Electrophysiology

The Regional Distribution and Correlation between Complex Fractionated Atrial Electrograms and Dominant Frequency during Atrial Fibrillation

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Background: Complex fractionated atrial electrograms (CFAEs) and dominant frequency (DF) mapping have been proposed to be promising targets for atrial fibrillation (AF) ablation. However, the relationship between CFAEs and DF is unknown. This study investigated the regional distribution, electrogram morphology, and spectral characteristics of complex fractionated atrial electrograms (CFAEs).

Methods: Sixteen patients with paroxysmal AF (age = 45 ± 10, male = 12) and 18 with persistent AF (age = 51 ± 13, male = 16) undergoing AF ablation were included in the study. Frequency domain analysis was performed on the intracardiac electrograms (6.82 seconds, 1 KHz/channel) recorded from each of pulmonary veins (PVs), left atrium (LA), right atrium, and coronary sinus during AF. The largest peak frequency was identified as the DF.

Results: Intracardiac atrial bipolar electrograms during AF were classified into 3 types; CFAE-I defined as rapid discrete electrograms; CFAE-II defined as continuous fractionated electrograms; and other electrograms were defined as non-CFAE. CFAE-I were found mostly in PV, while CFAE-II were observed more frequently in LA in both persistent and paroxysmal AF. CFAE-I were associated with high DF, whereas non-CFAE were associated with the low DF. CFAE-I consistently related with high DF in all areas of interest in both AF groups. However, CFAE-II was related with high DF only in PV and LA in persistent AF.

Conclusion: The disparities found between persistent and paroxysmal AF in morphology, distribution, and DF value may reflect the different roles of CFAEs in AF maintenance observed between both groups.

Key Words: Atrial fibrillation • Complex fractionated electrogram • Dominant frequency

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia, contributing to a significant morbidity and mortality. 1, 2 The multiple wavelet hypothesis by Moe et al. is well-established as one of the mechanisms of AF maintenance. 3 Nevertheless, the emerging evidence has suggested that in some episodes, AF is not a totally random process, but is maintained by stable rapid reentrant circuits with fibrillatory conduction throughout the atria. 4-7 Ablation targeted either at the fractionated potentials or dominant frequency (DF) re-
gions during AF has recently been proposed to be a novel strategy for AF ablation.8-10 The studies by Jalife’s group have demonstrated spatiotemporally organized activity during stable AF.4,11,12 Using high-density mapping, they observed that the areas harboring spiral waves which maintained the fibrillatory process were consistent with the highest DF sites and were regarded as the source of AF. Recently, Sanders et al. further reported that the high DF sites near the pulmonary vein (PV) ostia were compatible with the successful ablation sites that prolonged the AF cycle length and terminated the AF.8 Moreover, the study by Lin et al., using endocardial mapping with an Ensite system, have shown that AF reentrant sources were identified in AF patients without any thoracic vein triggers.13 In those patients, the highest DF was observed at the stationary reentrant circuits in the right atrium.

Previous studies have shown that complex fractionated atrial electrograms (CFAEs) were found mostly in the slow conduction areas or pivot points where the wavelets turn around the end of the functional block arch14 and the occurrence of CFAEs may be related to tissue anisotropy.15 According to those observations, Nademanee et al. reported that ablation performed at sites with complex fractionated atrial electrograms (CFAEs) resulted in AF termination.10

However, the relationship between the CFAEs and high-frequency activity has not been elucidated. Therefore, the purpose of the present study was to study the regional distribution of CFAEs and investigate the relationship between the atrial electrogram characteristics and DF obtained during AF in persistent and paroxysmal AF patients.

METHODS

Patient selection

Thirty-four drug-refractory AF patients who underwent AF ablation were included in the study, 16 patients with paroxysmal AF (age 45 ± 10 y/o, 12 male) and 18 with persistent AF (age 51 ± 13 y/o, 16 male).

Study protocol

Each patient underwent an electrophysiological study and catheter ablation in the fasting, nonedative state after written informed consent was obtained. After completing an intact right atrial (RA) and left atrial (LA) geometry reconstruction, if spontaneous initiation of AF did not appear, burst atrial pacing was used to induce AF. If the AF patients presented to the electrophysiology laboratory in sustained AF, all the bipolar recordings for the frequency analysis were made immediately after the transseptal puncture. Patients with induced or spontaneous initiation of AF had at least a 2-min waiting period before the bipolar recordings were made. If the patients required isoproterenol to induce the AF, the drug was discontinued after the AF occurred and a 5-min waiting period was carried out before any intracardiac recordings were made for the frequency analysis.

Data acquisition and signal analysis

The techniques used for the data acquisition and signal analysis have been described in our work previously.17 We divided areas of interest into 4 major regions consisting of PVs, LA, RA, and coronary sinus (CS), and subdivided LA and RA into 10 regions as follows; LA roof, LA posterior wall, LA appendage (LAA), LA septum, lateral mitral isthmus, SVC, crista terminalis, RA appendage (RAA), RA septum, RA anterior and lateral free wall. Both the surface ECG lead V1 and bipolar atrial electrograms obtained from a 4-mm tipped ablation catheter (EP technologies Boston Scientific, Inc., MA, USA) from the divided regions (as mentioned above) during AF were recorded sequentially using a Cardiolab system (Prucka Engineering Inc., Houston, TX, USA). Seven-second recordings were sampled at 1 KHz and stored on removable hard disc for offline analysis. Each intra-atrial recording was filtered with a second-order, zero-phase Butterworth filter at 40-250 Hz. A second-order, zero-phase filter at 20 Hz was then applied to the absolute value of the resulting signal. The attenuation of the QRS-T complex in surface ECG lead V1 was performed by an adaptive cancellation technique before the frequency analysis, which has been previously described.18 Lead V1 was chosen because it had the largest amplitude of the fibrillatory activity and represented the dominant activation of the RA according to the results of a previous study.19 The final step of the process involved the frequency analysis. A fast Fourier transform (FFT) with a Hamming window was per-
formed for each 6.82-second continuous segment from the multiple recording sites in the PVs, LA, RA and CS and ECG lead V1. Concerning the duration for FFT analysis, a longer analysis interval (over 8 seconds) may have resulted in spectral noise, which may have interfered with the identification of the DF. The largest peak frequency of the resulting spectrum was identified as the dominant frequency (DF). The ratio of the power of the DF and its harmonic peaks to the total power was defined as the regularity index (RI), representing the organization of the AF during the 6.82-second time segment. A spectrum with a dominant peak and discrete harmonics represented fewer wavelets circulating within the atria and thus a higher RI. With a higher number of wavelets, more frequency components were added to the atrial signal, which appeared in the spectrum and resulted in a lower RI. The mean number of mapping sites for the DF and intracardiac electrogram analysis was 41 sites, consisting of 8 PV mapping sites, 13 LA mapping sites, 14 RA mapping sites and 6 CS mapping sites. Regarding the reproducibility of DF value over time, previous study in this laboratory confirmed the reproducibility of DF value, obtained from recordings 5 min apart at the same sites.

Definitions of the atrial electrogram characteristics

We classified the atrial intracardiac electrograms during AF into 2 groups (Figure 1). Group I: Complex fractionated electrogram (CFAE) which was subdivided into 2 subtypes. Type I: CFAE-I was defined as rapid discrete electrograms with isoelectric segment and short cycle length < 120 ms, averaged over an 8-second recording period. Type II: CFAE-II was defined as fractionated electrograms (> 2 deflections) with continuous activity (without isoelectric segment), consistently over an 8-second recording period. Group II: Non-complex fractionated electrogram (Non-CFAE) was defined as electrograms which did not fit the definition of CFAE-I or CFAE-II.

The types of electrograms were determined by 2 investigators who were unaware of the patients’ data and clinical status. The intraobserver and interobserver variability assessment for the electrogram type showed good agreement, with interclass correlation coefficients of 0.93 and 0.94, respectively.

Statistical analysis

All continuous data were presented as the mean value ± standard deviation (SD). Comparisons between patients with persistent AF and paroxysmal AF were made with Student’s t test or chi-square test as appropriate. Statistical significance was considered when the two-sided p value was < 0.05. The regional differences in the DFs from multiple mapping sites were compared among the three electrogram types by one-way ANOVA. The post-hoc analysis by a Bonferroni correction was used to compare the mean DF between each electrogram type. Statistical significance was considered when the two-sided p value was < 0.01 after performing a Bonferroni correction.
RESULTS

The clinical characteristics of the patients with persistent AF and paroxysmal AF, including the age, gender and structural heart disease were similar. The data are presented in Table 1.

Figure 1A shows the morphologies of the three electrogram types with the associated RI. We demonstrated a difference in the RI among the three electrogram types (Figure 1B). The average RI obtained from the sites harboring CFAE-I was the highest and the average RI recorded from the sites harboring CFAE-II was the lowest, when compared among the three electrogram types, in both persistent and paroxysmal AF (p < 0.05). This finding was consistently observed in the PVs, LA, RA and CS (Figure 1B).

Regional distribution of the CFAEs

Compared among the 4 major regions consisting of the PVs, LA, RA, and CS, the CFAE-I electrograms were observed most frequently in the PV regions, whereas CFAE-II electrograms were observed mostly in the LA, in both persistent (p < 0.05) and paroxysmal AF patients (p < 0.05).

The regional distribution of the electrogram morphology in persistent and paroxysmal AF patients among 4 major regions is shown in Figure 2. In the PV region, CFAE-I electrograms were found more often in persistent than paroxysmal AF (p < 0.05), while CFAE-II electrograms were found comparably in both groups (Figure 2A). On the contrary, in the LA region, CFAE-II electrograms were observed more often in persistent AF (p < 0.05), but CFAE-I electrograms were present similarly in both groups (Figure 2B). With respect to subdivided regions in LA, we found that the LA roof, LA posterior wall and LA septum were the most common sites

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Paroxysmal AF</th>
<th>Persistent AF</th>
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<tbody>
<tr>
<td>N</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>12 (75)</td>
<td>16 (88)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>45 ± 10</td>
<td>51 ± 13</td>
</tr>
<tr>
<td>LA dimension (mm)</td>
<td>36 ± 6</td>
<td>39 ± 4</td>
</tr>
<tr>
<td>LV diastolic dimension (mm)</td>
<td>48 ± 4</td>
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<tr>
<td>LV ejection fraction (%)</td>
<td>60 ± 7</td>
<td>55 ± 7</td>
</tr>
<tr>
<td>Structural heart disease (%)</td>
<td>37</td>
<td>38</td>
</tr>
</tbody>
</table>

Figure 2. Regional distribution of the three electrogram types during AF in persistent and paroxysmal AF patients. (A)-(D) show the incidences of different electrogram types found in the PVs, LA, RA and CS, respectively. (N indicates the total number of electrogram recording sites in each region). Abbreviations as in Figure 1.
of CFAE-II in persistent AF group, whereas LA septum was the most common CFAE-II site in paroxysmal AF patients. In the RA and CS regions, the CFAE-I and CFAE-II electrograms were observed comparably in both the persistent and paroxysmal AF groups (Figures 2C and D).

The relationship between the CFAEs and DF

We demonstrated the relationship between the atrial electrogram characteristics and corresponding DF according to the 4 different major regions; PVs, LA, RA and CS, in paroxysmal and persistent AF patients (Figure 3).

There were significant differences in DF among the three electrogram types in each of the 4 regions in both persistent and paroxysmal AF patients (p < 0.01). In the paroxysmal AF group (Figure 3A), in all 4 regions, the average DF obtained from the sites harboring CFAE-I was the highest and that from the sites harboring non-CFAE was the lowest, when compared among the three electrogram types (p < 0.01).

In the persistent AF group (Figure 3B), we observed findings similar to those of paroxysmal AF in RA and CS regions. However, in the PVs and LA regions, the average DF from the CFAE-I sites and the CFAE-II sites were not different, both were higher than the average DF obtained from the non-CFAE sites (p < 0.01).

Figures 4A-D show a comparison between the persistent and paroxysmal AF patients in terms of the average DF recorded from the sites harboring each of the three electrogram types from PVs, LA, RA and CS regions, respectively. We demonstrated that there were no differences between persistent and paroxysmal AF pa-
tients in average DF from the CFAE-I sites in any of the regions (p > 0.05). Nevertheless, the average DF obtained from the CFAE-II sites was significantly higher in persistent AF, compared to paroxysmal AF patients in PV and LA regions (p < 0.05), but not in RA and CS regions (p > 0.05). With respect to the subdivided areas of LA, we found that the DF of the CFAE-II sites were significantly higher in persistent AF than paroxysmal AF patients only in LAA (7.8 ± 1.6 Hz vs. 6.4 ± 0.8 Hz, p < 0.05) and LA septum (7.3 ± 1.6 Hz vs. 6.2 ± 1.0 Hz, p < 0.05), whereas no differences were found in the LA roof, LA posterior wall and lateral isthmus.

DISCUSSION

We demonstrated the major findings as follows: (1) Different types of CFAE could be characterized by the electrogram morphology, regional distribution, and the frequency analysis results; (2) the rapid repetitive electrograms (CFAE-I) were found mostly in the PVs, while CFAE-II electrograms were observed more frequently in the LA; (3) the CFAE-I electrograms were consistently associated with the high DF and RI value in all areas of interest, including the PVs, LA, RA and CS, in both persistent and paroxysmal AF. However, the CFAE-II electrograms were associated with the lower RI, and the high DF only in the PVs and LA, particularly in LAA and LA septum in persistent AF.

Relationship between the DF and electrogram characteristics

A recent experimental study by Kalifa et al. showed that the highest DF areas harbored the most regular, fastest, and most highly organized activity, while the surrounding areas harbored the irregular fractionated activity. Therefore, with respect to this model, the AF sources are likely to present with rapid-organized electrograms with the highest DF, while the surrounding area with fibrillatory conduction may exhibit more irregular-activity electrograms and lower DF.

According to our findings, the CFAE-I corresponding to the rapid-discrete electrograms was significantly associated with a higher RI as compared to the other two electrogram types. Previous studies showed that the higher RI reflected more organized fibrillation waves. As we found that CFAE-I is consistently associated with the high DF harbored areas, it is therefore likely that CFAE-I may represent the driver areas, which corresponds to the findings reported by Kalifa et al. In addition, previous study from our group demonstrated the relationship of bipolar repetitive (CFAE-I) and continuous (CFAE-II) CFAEs with non-contact unipolar electrograms. Most of the CFAE-I electrograms in both paroxysmal and persistent AF were found associated with an S-wave-predominant unipolar morphology, which were representative of an arrhythmogenic ectopic site and pivot point of the wavefronts. Moreover, in the present study, CFAE-I electrograms were observed mostly in the PVs. These findings reinforce the importance of the PVs in the maintenance of AF, in which they function as a breakthrough point of a rotor or triggering focus in both persistent and paroxysmal AF patients.

We found that the CFAE-II electrograms which corresponded to the continuous fractionated electrograms were more significantly associated with lower RI than did those obtained from the sites harboring CFAE-I and non-CFAE electrograms, implying that CFAE-II electrograms may be associated with less organized fibrillation waves than the other two types. In all regions in the paroxysmal AF patients and only in the RA and CS regions in the persistent AF patients, the DF obtained from the sites harboring CFAE-II electrograms was significantly lower than that in the CFAE-I sites. These findings, again, were consistent with the study by Kalifa et al., which showed that the area harboring the high fragmentation potentials may not always represent the high DF area, particularly in paroxysmal AF patients. Similarly, our previous study of unipolar electrograms and CFAEs showed that most of CFAE-II electrograms were associated with passive activation or slow conduction. Altogether, these may explain the clinical observation in paroxysmal AF patients that only PV isolation without ablation at the continuous fractionated electrogram areas (CFAE-II) could cure AF in the majority of patients.

Interestingly, we observed that the DF obtained from the sites harboring CFAE-II electrograms were associated with high DF and did not differ from the DF obtained from the sites harboring CFAE-I electrograms in the PVs and LA regions from persistent AF patients. Correspondingly, Nademanee et al. reported the highly
successful AF termination rate when radiofrequency ablation was applied at the continuous fractionated electrogram areas in the study consisting of a considerable number of persistent AF patients. According to the unipolar electrograms study by our group, 23 25% of the CFAE-II electrograms were associated with the pivot of turning points and 3% of those were found near by the firing ectopies. These findings may suggest the important role of the continuous fractionated electrograms (CFAE-II) in persistent AF in AF maintenance and indicated the potential culprit ablation target, particularly in the PVs and LA. On the other hand, in paroxysmal AF patients, and in the RA and CS regions of persistent AF patients, as mentioned above, the CFAE-II electrograms may represent the passive activation or slow conduction and may not be the important target sites for AF ablation. Considering the extensive area of CFAE-II demonstrated in LAs of our persistent AF patients, the question of whether if we should ablate all the CFAEs area in this group of patients remains unanswered. As we demonstrated in the present study that the DF of CFAE-II sites in LAA and LA septum were associated with the high DF, the CFAE-II electrograms present in these particular areas may be considered as the potential target for ablation. Further studies are needed to address this issue.

Limitations of study
Among 16 patients with paroxysmal AF, six of them had spontaneous sustained AF before the mapping procedure, while the other 10 patients were in sinus rhythm and received provocation of AF (with rapid coronary sinus pacing, with or without an isoproterenol infusion) before the catheter ablation procedure. The different methods used for AF induction in our study may have changed the characteristics of intracardiac atrial electrograms during AF.

CONCLUSION
We characterized the different types of complex fractionated electrogram by electrogram morphology and frequency characteristics. The CFAE-I electrograms harbored in any area in both persistent and paroxysmal AF and the CFAE-II electrograms harbored in PV and LA, particularly in LAA and LA septum in patients with persistent AF, were associated with high DF. The disparities found between persistent and paroxysmal AF may reflect the different roles of CFAEs in the maintenance of AF between both groups.

REFERENCES


