Dominant Frequencies and Fractionation Intervals:
A Comparison of Bipolar and Unipolar Electrogram-Derived Values

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Background: Sites of high dominant frequency (DF) and complex fractionated atrial electrograms (CFAEs) are used as ablation targets to eliminate atrial fibrillation (AF). These sites are identified using spectral and time domain analyses. The frequency spectrum of the signal is determined by its cycle length as well as the morphology and amplitude of the electrogram, and these factors can affect the DF analysis. We determined the DFs, mean AF cycle lengths (fractionation intervals [FIs]), and voltages from bipolar and unipolar electrograms—and compared the values derived from the 2 types of recordings.

Methods: Five patients with paroxysmal AF and 5 patients with persistent AF were included in the study. High-density unipolar electrograms recorded through a band-pass filter of 1–400 Hz and bipolar electrograms recorded through a band-pass filter of 30–400 Hz were obtained with the use of a 20-pole circular mapping catheter positioned in the left atrium (LA), and DF, AF cycle length, and unipolar and bipolar voltages during sinus rhythm (SR) were analyzed with the use of NavX software.

Results: While the unipolar FIs were longer than the bipolar FIs, the bipolar and unipolar DFs were similar. The SR voltages of the unipolar and bipolar electrograms at CFAE sites (FIs <120 msec) were higher than those at the non-CFAE sites, but did not differ between the high DF (>8 Hz) and other DF sites. Overlap between the CFAE sites and the high DF sites identified from both bipolar and unipolar electrograms was only 7.9%.

Conclusion: FIs and DFs may represent different electrophysiologic substrates.

Key words: unipolar electrogram, bipolar electrogram, atrial fibrillation, dominant frequency, complex fractionated atrial electrogram

Introduction

Eliminating the triggers of atrial fibrillation (AF) through electrical isolation of the pulmonary veins (PVs) has been the basis of most AF ablation strategies to date1). However, alternative ablation approaches that target specific AF signals to modify the substrate responsible for AF perpetuation have been proposed2–5). Complex fractionated atrial electrograms (CFAEs) derived from time domain analysis and dominant frequencies (DFs) identified by Fast Fourier Transform (FFT) spectral analysis have been widely used as electrical parameters for understanding the initiation and perpetuation of AF6–12). However, less than 50% overlap between the CFEA and high DF regions has been shown, and CFAE values have been shown to depend on the inter-electrode distance, whereas DFs do not13,14). In addition, the frequency spectrum of a signal is determined not only by its cycle length but also by the morphology and amplitude of the electrogram, and these factors can affect the DF analysis15). Furthermore, the influence of wavefront propagation direction on the CFAE and DF is not determined yet. Thus, we conducted a prospective study to compare the AF cycle length by time domain analysis and DF by spectral analysis from unipolar and bipolar electrograms.

Material and Methods

1. Study patients

The study group comprised 10 consecutive patients (5 men, 5 women; mean age: 66.9 ± 10.4 years) scheduled for their first catheter ablation of AF. Five had paroxysmal AF (PAF: AF lasting less than 7 days), and 5 had persistent AF (PerAF: AF lasting 7 days or more). No patient with cardiomyopathy, valvular heart disease, or congenital heart disease was included in the study. Adequate oral anticoagulation therapy was given for at least 1 month before the ablation procedure, and all antiarrhythmic drugs were discontinued for at least 5 half-lives before the procedure. Upon admission, transesophageal and
Electrophysiologic study

Electrophysiologic study was performed in all patients under conscious sedation achieved with dexmedetomidine, propofol, and fentanyl, as described previously. After vascular access was obtained, a single transseptal puncture was performed, and intravenous heparin was administered to maintain an activated clotting time of more than 300 seconds. After 2 long sheaths (1 SL0 sheath and 1 Agilis sheath; St. Jude Medical, Inc., St. Paul, MN, USA) were inserted into the LA via a transseptal puncture, the 3D geometry of the LA and the pulmonary veins (PVs) was reconstructed with the use of an EnSite NavX Classic system (St. Jude Medical, Inc.) and a 20-pole circular mapping catheter with 4-4-4-mm interelectrode spacing (AFocus II catheter, St. Jude Medical, Inc.). We recorded multiple unipolar and bipolar signals (filter setting: 1–400 Hz and 30–400 Hz, respectively) simultaneously during sinus rhythm (SR) and during AF. If the patient was in SR, AF was induced by rapid atrial pacing from the coronary sinus ostium, and the CFAEs and DFs were recorded 5 minutes after AF induction. If the patient was in AF, SR electrograms were recorded after cardioversion. The reference electrode (4F, quadripolar catheter, St. Jude Medical) for unipolar electrogram recording was placed at the aortic cusp via the left femoral artery.

3. Bipolar and unipolar signal recordings

Nineteen bipolar electrograms (12...19–20) and 20 unipolar electrograms (1...20) were recorded simultaneously from the 20-pole circular catheter for 5 seconds during SR and AF simultaneously from the 20-pole circular catheter. For the FFT analysis, the DF (highest power frequency) was analyzed by the DF software installed in the NavX mapping system (sampling rate: 1200 Hz; resolution: 0.14 Hz; low-pass filter: 20-Hz; Hamming-windowed high-pass filter: 1-Hz) as previously reported. Five-second bipolar signals recorded during AF were used for the DF analysis. A high DF site was defined as a site with a frequency of >8 Hz. The regularity index was taken as the area within the 0.75-Hz band around the DF divided by the area of sampled frequencies of 3–14 Hz. Regularity indices of <0.2 were excluded from the analysis.

6. LA segmentation

The LA was divided into 7 segments (LA anterior, LA septum, LA floor, LA posterior, LA roof, LA appendage, and LA mitral isthmus) (Fig. 1), and CFAE sites, high DF sites, and bipolar and unipolar electrogram amplitudes at CFAE and non-CFAE sites, and high-DF and DF < 8 Hz sites were compared for each segment. Percentage of the overlapped segment(s) of the bipolar CFAE and bipolar high-DF and percentage of the overlapped segment(s) of the unipolar CFAE and unipolar high-DF among the 7 LA segments, and percentage of the overlapped segment(s) of the bipolar and unipolar CFAE and percentage of the overlapped segment(s) of the bipolar and unipolar high-DF among the 7 LA segments were calculated.

7. Statistical analysis

Continuous variables are expressed as mean ± SD values. Baseline echocardiographic variables were compared between the PAF and PerPAF patients. Mean FIs and mean DFs were compared between the bipolar and unipolar electrograms. Mean bipolar and unipolar SR voltages were analyzed in relation to bipolar and unipolar mean FIs classified as ≤120 ms or >120 ms, and mean bipolar and unipolar SR voltages were also analyzed in relation to bipolar and unipolar DFs classified as >8 Hz or ≤8 Hz. The final comparisons were performed between the percentages of CFAE-positive LA segments identified from the bipolar and...
For the purpose of the study, the LA was divided into 7 segments. Modified from Kumagai K, et al. (ref. 12)

Table 1 Mean bipolar and unipolar voltages per FIs measured on local bipolar and unipolar electrograms recorded during SR

|                       | ≤ 120 ms | > 120 ms | p Value |
|-----------------------|----------|----------|---------|
| **Bipolar mean FI**   |          |          |         |
| Bipolar SR voltage (mV) | 2.7 ± 1.0 | 2.1 ± 1.0 | 0.00436 |
| Unipolar SR voltage (mV) | 2.9 ± 1.4 | 1.9 ± 0.7 | 0.0167  |
| **Unipolar mean FI**  |          |          |         |
| Bipolar SR voltage (mV) | 3.0 ± 1.0 | 1.8 ± 0.6 | < 0.0001 |
| Unipolar SR voltage (mV) | 3.1 ± 1.4 | 1.9 ± 0.8 | 0.0004  |

Table 2 Mean bipolar and unipolar voltages per high DFs vs. other DFs derived from local bipolar and unipolar electrograms recorded during SR

|                       | > 8 Hz | ≤ 8 Hz | p Value |
|-----------------------|--------|--------|---------|
| **Bipolar DF**        |        |        |         |
| Bipolar SR voltage (mV) | 2.3 ± 1.0 | 2.6 ± 1.1 | 0.4653  |
| Unipolar SR voltage (mV) | 2.2 ± 1.0 | 2.8 ± 1.4 | 0.3727  |
| **Unipolar DF**       |        |        |         |
| Bipolar SR voltage    | 2.4 ± 0.7 | 2.7 ± 1.1 | 0.3869  |
| Unipolar SR voltage   | 2.3 ± 0.8 | 2.8 ± 1.4 | 0.2440  |

DF, dominant frequency; SR, sinus rhythm.

unipolar electrograms and between the percentages of high DF-positive LA segments identified from the 2 types of recordings. Differences were analyzed by Mann-Whitney U test. All statistical analyses were performed with JMP 8 software (SAS Institute, Cary, NC, USA), and p < 0.05 was considered significant.

Results

1. Patients’ baseline echocardiographic characteristics

In comparing patients’ baseline echocardiographic characteristics, we found that the LA dimension and LA volume were significantly greater in the PerAF group than in the PAF group (LA dimension: 42.3 ± 6.8 mm vs. 35.9 ± 5.5 mm, respectively [p = 0.0038] and LA volume: 61.0 ± 21.1 cm³ vs. 37.3 ± 11.4 cm³ vs. respectively [p = 0.0019]), but left ventricular ejection fraction (59.3 ± 6.6% vs. 62.2 ± 4.4%, respectively [p = 0.13]) did not differ significantly between the 2 groups.

2. Mean FIs and DFs on bipolar and unipolar electrograms

The mean FI obtained from bipolar electrograms (97.4 ± 29.5 ms) was significantly shorter than that obtained from the unipolar electrograms (111.5 ± 26.9 ms).
**CFAEs and DFs from Unipolar and Bipolar Electrograms Recorded during AF**

**Table 3** Percentages of CFAE-positive and high DF positive LA segments* determined by analyses of bipolar and unipolar electrograms

|                      | Bipolar | Unipolar | Overlapped segments (%) |
|----------------------|---------|----------|-------------------------|
| CFAE site (% of LA segments) | 81.0 ± 15.1 | 68.3 ± 33.5** | 58.7 ± 31.9 |
| High DF site (% of LA segments) | 9.5 ± 15.1 | 17.5 ± 18.8† | 1.6 ± 4.5 |
| Overlapped segments (%) | 7.9 ± 11.9 | 7.9 ± 13.7 | |

CFAE, complex fractionated atrial electrogram; DF, dominant frequency.

*The LA was divided into 7 segments.

**p = 0.1720 vs. bipolar CFAE sites; †p = 0.5000 vs. bipolar high DF sites.

ms, p = 0.0011), but the mean DFs obtained from the bipolar (7.0 ± 0.9 Hz) and unipolar electrograms (7.3 ± 1.8 Hz) did not differ significantly (p = 0.211).

### 3. FIs obtained from bipolar and unipolar SR electrograms and bipolar and unipolar SR electrogram voltages

Mean FIs derived from the bipolar and unipolar electrograms recorded during SR were classified as ≤120 ms or >120 ms. The bipolar and unipolar voltages recorded during SR are shown per FI classification in Table 1. The mean bipolar and unipolar voltages at FI ≤120 ms were significantly higher than those at FI >120 ms.
4. DFs obtained from bipolar and unipolar SR electrograms and bipolar and unipolar SR electrogram voltages

Mean DFs derived from the bipolar and unipolar electrograms recorded during SR were classified as >8 Hz or ≤8 Hz, and the bipolar and unipolar voltages recorded during SR are shown per DF classification in Table 2. The mean bipolar and unipolar electrogram voltages recorded during SR at did not differ significantly between DF > 8 Hz and DF ≤ 8 Hz.

5. CFAE sites and high DF sites determined from unipolar and bipolar electrograms

We counted the numbers of LA segments in each patient that, according to the bipolar and unipolar electrograms, contained ≥1 CFAE site(s) out of the 5 electrograms and those that contained ≥1 high DF site(s) out of the 5 electrograms. We then calculated the percentages of the total 70 segments (7 LA segments × 10 patients) with each of these features. We also counted the number of overlapping sites in each patient, with overlap defined as the existence of ≥1 CFAE and ≥1 high DF site in the same segment, and we calculated the percentage of overlapping sites as the number of segments with overlapping sites/7. An example of the distribution of CFAE sites, high DF sites, and low voltage sites within the LA in a patient with PerAF is shown in Fig. 2. The overall percentages of CFAE sites, high DF sites, and overlapping sites are shown in Table 3. The percentage of CFAE-positive segments identified from the bipolar electrograms tended to be greater than that derived from the unipolar electrograms, whereas the percentage of high DF-positive segments derived from the bipolar electrograms tended to be lower than that derived from the unipolar electrograms. There was no difference in the percentages of overlapping CFAE-positive and high DF-positive segments derived from the unipolar vs. bipolar electrograms. Overlap of unipolar and bipolar CFAE segments was greater than that of high DF segments.

Discussion

1. Major findings

In this study, we examined correspondence between mean AF cycle lengths derived from time-domain analysis and DFs derived from frequency-domain analysis of local bipolar and unipolar electrograms to qualify local activation, and we found that: (1) mean AF cycle lengths (described as FIs) derived from the unipolar electrograms were significantly longer than those derived from the bipolar electrograms, but the DFs derived from unipolar and bipolar electrograms were similar; (2) the bipolar and unipolar electrogram amplitudes during SR were significantly greater at FIs ≤ 120 ms (CFAE sites) than at FIs > 120 ms, but the bipolar and unipolar electrogram amplitudes did not differ significantly between sites with DFs > 8 Hz (high DF) and those with DFs ≤ 8 Hz; and (3) the percentages of LA CFAE segments determined from both bipolar and unipolar electrograms were greater than the percentages of high DF-positive segments. LA segment(s) of CFAE identified from bipolar and unipolar electrograms was similar (81.0% vs. 68%), LA segment(s) of high DF identified from bipolar and unipolar electrograms was similar (9.5% vs. 17.5%). Furthermore, overlapping segment(s) of the CFAE identified from the bipolar and unipolar electrograms was higher than overlapping segment(s) of the high DF identified from the bipolar and unipolar electrograms (57.7% vs. 1.6%).

2. Effect of electrogram characteristics on the relation between DF and FI

Earlier works have shown that DFs correspond well with, but do not specifically reflect, mean or median activation rates. DFs were significantly influenced by variation in the signal frequency, combined amplitude and frequency variation, ordering of the activation intervals, and identification of local activation. DFs from unipolar and bipolar electrograms recorded during AF have also been shown to correlate poorly with mean, median, and modal FIs, and areas with the shortest FIs do not correspond to areas of the highest DFs in the majority of cases. Berenfeld et al., in an experimental study, found good correlation between DFs obtained from bipolar and unipolar electrical signals and DFs obtained from optical signals but poor correlation between FIs obtained from bipolar and unipolar electrical signals and FIs obtained from optical signals. Lau et al. reported poor correlation between CFAEs derived from bipolar electrograms and fractionation indices derived from unipolar electrograms, increases in bipolar CFAEs with increases in inter-electrode spacing, and good correlation between unipolar fractionation indices and AF substrate complexity measures, indicating that the unipolar fractionation index can serve as a marker for conduction block. We too have shown that the FIs decreased with increases in bipolar inter-electrode spacing, whereas the DFs were not influenced by the inter-electrode spacing, but the regularity index, and organization index were reduced. Therefore, electrogram characteristics, i.e., bipolar vs. unipolar electrogram characteristics and inter-electrode spacing should be considered for evaluating FIs in particular.

3. LA voltages in SR and AF

We showed previously that most CFAE and high DF sites do not correspond to the low voltage areas
during SR\textsuperscript{22}. In the present study, we demonstrated that SR unipolar and bipolar voltages at the CFAE sites were higher than non-CFAE sites, but that SR unipolar and bipolar voltages at the high DF sites did not differ from no high DF sites.

Previously reported studies have also shown that areas of CFAEs derived from bipolar and unipolar recordings are frequently characterized by normal bipolar and unipolar voltages during SR\textsuperscript{23–25}. Furthermore, LA wall thickness correlated well with CFAE areas, and also higher unipolar voltage sites were associated with thicker LA wall thickness\textsuperscript{26,27}. Therefore, CFAEs probably represents a focal driver or source occurring in a region of normal atrial myocardium or the response of normal healthy atrial tissue to rapid PV activation. Data we obtained in the present study confirmed that bipolar and unipolar SR voltages are significantly greater within the bipolar and unipolar CFAE areas than within the non-CFAE areas. However, bipolar and unipolar SR voltages do not differ between high DF areas and other DF areas.

4. Relation between FI sites and highest DF sites

Previous clinical studies have revealed poor point-by-point correlation between FIs and DFs and different distribution patterns for high DFs and areas of high fractionation\textsuperscript{28,29}. Lee et al. reported poor point-by-point correlation between CFAEs and high DF sites but that CFAEs were found adjacent to and partially surrounding (≤5 mm) high DF sites\textsuperscript{30}. Verma et al. reported a significant, inverse correlation between DF and CFAE values at each recording site but overlap of only about 50% between high DF and CFAE sites\textsuperscript{31}. We found 7.9% overlap between the CFAE and high DF sites calculated from bipolar and unipolar electrograms. Verma et al. demonstrated that AF termination occurred on overlapping CFAE/DF sites where DF was above the mean. However, prospective ablation of DF (>8 Hz) sites plus PVI resulted in low AF termination rates, and did not improve 1-year success over PVI alone\textsuperscript{32}. Kumagai et al. demonstrated that a combined high-DF (≥8 Hz) and continuous CFAE site ablation in all chambers after circumferential PVI were effective for long-term outcome in the PAF and PerAF patients\textsuperscript{33}. Verma et al. demonstrated that no reduction in the rate of recurrent AF when ablation of CFAEs was performed in addition to PVI in patients with persistent atrial fibrillation\textsuperscript{34,35}. Jadidi et al. reported that all sites with CFAEs in atrial fibrillation displayed normal voltage in sinus rhythm, suggesting absence of structural scar, and atrial fibrosis is associated with slower and more organized electrical activity but with lower voltage than healthy atrial areas\textsuperscript{36,37}. Thus, the pathophysiologic roles of CFAE and high DF sites in the maintenance of AF remain controversial.

5. Clinical implications

The unipolar FIs and bipolar FIs did not match, but the bipolar and unipolar DFs demonstrated similar values. SR voltages of the unipolar and bipolar electrograms at CFAE sites were higher than those at other CFAE sites, but SR voltages did not differ between the high DF and other DF sites. Furthermore, overlap of the CFAE sites and high DF sites identified from both bipolar and unipolar electrograms was only 7.9%. Thus, CFAE and high DF values might be influenced by the wavefront propagation direction during AF, filter setting and underlying atrial voltage. Therefore, further studies are needed to compare the efficacy of bipolar and unipolar electrogram-based CFAE- and high DF-based ablation.

6. Study limitations

Our main study limitation was the small sample size, therefore, we did not separate the data from PAF and PerAF patients. In addition, we used the NavX system-automated algorithm to define and detect FIs and DFs. We cannot rule out the possibility that use of a different automated algorithm with a different mapping system or use of a mapping catheter with different inter-electrode spacing would have yielded different results. Our study included patients with PAF and patients with PerAF, all of whom had preserved left ventricular function and for whom cardioversion prior to ablation was feasible. Thus, our findings may not necessarily apply to the broader AF population.

Conclusion

Our study results indicate that FIs determined by time domain analysis of bipolar and unipolar electrograms differ in value, but DFs determined by frequency domain analysis of bipolar and unipolar electrograms are similar in value. SR voltage at CFAE sites is greater than that at non-CFAE sites, but SR voltage does not differ significantly between high DF sites and other sites. Overlap of CFAE and high DF sites determined by analysis of either bipolar or unipolar electrograms is rather small. Therefore, FIs and DFs may represent different electrophysiologic substrates.

Disclosure

No financial support was received from any specific company of agency for this study.

Conflict of Interest

The authors have no conflicts of interest related to this study.
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