hz high pass filtering. The morphology recurrence plot is a modification of a recurrence plot analysis first described by Eckmann et al.¹⁷ To create the morphology recurrence plot, a 100 ms window for each detected activation was cross-correlated with every other activation in the recording. The maximum normalized cross-correlation value was determined for each combination of activations. The result was a set of N times N maximum cross-correlation values, where N is the number of activations. The process is illustrated in a six activation example in Figure 1A. The N by N cross-correlation values can then be plotted in a two-dimensional color map as shown in Figure 1B. In this plot, the x-axis and y-axis represent the first and second activation template, respectively, that are cross-correlated. The points with dark red represent the combination with highest cross-correlation values near 1, while the blue represent cross-correlation values near 0. The line of identity where the x-value equals the y-value always has cross-correlation values of 1, as each activation is compared with itself. The recurrence plot provides a visual means to assess how often electrogram morphologies recur and the pattern of recurrence. The “checker board” pattern of Figure 1B suggests there is a dominant morphology that periodically recurs for the duration of the recording.

To quantify the amount of morphology recurrence, we determined the activation that best represented the most common morphology of the set of activations. This was accomplished by finding the column on the morphology recurrence plot that had the most number of cross-correlation values above 0.8, a cross-correlation value considered to be high. A sensitivity

analysis comparing the results of using the 0.8 threshold to other thresholds is described in the Data Supplement. We defined the recurrence percentage to be the number of the most common morphology as the percentage of the total number of activations. We also calculated the mean cycle length (CL) of the most recurrent morphology (CL_R) by dividing the average CL for all electrograms by the recurrence percentage. We hypothesize that sites with the shortest CL_R are more likely to be sites closest to a focal or reentrant driver. The CL_R measure will help distinguish fast repeatable activity from slower repeatable activity that would more likely represent passive activation. We also determined the CL for each site and identified the location of the shortest CL.

Reproducibility

Reproducibility of the recurrence percentage, CL_R , and CL was assessed using stable coronary sinus electrograms obtained simultaneously during the electrogram recordings of the other sites. The first and last recording during mapping of either the RA or LA was used.

Frequency Domain Analysis and CFAEs

Frequency domain analysis was used to determine dominant frequency (DF) and regularity index. Electrograms were classified as CFAE if their fractionation interval was less than 120 ms. Additional details are found in the Data Supplement.

Ablation Outcomes

Although the study did not employ morphology recurrence analysis to guide ablation nor was it designed to assess whether morphology recurrence analysis mapping predicts ablation outcomes, preliminary data on outcomes are reported. In all patients, catheter ablation was performed only in the LA. In addition to PV ablation, roof and mitral isthmus lines were performed in four patients. Two of these patients had additional ablation at sites with CFAE. Freedom from AF was assessed after a 3 month blanking period. AF recurrence was defined as any AF or atrial tachycardia episode of 30 seconds or more documented by Holter monitor, ECG, event monitor, pacemaker, or loop recorder. Patient follow-up was available for a minimum of 6 months.

Data Analysis

Data are presented as mean $\pm$ standard deviation. Linear regression was used to compare the frequency domain measures with morphology recurrence measures. Unpaired T tests were used to compare morphology recurrence between CFAEs and non-CFAEs. Paired T test was used to compare the relative RA/LA gradients of the recurrence measures. Cox regression was used to compare freedom from AF for patients categorized by site (RA or LA) for highest recurrence percentage, shortest CL_R , and shortest CL. Reproducibility of two separate coronary sinus recordings were assessed using the intraclass correlation coefficient. A p-value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Electrograms were collected from nineteen patients (17 male, 56 ± 11 years old). Of the 19 patients, 15 had a history of persistent AF and 4 had paroxysmal AF. Hypertension was noted in 5 patients, left ventricular systolic dysfunction (ejection fraction $< 50\%$) in 6 patients, and coronary artery disease in 2 patients.

Electrogram Analysis

Figure 2 shows examples of morphology recurrence plots of electrograms recorded from multiple RA and LA sites from two patients. The morphology recurrence plots show distinct checker board patterns in the different sites indicating that the activation patterns have different levels of complexity, yet these patterns tend to be repeatable over the course of the recording. For Patient A, the highest recurrence percentage was 79%, which was found both near the superior vena cava and the left inferior PV. The right superior PV also had a high recurrence percentage of 77%. These sites can be easily identified in the figure as the sites with the most red, indicating high cross-correlation for the majority of the activations. The CL_R of the left inferior PV (201 ms), however, was much shorter than those of the right superior PV (215 ms) or of the superior vena cava (246 ms). The patient has had freedom from AF during the 13 months following his AF ablation targeting antral PV isolation. For Patient B, the highest recurrence percentage (71%) and shortest CL_R (231 ms) were found in the RA septum. The morphology recurrence plot for this site was most red compared to the other sites in both atria. Patient B had a recurrence of AF 9 months following ablation targeting PV isolation. Figure 3 shows examples of morphology recurrence plots and electrograms with different recurrence percentages and CLs.

Table 1 shows the mean and standard deviations of CL, recurrence percentage, and CL_R for the 14 atrial sites as well as the distribution of the minimum CL and CL_R sites and maximum recurrence percentage sites. The sites with the highest recurrence percentage had an average value of $83 \pm 17\%$, located in the RA in 5 patients and in the LA in 14 patients. The sites with the shortest CL had an average CL of 125 ± 15 ms. The shortest CL sites were in the RA in 11 patients and in the LA in 8 patients. The sites with the shortest CL_R had an average CL_R of 230 ± 91 ms. The shortest CL_R sites were in the RA in 3 patients and in the LA in 16 patients. Figure 4 displays schematically the differences at each site between the CL and CL_R for one patient. The impulses for the left plots represent all activation times for each site. The impulses on the right represent only the activation times for the most common morphology for that site. The left inferior PV in this patient can be seen to clearly have the highest Rec% and the shortest CL_R .

There was a substantial decrease between the site of highest recurrence percentage and the second highest percentage ($81.9 \pm 17.0\%$ vs. $72.2 \pm 13.5\%$). Similarly, there was a substantial increase between the shortest CL_R and the second shortest CL_R (224 ± 90 ms vs. 254 ± 94 ms). The percent difference between the shortest CL_R and the shortest CL_R in the contralateral atrium was $35 \pm 7\%$. For maximum recurrence percentage and the maximum recurrence percentage in the contralateral atrium, the percent difference was $25 \pm 5\%$. Both of

these were significantly greater than the corresponding percent difference for minimum CL which was $11 \pm 2\%$ ($p < 0.02$).

Reproducibility and comparison to atrial flutter

Reproducibility of recurrence percentage, CL_R , and CL was assessed using coronary sinus recordings taken 14.4 ± 7.8 minutes apart. Intraclass correlation coefficients for recurrence percentage, CL_R , and CL were 0.91, 0.98, and 0.82, respectively. The average recurrence percentage for atrial flutter recordings was $91 \pm 12\%$ which was significantly higher than the maximum recurrence percentages of AF patients ($82 \pm 17\%$, $p < 0.05$).

Correlations with Frequency Domain Measures and CFAEs

DF was highly correlated with the reciprocal of CL ($R = 0.75$, $p < 0.0001$). Regularity index was only weakly correlated with recurrence percentage ($R = 0.16$, $p = 0.008$). CFAEs had significantly lower Rec% than non-CFAEs ($31 \pm 14\%$ vs. $62 \pm 20\%$, $p < 0.0001$). Addition results are in the Data Supplement.

Outcomes

With a median follow-up time of 13 months, 7 of the 19 patients had documented AF recurrences after a 3 month blanking period post-ablation. Four of 5 patients (80%) with sites of highest recurrence percentage located in the RA had AF recurrences while 3 of 14 patients (21.4%) with sites of highest recurrence percentage located in the LA had AF recurrences (hazard ratio=6.76; 95% confidence interval: 1.05 to 32.3; $p = 0.04$). All three patients with sites of shortest CL_R located in the RA had AF recurrences while 4 of 16 patients (25%) with sites of minimum CL_R located in the LA had AF recurrences (hazard ratio=4.95; 95% confidence interval: 1.05 to 25; $p = 0.05$). AF recurrences occurred in 3 of 11 (27.3%) and 4 of 8 (50%) patients with minimum CL located in the RA and LA, respectively (hazard ratio=1.45; 95% confidence interval: 0.31 to 6.72; $p = 0.63$). When comparing PV and non-PV sites, 5 of 9 patients (55%) with sites of minimum CL_R located in a non-PV site had AF recurrences while 2 of 10 patients (20%) with sites of minimum CL_R located near the PV had AF recurrences (hazard ratio=3.3; 95% confidence interval: 0.6 to 16.1; $p = 0.16$).

DISCUSSION

This study demonstrates a new technique for electrogram mapping in patients with AF. Because of the complexity of the electrical activity of the atria during AF and the limitations of the technology available to record electrograms and “map” the atria, the ability to characterize the activation patterns during AF is extremely difficult. Catheter ablation for non-AF supraventricular tachycardias based on well-established mapping techniques is often associated with success rates exceeding 95%.¹⁸ In contrast, AF has electrograms where the relative timings and morphologies are constantly changing, precluding the use of the standard mapping techniques that have been applied to regular tachycardias. Electrogram morphology recurrence analysis can be used to quantify both the degree of repeatability of electrogram morphologies and the CL of the most recurring electrogram morphology. This

initial report of this novel mapping technique provides a promising new approach to map AF.

There is continuing evidence that AF in many patients is perpetuated by stable sources (focal or reentrant) in the LA or RA. If electrical activation near stable sources results in bipolar electrogram recordings with repeatable activation waveform morphologies due to stable activation directions, quantifying electrogram repeatability could be an important new mapping tool. The sites of frequent morphology recurrence were easily identifiable from the morphology recurrence plots as being primarily red due to the color coding of the cross correlation coefficients. Interestingly, patients with sites of highest morphology recurrence in the LA were more likely to remain in sinus rhythm following LA/PV-based ablation than patients who had sites of highest morphology recurrence in the RA. The location of the shortest CL was not predictive of ablation success.

Notably, electrogram recurrence is a property of all sites/recordings. Even sites with less frequent morphology recurrences had checkerboard patterns in their morphology recurrence plots indicating that there were periodic recurrences of specific morphologies. As sites that are passively activated could potentially also have frequent morphology recurrence but with slower activation rates, we proposed recurrence CL as a measure of the average interval between activations with the most common morphology. To determine whether mapping to identify the site(s) of minimum CL_R can identify effective ablation targets requires further study.

The proposed morphology recurrence plot method is a modification of a more commonly used recurrence plot analysis first developed by Eckmann et al in 1987 as a graphical tool for the study of the non-linear dynamics¹⁷ and has since been used in a variety of applications¹⁹. Recurrence plots have also been used in other studies for AF-related analysis.²⁰⁻²² Repeatability of waveform morphology in AF have also been observed using other signal processing methods²³⁻²⁵. The advantage of using morphology recurrence plots to quantify similarity is not only the rapid visual identification of high recurrence, but also the ability to see the patterns of morphology recurrence, their stability, and the CL of the most recurrent morphology.

Investigators have long sought a patient specific approach to AF ablation guided by electrogram recordings as an alternative to strategies based upon PV isolation and/or other empiric ablation lesions. Other proposed electrogram-based strategies for ablation such as DF analysis^{11, 13, 26} and CFAE²⁷⁻²⁹ have shown effectiveness in some patients, although superiority over PV isolation with these techniques have not been clearly demonstrated. The recently developed FIRM mapping uses a basket catheter to characterize the activation directions of AF in the atria to identify rotors and origins of focal activity.^{15, 30} Early reports show that roughly 24% of these patients were found to have sources located in the RA using FIRM mapping, a comparable percentage to the number of highest recurrence percentage sites observed in the RA in this study. Therefore, it is possible that sites identified by recurrence plot mapping using sequential recordings represent the same sites determined by FIRM mapping with the basket catheter.

LIMITATIONS

As with all mapping techniques, catheter stability has the potential to affect morphology recurrence. Analysis of atrial flutter electrograms showed high but not necessarily 100% recurrence percentages which may be in part due to catheter instability. We found good stability of the recurrence measurement from the CS. However, the stability of the locations of the maximum recurrence sites was not assessed. Habel et al showed instability of maximum DF and CFAE locations³¹. Additionally, electrode size and spacing may affect electrogram morphology, which was not assessed in the present study. Although this study has a small sample size and detailed mapping of morphology recurrence was not performed, the present findings highlight the potential of this technique and need for developing a real-time analysis platform. Further studies will also need to perform more detailed mapping to address the patterns of morphology recurrence plots in areas of focal and rotor activation.

CONCLUSIONS

Current approaches to catheter ablation of AF do not employ mapping for AF sources and have suboptimal success rates. Given the high success rates for catheter ablation for supraventricular arrhythmias that can be precisely mapped¹⁸, the development of an easily performed technique to map and identify AF sources could be a major advance. For most patients, there appear to be sites with highly repetitive morphology patterns that can be easily identified with the proposed morphology recurrence plots. Further evaluation of this promising new mapping technique for AF is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AF	atrial fibrillation
CL	cycle length
CL_R	cycle length of the most recurrent morphology
CFAE	complex fractionation atrial electrograms
DF	Dominant frequency
FIRM	focal impulse and rotor modulation
LA	left atrium
PV	pulmonary vein
RA	right atrium

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CLINICAL PERSPECTIVES

Morphology recurrence analysis is a novel method to map atrial fibrillation. It is based on the premise that sources of atrial fibrillation will have fast and consistent activation directions and therefore have electrograms with fast and repeating activation waveforms. This study showed that high rates of recurrence as measured by the proposed recurrence cycle length appear to be localized in specific regions of the atria and are distinct from sites that are simply fast or just regular. As the most common strategy for atrial fibrillation ablation are empirically derived variants of pulmonary vein isolation, morphology recurrence analysis may allow atrial fibrillation sources to be identified in an intuitive way for a more personalized approach to ablation of atrial fibrillation. Further study is required to determine how information obtained from real time mapping of morphology recurrences can be used to direct ablation and whether it offers clinical benefit over currently used ablation approaches.

Figure 1.

A) Illustration of a cross-correlation matrix for the first six activations of an AF electrogram.

B) Illustration of a color coded cross-correlation matrix of all activations. Areas of red indicate high cross-correlation values thus morphology recurrence. Non-red areas indicate pairs of activations with less similar morphologies.

Figure 2.

Examples of morphology recurrence plots from electrograms collected from two patients from different areas of the right and left atria. For Patient A, the SVC and the LIPV had the highest recurrence percentage values (Rec%) at 79%. The RSPV also had a high Rec% value at 77%. The shortest recurrence cycle length (CL_R) was found in the LIPV (201 ms). For Patient B, the right atrial septum had both the highest Rec% (71%) and the shortest CL_R (231 ms).

Figure 3.

Examples of morphology recurrence plots the corresponding electrograms used to create the plot. A and B show plots of electrograms with similar cycle lengths (CLs), but different recurrence percentages (Rec%) and as a result different recurrence cycle lengths (CL_R). C shows electrograms with similar Rec% to those in example B but with much longer CL and CL_R.

Figure 4.

Impulse diagrams showing the timings of detected activations from different sites in the right and left atria in one patient. The impulse diagrams on the left column depict the timings of all detected activations from each site and their corresponding cycle length (CL). The impulse diagrams on the right depict only the timings of activations with the most common morphology for each recording. The recurrence percentage (Rec%) and recurrence cycle length (CLR) for each site are also shown on the right. The LIPV in this patient can be seen to clearly have the highest Rec% and the shortest CLR.

Table 1

Average cycle length (CL), recurrence percentage (Rec%), and recurrence cycle length (CL_R) per recording site for all patients and the number of patients that have maximum or minimum values in that recording site.

Atrium	Site	CL		Rec%		CL _R	
		Mean±SD (ms)	# of min	Mean±SD (%)	# of max	Mean±SD (ms)	# of min
Right atrium	Appendage	150±20	2	40±17	0	467±236	1
	Lateral Wall	154±35	4	43±24	1	1874±6362	1
	SVC/RA Junction	171±39	1	52±26	2	493±425	0
	Posterior Wall	155±28	1	35±15	0	572±293	0
	IVC/RA Junction	166±36	1	39±15	1	551±440	0
	Septum	162±29	1	34±19	1	669±477	1
Left atrium	Septum	156±25	0	36±20	2	676±613	1
	RSPV	159±16	0	45±27	0	845±1462	0
	RIPV	156±19	1	40±23	2	614±536	2
	Roof	153±18	5	46±25	1	636±1010	2
	Posterior Wall	155±24	1	38±20	1	570±365	1
	LSPV	156±19	0	57±29	4	420±331	3
	LIPV	157±13	2	50±26	3	492±543	5
	Appendage	154±21	0	58±23	1	322±137	2