Electrogram morphology recurrence patterns during atrial fibrillation

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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 men; mean age 59 ± 10 years) before 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 recurrent morphology 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 mean cycle length of activations with the most recurrent morphology in the LA and RA had ablation failure rates of 25% and 100%, respectively (hazard ratio 4.95; P = .05).

CONCLUSION 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.

KEYWORDS Atrial fibrillation; Electrograms; Mapping; Signal processing

ABBREVIATIONS AF = atrial fibrillation; CL = cycle length; CLm = cycle length of the most recurrent morphology; CFAE = complex fractionated atrial electrogram; DF = dominant frequency; FIRM = focal impulse and rotor modulation; LA = left atrium/atrial; PV = pulmonary vein; RA = right atrium/atrial; Rec% = recurrence percentage

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Introduction

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 wavefronts,3–5 or rotors.6,7 The pulmonary veins (PVs) have been shown to be a common location for AF triggers and drivers.8 However, ablation strategies that isolate the veins are effective in only a subset of patients with AF.9 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 use 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 sites.12 Sanders et al11 showed that sites of high-frequency activation could be located and ablated in patients with paroxysmal AF. However, mapping of activation rates in persistent AF could not identify the culprit sources.11,13 Complex fractionated atrial electrograms...
(CFAEs) 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 ablation. 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 into 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 before 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), 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 electroanatomic mapping system (NavX, St Jude Medical, Inc, Saint Paul, MN; or Carto XP, 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 4 PVs) locations.

In addition, we analyzed 36 electrograms recorded from multiple sites in the RA in 7 patients with typical atrial flutter to compare recurrence analysis during AF with a nonfibrillatory arrhythmia where stable activation patterns were expected.

**Electrogram morphology recurrence analysis**

MATLAB (MathWorks, Inc, 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 laboratory. The same algorithm was used for the detection of complex activations and in the setting of continuously fractionated sites. Other details are in the Online 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. 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 6-activation example in Figure 1A. The $N \times N$ cross-correlation values can then be plotted in a 2-dimensional color map, as shown in Figure 1B. In this plot, the x-axis and y-axis represent the first and the second activation template, respectively, that are cross-correlated. The points in dark red represent the combination with highest cross-correlation.
cross-correlation values near 1, while the points in 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 “checkerboard” pattern of Figure 1B suggests that 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 that is considered to be high. A sensitivity analysis comparing the results of using the 0.8 threshold to other thresholds is described in the Online Supplement. We defined the recurrence percentage (Rec%) 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 (CLR) by dividing the average CL for all electrograms by Rec%. We hypothesize that sites with the shortest CLR are more likely to be sites closest to a focal or reentrant driver. The CLR 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 Rec%, CLR, and CL was assessed using stable coronary sinus electrograms obtained simultaneously during the electrogram recordings of other sites. The first and last recordings during mapping of either the RA or the LA were 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. Other details are found in the Online Supplement.

Ablation outcomes
Although the study did not use 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 4 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, electrocardiogram, event monitor, pacemaker, or loop recorder. Patient follow-up was available for a minimum of 6 months.

Data analysis
Data are presented as mean ± SD. 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. A paired t test was used to compare the relative RA/LA gradients of recurrence measures. Cox regression was used to compare freedom from AF for patients categorized by site (RA or LA) for highest Rec%, shortest CLR, and shortest CL. Reproducibility of 2 separate coronary sinus recordings were assessed using the intraclass correlation coefficient. A P value of <.05 was considered statistically significant.

Results
Patient characteristics
Electrograms were collected from 19 patients (17 men; mean age 56 ± 11 years). 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 in 2 patients. The morphology recurrence plots show distinct checkerboard patterns in 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 Rec% was 79%, which was found near both the superior vena cava and the left inferior PV. The right superior PV also had a high Rec% of 77%. These sites can be easily identified in the figure as the sites with the most red points, indicating high cross-correlation for the majority of activations. The CLR of the left inferior PV (201 ms), however, was much shorter than that of the right superior PV (215 ms) or that of the superior vena cava (246 ms). The patient has had freedom from AF during the 13 months after his AF ablation targeting antral PV isolation. For patient B, the highest Rec% (71%) and shortest CLR (231 ms) were found in the RA septum. The morphology recurrence plot for this site was mostly red compared with the other sites in both atria. Patient B had a recurrence of AF 9 months after ablation targeting PV isolation. Figure 3 shows examples of morphology recurrence plots and electrograms with different Rec% values and CLs.

Table 1 shows the mean and SD of CLR, Rec%, and CLR for the 14 atrial sites as well as the distribution of the minimum CLR and CLR sites and maximum Rec% sites. The sites with the highest Rec% had an average value of
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 CLR had an average CLR of 230 ± 91 ms. The shortest CLR 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 CLR for 1 patient. The impulses for the left plots represent all activation times for each site. The impulses on the right plots represent the activation times only for the most common morphology for that site. The left inferior PV in this patient can be clearly seen to have the highest Rec% and the shortest CLR.

83 ± 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 CLR had an average CLR of 230 ± 91 ms. The shortest CLR sites were in the RA in 3 patients and in the LA in 16 patients. Figure 4 displays schematically the
There was a substantial decrease between the site of highest Rec% and the second highest percentage (81.9 ± 17.0% vs 72.2 ± 13.5%). Similarly, there was a substantial increase between the shortest CLR and the second shortest CLR (224 ± 90 ms vs 254 ± 94 ms). The percent difference between the shortest CLR and the shortest CLR in the contralateral atrium was 35 ± 7%. For the maximum Rec% and the maximum Rec% in the contralateral atrium, the percent difference was 25 ± 5%. Both these were significantly greater than the corresponding percent difference for minimum CL, which was 11 ± 2% (P < .02).

Reproducibility and comparison to atrial flutter
Reproducibility of Rec%, CLR, and CL was assessed using coronary sinus recordings taken 14.4 ± 7.8 minutes apart. Intraclass correlation coefficients for Rec%, CLR, and CL were .91, .98, and .82, respectively. The average Rec% for atrial flutter recordings was 91 ± 12%, which was significantly higher than the maximum Rec% values of patients with AF (82 ± 17%; P < .05).

Correlations with frequency domain measures and CFAEs
DF was highly correlated with the reciprocal of CL (R = .75; P < .0001). The regularity index was only weakly correlated with Rec% (R = .16; P = .008). CFAEs had significantly lower Rec% than did non-CFAEs (31 ± 14% vs 62 ± 20%; P < .0001). Addition results are in the Online Supplement.

Outcomes
With a median follow-up time of 13 months, 7 of 19 patients had documented AF recurrences after a 3-month blanking period postablation. Four of 5 patients (80%) with sites of highest Rec% located in the RA had AF recurrences, while 3 of 14 patients (21.4%) with sites of highest Rec% located in the LA had AF recurrences (hazard ratio 6.76; 95% confidence interval 1.05–32.3; P = .04). All 3 patients with sites of shortest CLR located in the RA had AF recurrences, while 4 of 16 patients (25%) with sites of minimum CLR located in the LA had AF recurrences (hazard ratio 4.95; 95% confidence interval 1.05–25; P = .05). AF recurrences occurred in 3 of 11 patients (27.3%) and 4 of 8 patients (50%) with minimum CL located in the RA and LA, respectively (hazard ratio 1.45; 95% confidence interval 0.31–6.72; P = .63). On comparing PV and non-PV sites, we found that 5 of 9 patients (55%) with sites of minimum CLR located in a non-PV site had AF recurrences while 2 of 10 patients (20%) with sites of minimum CLR located near the PV had AF recurrences (hazard ratio 3.3; 95% confidence interval 0.6–16.1; P = .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

Table 1  Average cycle length (CL), recurrence percentage (Rec%), and recurrence cycle length (CLR) per recording site for all patients as well as the number of patients who have maximum or minimum values in that recording site

<table>
<thead>
<tr>
<th>Atrium</th>
<th>Site</th>
<th>CL</th>
<th>Rec%</th>
<th>CLR</th>
<th>Site</th>
<th>CL</th>
<th>Rec%</th>
<th>CLR</th>
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</thead>
<tbody>
<tr>
<td>Right atrium</td>
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<td>150</td>
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<td>467</td>
<td>Septum</td>
<td>156</td>
<td>36</td>
<td>676</td>
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<td>1874</td>
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<td>154</td>
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<td>845</td>
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<td></td>
<td>SVC/RA junction</td>
<td>171</td>
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<td>493</td>
<td>SVC/RA junction</td>
<td>166</td>
<td>39</td>
<td>551</td>
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<td></td>
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<td>35</td>
<td>572</td>
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<td>152</td>
<td>38</td>
<td>570</td>
</tr>
<tr>
<td></td>
<td>IVC/RA junction</td>
<td>166</td>
<td>39</td>
<td>551</td>
<td>IVC/RA junction</td>
<td>166</td>
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<td>551</td>
</tr>
<tr>
<td></td>
<td>Septum</td>
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<td>669</td>
<td>Septum</td>
<td>162</td>
<td>36</td>
<td>676</td>
</tr>
<tr>
<td>Left atrium</td>
<td>Septum</td>
<td>156</td>
<td>36</td>
<td>676</td>
<td>Septum</td>
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<tr>
<td></td>
<td>Roof</td>
<td>153</td>
<td>46</td>
<td>636</td>
<td>Roof</td>
<td>153</td>
<td>46</td>
<td>636</td>
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<tr>
<td></td>
<td>Posterior wall</td>
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<td>38</td>
<td>570</td>
<td>Posterior wall</td>
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<td></td>
<td>LSPV</td>
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<td>570</td>
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<tr>
<td></td>
<td>LIPV</td>
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<td>50</td>
<td>492</td>
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<td>157</td>
<td>50</td>
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<td></td>
<td>Appendage</td>
<td>154</td>
<td>58</td>
<td>322</td>
<td>Appendage</td>
<td>154</td>
<td>58</td>
<td>322</td>
</tr>
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IVC = inferior vena cava; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RA = right atrial; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; SVC = superior vena cava.

Figure 4  Impulse diagrams showing the timings of detected activations from different sites in the right and left atria in 1 patient. The impulse diagrams on the left depict the timings of all detected activations from each site and their corresponding cycle lengths (CLs). 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 clearly seen to have the highest Rec% and the shortest CLR. IVC = inferior vena cava; LA = left atrial; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RA = right atrial; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; SVC = superior vena cava.
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%. In contrast, AF has electrogrograms 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 the 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 because of 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 after LA/PV-based ablation than were 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 CLR 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 nonlinear dynamics and has since been used in a variety of applications. Recurrence plots have also been used in other studies for AF-related analysis. Repeatability of the waveform morphology in AF has also been observed using other signal processing methods. 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 CLR.

Investigators have long sought a patient-specific approach to AF ablation guided by electrogram recordings as an alternative to strategies based on PV isolation and/or other empiric ablation lesions. Other proposed electrogram-based strategies for ablation such as DF analysis and CFAE 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. Early reports show that roughly 24% of these patients were found to have sources located in the RA by using FIRM mapping, a comparable percentage to the number of highest Rec% 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.

Study 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% Rec% values, which may be partly due to catheter instability. We found good stability of the recurrence measurement from coronary sinus. However, the stability of the locations of maximum recurrence sites was not assessed. Habel et al showed the instability of maximum DF and CFAE locations. In addition, 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.

Conclusion
Current approaches to catheter ablation of AF do not use mapping for AF sources and have suboptimal success rates. Given the high success rates of catheter ablation for supraventricular arrhythmias that can be precisely mapped, 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.

Appendix

Supplementary data
Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2014.08.002.

References


**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 strategies 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.