Ablation of complex fractionated atrial electrograms (CFAEs) during atrial fibrillation (AF) has been used as adjunct to contemporary techniques or as an alternative. Temporo-spatial stability of CFAE has been demonstrated in single episodes of AF. We examined temporo-spatial reproducibility of CFAE in two distinct episodes of AF.

The left atrium (LA) was mapped using the EnSite™ system during an episode of induced or spontaneous AF in patients with paroxysmal AF. Sinus rhythm was restored with electrical cardioversion and maintained for 10 min before re-induction of AF and repeat mapping. Maps were compared examining the mean cycle length at identical vertices, provided the anatomical point had data on both maps. Complex fractionated atrial electrograms were considered stable if the compared electrogram was within 50 ms—delta to 120 ms + delta. Eleven patients were studied; 10 were included [3 female, mean age 59.5 years (32–76)]. Complex fractionated atrial electrograms were observed in all regions of the LA. Complex fractionated atrial electrograms were evenly distributed throughout the LA but most reproducible at the roof and antero-lateral wall. Complex fractionated atrial electrograms were highly conserved between two episodes of AF with 76.1 ± 11.8% of CFAE reproducible at delta of 20 ms.

Complex fractionated atrial electrograms are reproducible at the same anatomic site in a separate episode of AF.

Introduction

Fractionated potentials (high-frequency complex low-amplitude electrograms) have been observed in the left atrium (LA) during episodes of atrial fibrillation (AF). These areas are thought to be pro-arrhythmic and contributors to AF perpetuation. Indeed, some investigators have abandoned traditional pulmonary vein-based approaches in favour of a targeted approach to the ablation of complex fractionated atrial electrograms (CFAEs) with acute and sustained procedural success. Recently, Haïssaguerre and colleagues demonstrated that the characteristics of fractionated electrograms were different when examined in the context of ablation outcome. Most of these investigators targeted fractionated potentials as part of a repeat study or during attempts to address persistent AF.

The electrophysiological basis for CFAE is still debated and may have an anatomic substrate such as fibrosis or areas of dense autonomic innervation. Alternatively, the theories of AF perpetuation support the presence of ‘meandering’ areas of CFAE that may anchor rotors or simply result in wave break-up. Importantly, ablation strategies are being employed using automated CFAE detection without a clear mechanistic rationale. Only recently has reproducibility of fractionated electrograms been subjected to close scrutiny and, in all, during the same episode of AF. On the whole, it appears that the CFAE is a reproducible measure using contemporary algorithms; however, it remains unknown whether the same anatomic locale will present the same degree of fractionation in a separate and distinct episode of AF. This is an important point, as current ablation strategies designed to abolish CFAE do so under the implicit assumptions that these
areas of CFAE are both important for each episode of AF and that they are anatomically stable.

We present data that support a stable anatomic substrate for CFAE by examining reproducibility of CFAE in two separate and distinct episodes of AF. We also investigate the electrogram characteristics of temporo-spatially stable CFAE.

**Methods**

Patients over the age of 18 attending for catheter ablation of paroxysmal AF were invited to participate in the study. Amiodarone use in the last 3 months was an exclusion criterion. All other anti-arrhythmics were stopped 5 half-lives prior to the study. Patients with persistent AF or who were unable to maintain sinus rhythm for any reason prior to the catheter ablation were excluded from the study. The protocol was approved by the Queen’s University Research Ethics Board.

The procedure was performed under conscious sedation; deeper sedation was used for cardioversion, but propofol anaesthesia was not employed. Venous access was gained from the right femoral vein and left subclavian vein. A decapolar catheter (Daig Inc., Minnetonka, MN, USA) was placed via the subclavian vein into the coronary sinus, and a quadrapolar catheter (St Jude Medical, St Paul, MN, USA) was placed at the right ventricular apex and at the His bundle location prior to two transseptal punctures using a standard Brockenbrough technique. SL1 sheaths (St Jude Medical), under continuous irrigation, allowed the passage of a LASSO catheter (Biosense-Webster, Diamond Barr, CA, USA) and an open irrigated ablation catheter (Thermocool, Biosense-Webster, Diamond Barr, CA, USA) into the LA; the EnSite NavXTM system (St Jude Medical) was employed to create geometry. Atrial fibrillation, if not present, was induced with rapid atrial pacing [cycle length (CL) 180–200 ms; 10 s bursts] via either the distal coronary sinus catheter or the LASSO catheter situated in the left superior pulmonary vein. Mapping was performed to record CFAE using the algorithms present in the NavXTM software once AF had been sustained >5 min. Anatomic locations were sampled over 4 s using the Diagnostic Landmarking (DxL) CFE software.11 For electrograms with a mean CL of <120 ms, a 4 s section was deemed adequate for sampling.14

Points throughout the LA geometry were collected using visual assessment to ensure complete coverage of the anatomy. Width and refractory DxL parameters were set to 10 and 30 ms, respectively, to exclude non-physiological signals.11 Peak-to-peak sensitivity was set from 0.03–0.05 mV, depending on the noise level determined by the investigator. Finally, interpolation and interior and exterior projections were set to 5 mm for all maps. Sinus rhythm was restored with direct electrical cardioversion using standard sedation with intravenous midazolam and fentanyl. Sinus rhythm was maintained for 10 min and then AF was re-induced using the same catheter site as the previous episode. The LA was mapped as before during this second, sustained episode. Two patients attended in AF and thus did not require induction of the first episode; the second episode was induced from the decapolar catheter placed in coronary sinus.

Data from the two CFAE maps were compared off-line using custom software, written in the MATLAB environment, for the location of CFAE and reproducibility of electrograms as described in what follows.

**Electrogram assessment**

The EnSite system creates a geometry that consists of a mesh of triangles (Figure 1); each intersection is a vertex that has a unique geometric identifier. Data collected for that area are associated with the vertex nearest to the roving catheter collecting the data; several vertices may be allocated the same value, depending on user-defined parameters of distance from the surface of the shell (interior and exterior projections) and adjacent vertices (interpolation). The exact same geometry was used for each pair of maps. Each pair of pre-cardioversion and post-cardioversion DxL map data was compared by examining the DxL value (e.g., CFE mean) at identical XYZ co-ordinates in a MATLAB program, provided the anatomical point had data on both maps—vertices that did not have a correlate in both maps were excluded.

The DxL maps were analysed in regions defined a priori according to simple rules (Box 1). Every recorded segment from each DxL map was visually assessed by two experienced operators for noise...
contamination and appropriate detection of electrogram deflections by the automated software. Electrograms showing inappropriate detection because of under-sensing, over-sensing, or noise were deleted from the map prior to analysis. Electrograms were processed off-line and the values for CFE mean and standard deviation of CFE mean (CFE-SD) for each electrogram were compared using a purpose-written program.

Box 1 Lines generated to divide the LA
Right pulmonary veins (RPV): circle around the veins at a point roughly 1 cm from the tubular ostium.
Left pulmonary veins (LPV): circle around the veins as above.
Mitral annulus: separate marker to delineate the annulus.
Posterior roof line: line starting between the right superior pulmonary veins (RSPV) and the right inferior pulmonary veins (RIPV), continuing along the roof to its final point located between the left superior pulmonary veins (LSPV) and the left inferior pulmonary veins (LIPV).
Anterior roof line: line starting at the base of the RPV marker and ending at the base of the LPV marker.
Septal line: base of the RPV to the mitral valve annulus taking the shortest route.
Lateral line: base of the LPV to the mitral valve annulus taking the shortest route.
Anterior vertical: begins at the midpoint of roof line to the annulus via the shortest route.
Regions
LPV region: encompassing LPV inclusive of the PV junction.
RPV region: encompassing RPV inclusive of the PV junction.
Posterior region.
Antero-septal region: encompassing the septum.
Antero-lateral region: encompassing the left atrial appendage.
Roof region.

When judging reproducibility, it was observed that a value of, say, 119 ms and a subsequent value of 121 ms at the same anatomic location would lead to a designation as a ‘non-reproducible’ electrogram; therefore, a variable ‘delta’ was introduced from 0 to 50 ms.

Complex fractionated electrogram mean
The algorithm employed by the NavX Dxl CFE software uses a voltage cut-off determined at the outset of the study. Deflections that cross this cut-off are tagged and the interval between each marker calculated. The mean of all the intervals is determined for the segment recorded, and a value is delivered. This can be illustrated in real-time using colour on the geometry. The SD of the CFE mean is also calculated and can display the resultant value as a colour range in real-time on the geometry.

Statistical analysis
Data were inspected for normality using the Anderson–Darling test. Continuous data were compared with a Student’s t-test or ANOVA. Categorical data were compared with a χ² table for each region. Analysis was performed using Minitab® 15 (Minitab Inc., State College, PA, USA). Prior data were not available to estimate the sample size, and analysis was planned after 10 subjects were recruited.

Results
Fifteen eligible patients were approached, 11 agreed to be studied, of whom 1 failed to cardiovert to SR before ablation and was therefore excluded. Results are presented on the remaining 10 patients. All patients had drug refractory paroxysmal AF. There were seven men, the mean age was 59.5 ± 12.6 years, and the left atrial size was 42.2 ± 5.6 mm. The mean duration of AF symptoms was 65 ± 58 months (12 to 204).

The median number of points collected per map was 284.5. After electrograms had been inspected and ‘cleaned’, a total of 827 points from the 20 maps were deleted, leaving a median of 239.0 (IQR 166.3–358.5) per Dxl map. Of these, 43.7% of the sampled points were common to both Dxl maps (a mean of 3351 ± 1042 vertices). These points were distributed equally throughout the LA in all the 10 patients and were used in the electrogram and reproducibility analyses.

Fractionated electrograms
Of the common vertices from all the 20 Dxl maps, a mean of 42.3 ± 15.7% was in the range of 50–120 ms. These data were examined on a regional basis, and the results are presented in Table 1. The table shows that the roof and septum demonstrated the highest percentage of fractionated electrograms; however, this did not achieve statistical significance.

Reproducibility
A mean CL range of < 120 ms has been generally accepted as representing CFAE. The reproducibility of the mean CL of signals in this range is represented in Table 2 at variable delta values. With a value of 20 ms, the overall reproducibility for the mean CL of fractionated electrograms in a separate episode of AF was 76.1 ± 11.7%. Table 1 also shows reproducibility per region for fractionated electrograms at a delta value of 20 ms. There was significantly more reproducibility at the lateral anterior wall than at the septum (P = 0.028).

Table 1 Regional distribution of complex fractionated atrial electrogram

<table>
<thead>
<tr>
<th>Region</th>
<th>%CFAE</th>
<th>%Repro [50–120 ms (Δ20)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roof</td>
<td>54.4 ± 20.9</td>
<td>73.9 ± 26.3</td>
</tr>
<tr>
<td>Septum</td>
<td>49.6 ± 19.7</td>
<td>55.7 ± 22.7*</td>
</tr>
<tr>
<td>Left PV</td>
<td>45.7 ± 15.4</td>
<td>69.0 ± 30.3</td>
</tr>
<tr>
<td>Posterior wall</td>
<td>45.3 ± 21.4</td>
<td>68.4 ± 25.5</td>
</tr>
<tr>
<td>Antero-lateral</td>
<td>45.0 ± 20.3</td>
<td>76.1 ± 14.5*</td>
</tr>
<tr>
<td>Right PV</td>
<td>38.4 ± 21.1</td>
<td>63.3 ± 27.7</td>
</tr>
<tr>
<td>Mean</td>
<td>42 ± 15.7</td>
<td>76.1 ± 11.7</td>
</tr>
<tr>
<td>P-value</td>
<td>0.539</td>
<td>*0.028</td>
</tr>
</tbody>
</table>

Regions as defined previously. %CFAE represents the mean percentage of common vertices in the anatomic region within the 50–120 ms range. %Repro represents the mean percentage of signals in the 50–120 ms range (delta 20) that were reproduced at common vertices expressed for each anatomic region. *Denotes the two anatomic sites with a statistically significant difference in reproducibility with the P-value shown.
Electrogram characteristics

Data from all the 10 maps were collated and examined in terms of reproducibility (Table 3). Fully two-thirds of fractionated vertices were reproducible; however, discrimination between reproducible and non-reproducible CFAE from map 1 was not possible based on the mean CL or SD. The 50–120 ms range was roughly divided into two, depending on CL ≥ 80 ms. Although a statistically significant difference was observed in the SD of reproducible signals compared with non-reproducible signals (54.4 ± 27.6 vs. 56.0 ± 38.2, P = 0.031, respectively), there was no clinically significant discrimination of reproducible vs. non-reproducible signals based on the measure of the mean CFE-SD (Table 3).

Discussion

As catheter ablation for AF has developed, many investigators have observed CFAE within both atria but particularly within the LA. Ablation at these sites can occasionally terminate AF, and published data have provided credible evidence for targeting CFAE during catheter ablation of AF.2 However, the substrate that is being ablated is still debated. Experimental studies have shown that fractionation might occur in otherwise normal atrial tissue should the correct electrophysiological conditions be met.8 Thus, one explanation of fractionated electrograms would be a functional consequence of shortened refractory periods and anchor points for spiral waves. Another putative explanation is the innervations of parasympathetic nerve fibres resulting in local shortening of refractory period and fractionation.8,13 The third possible explanation would be an anatomic substrate due to either fibrosis or complexity in myocyte bundle architecture.15 It is possible that the aetiology of fractionated potentials involves all three putative mechanisms. Given the multifactorial origin postulated for CFAE, one might have expected that during the initiation of AF, the occurrence and location of CFAE would be dependent upon many variables and thus, although stable in each episode, be subjected to random fluctuations in position with each separate episode. The observation that this is not the case strongly supports an anatomic basis for CFAE and a ‘fixed’ pattern of disease within the atrial myocardium. This is a crucial point when considering ablative strategies for AF. Ablation of myocardium that happens to demonstrate CFAE during that episode of AF would have no rational basis if the occurrence of CFAE was random and peculiar to that specific paroxysm of AF. Our observations support a fixed anatomic substrate that presents an ablative target, as the occurrence of CFAE was not random but fixed to the same anatomic locale in the same individual. Modification of the substrate with ablation would have reduced the burden of CFAE in both episodes in our cohort.

We found that fractionated electrograms were highly conserved to within 5 mm in two distinct episodes of AF (76.1% of electrograms were reproducible at delta 20 ms). The location of reproducible CFAE was widespread (Table 1) and did not appear to favour a particular anatomic region. However, regional assessment of reproducibility suggested that CFAEs were less reproducible at the septum compared with the antero-lateral region and the other regions examined (Table 1). Complex fractionated atrial electrograms were also highly conserved on the roof of the LA.

Non-reproducible complex fractionated atrial electrogram

Approximately one-fifth of CFAE was non-reproducible at delta 20 ms. We examined the electrograms in more detail to determine the characteristics (if any) that might differentiate these electrograms from the reproducible CFAE. It was surprising to find the septum, a location traditionally associated with CFAE, was least reproducible. We examined the characteristics of reproducible electrograms further by inspecting the SD and reproducibility of signals (Table 3) but were unable to discriminate reproducible
and non-reproducible CFAE signals on the basis of these parameters despite the observation that more signals with an SD <50 ms were fractionated. This is perhaps related to the reproducibility of SD which appeared less robust than the mean CL. Data presented in Table 3 did appear to suggest that there was a stronger correlation between the SD and mean CL at shorter CL (50–80 ms, $p = 0.554$; $P < 0.001$) and showed a statistically significant difference between the SD of reproducible and non-reproducible signals that might be explored further.

Assured in the knowledge that the presence of CFAE is anatomically stable between separate episodes of AF, the pathogenesis is less likely to be functional and more related to the underlying myocardium. The observation of long fractionated electrograms in many arrhythmias heralds a ‘sweet spot’ for a re-entry circuit and target for ablation. It is less clear in AF whether a fractionated electrogram alone is sufficient to warrant ablation. The almost ubiquitous distribution of CFAE during AF in this paroxysmal group suggests that CFAE, by its current definition, will not present a subtle enough tool to detect areas critical to AF perpetuation. Further work needs to be performed to characterize the electrograms that result in the alteration of CL or termination of AF.

Limitations

We examined only 10 subjects for this protocol, and with small numbers the data should be interpreted with caution. In addition, the underlying etiology for AF appeared to be ‘lone’ for all, but we cannot assume the substrate will be the same in every individual with paroxysmal AF; indeed, patient 8 appeared to have no reproducible regular fractionated electrograms. Nonetheless, every included patient had a diagnosis of paroxysmal AF and was able to sustain 10 min of sinus rhythm before re-induction without anti-arrhythmic drugs. No patients had significant co-morbidities or structural heart disease.

The sampling time for estimating CFAE in this study was 4 s; a recent paper has suggested that 5 s was optimal for the assessment of atrial electrograms. However, the paper did not directly compare 4 and 5 s, and we considered the 4 s used in this study to be adequate for the 50–120 ms range.

Dominant frequency (DF) analysis was not used to differentiate reproducible from non-reproducible mainly because of issues with Fourier transform, making the DF unreliable with intermittent fractionated signals of variable phase and amplitude.

Thoracic veins and the coronary sinus were not mapped, as the primary objective of the study was to assess reproducibility within the LA in separate episodes of AF.

Conclusions

We present the first data on reproducibility of fractionated electrograms in two distinct and separate episodes of induced AF in humans. We demonstrated that CFAEs are highly conserved providing support for an anatomic basis for fractionation. Further investigation of the role played by CFAE in the perpetuation of AF is needed.

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Conflict of interest: none declared.

References


