Spectral Profiles of Complex Fractionated Atrial Electrograms Are Different in Longstanding and Acute Onset Atrial Fibrillation Atrial Electrogram Spectra

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Spectral Profiles of CFAE. ***Background:*** **Spectral analysis of complex fractionated atrial electrograms (CFAE) may be useful for gaining insight into mechanisms underlying paroxysmal and longstanding atrial fibrillation (AF). The commonly used dominant frequency (DF) measurement has limitations.**

Method: **CFAE recordings were acquired from outside the 4 pulmonary vein ostia and at 2 left atrial free wall sites in 10 paroxysmal and 10 persistent AF patients. Two consecutive 8s-series were analyzed from recordings >16s in duration. Power spectra were computed for each 8s-series in the range 3–12 Hz and normalized. The mean and standard deviation of normalized power spectra (MPS and SPS, respectively) were compared for paroxysmal versus persistent CFAE. Also, the DF and its peak amplitude (ADF) were compared for pulmonary vein sites only. Power spectra were computed using ensemble average and Fourier methods.**

Results: **No significant changes occurred in any parameter from the first to second recording sequence. For both sequences, MPS and SPS were significantly greater, and DF and ADF were significantly less, in paroxysmals versus persistents. The MPS and ADF measurements from ensemble spectra produced the most significant differences in paroxysmals versus persistents ($P < 0.0001$). DF differences were less significant, which can be attributed to the relatively high variability of DF in paroxysmals. The MPS was correlated to the duration of uninterrupted persistent AF prior to electrophysiologic study ($P = 0.01$), and to left atrial volume for all AF ($P < 0.05$).**

Conclusions: **The MPS and ADF measurements introduced in this study are probably superior to DF for discerning power spectral differences in paroxysmal versus longstanding CFAE.** *(J Cardiovasc Electrophysiol, Vol. 23, pp. 971-979, September 2012)*

atrial fibrillation, catheter ablation, complex fractionated atrial electrograms, Fourier, spectral profile

Background

Previously it has been shown that complex fractionated atrial electrogram (CFAE) recordings collected during paroxysmal atrial fibrillation (AF) manifest a relatively low degree of repetitiveness, and a higher degree of nonuniformity, particularly at the antral regions outside the ostia of the pulmonary veins (PVs), compared to similar recordings collected in patients with longstanding AF.[1] As evolution to persistent, longstanding AF occurs, the repetitive patterns in CFAE recordings become more prominent, resulting in a more uniform distribution of CFAE parameter values at disparate left atrial (LA) sites.[1] These prior measurements were done using the methods of linear prediction and Fourier reconstruction, quantifying the degree of periodicity in the CFAE signals indirectly. If the frequency spectra of CFAE could be quantitatively interpreted, then the detection of a relatively high degree of periodicity would be expected in the presence of discrete, disparate stationary sources of electrical activity driving AF, such as a stable rotor, a site-specific reentrant circuit, or a focal high-frequency firing. By contrast, if AF is driven by meandering rotors or secondary wavefronts resulting from changing wavebreak locations at the periphery of a source,[2] a different frequency spectrum may emerge, and these differences in CFAE spectra should be observable.

A major problem in detecting independent sources in CFAE recordings is the fact that harmonic interactions can render the frequency spectrum ambiguous.[3-6] This is especially a problem when constructing the Fourier power spectrum to analyze CFAE for the dominant frequency or DF.[7,8] Many harmonics may be needed to represent a unique source of electrical activation in the Fourier power spectrum, depending on the complexity of the signal produced by the source. The ensemble average spectrum is constructed from the ensemble average at each frequency,[9-11] so that if a particular source of electrical activity consists of only 1 periodic frequency component, regardless of whether or not it is sinusoidal, a single peak will appear in the ensemble average spectrum—no harmonics are needed to represent it. Yet, there can still be interactions between harmonics when they are present, as well as presence of subharmonics, which are spectral peaks at fractional values of the fundamental frequency ($^1/_2$, $^1/_3$, $^1/_4$, ...), in the ensemble average spectra.[9-11]

The clinical question is how to make use of the frequency spectrum to gain insight into the mechanisms underlying AF. In the present work we present a method to quantify

No disclosures.

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Manuscript received 28 December 2011; Revised manuscript received 9 March 2012; Accepted for publication 9 March 2012.

doi: 10.1111/j.1540-8167.2012.02349.x

periodicity directly from the spectral characteristics of CFAE, thus eliminating the need for selection of a DF. We also introduce a method to remove harmonic interactions from the ensemble average power spectra using an antisymmetry technique, expecting to detect remaining spectral peaks that might be more representative of independent sources of electrical activity maintaining AF. Based on our previous work,[1,12] we hypothesize that CFAE spectra of longstanding AF, with its higher degree of periodicity, can be distinguished from that of acute-onset AF in patients with paroxysmal AF, reflecting their underlying mechanistic differences.

Methods

Clinical Data and the Electrophysiology Procedure

Atrial electrograms were recorded in a series of 20 patients referred to the Columbia University Medical Center cardiac electrophysiology (EP) laboratory for catheter ablation of AF. These recordings were obtained prospectively as approved by the Institutional Review Board at Columbia University Medical Center, but analyzed retrospectively after the catheter ablation procedures were completed using our standard clinical protocols. Ten patients had documented clinical paroxysmal AF, and all 10 had normal sinus rhythm as their baseline cardiac rhythm in the cardiac electrophysiology laboratory. AF was induced acutely by burst atrial pacing from the coronary sinus or right atrial lateral wall, and allowed to persist for at least 10 minutes prior to data collection. Patients in whom only short runs of AF were inducible were excluded from this study. Ten other patients had longstanding persistent AF, and had been in AF without interruption for 6 months to 6 years prior to their catheter mapping and ablation procedure. The duration of uninterrupted AF in these patients was estimated as the period from the time of recurrence of AF after the last direct-current (DC) cardioversion (which converted AF to sinus rhythm) to the day of the catheter ablation procedure. Bipolar atrial mapping was performed with a NaviStar ThermoCool catheter, 7.5 F, 3.5 mm tip, with 2 mm spacing between bipoles (Biosense-Webster Inc, Diamond Bar, CA, USA). The electrogram signals were acquired using the GE CardioLab system (GE Healthcare, Waukesha, WI, USA), and filtered at acquisition from 30 to 500 Hz with a single-pole bandpass filter to remove baseline drift and high frequency noise. The filtered signals were digitally sampled by the system at 0.977 KHz and stored. Although the bandpass high end was slightly above the Nyquist frequency, negligible CFAE signal energy resides in this frequency range.[10]

Only signals identified as CFAEs by 2 cardiac electrophysiologists were included in this analysis.[9,10,12] CFAE recordings of at least 10 seconds in duration were obtained from 2 sites outside the ostia of each of the 4 PVs. Similar recordings were obtained at 2 LA free wall (FW) sites, one in the mid posterior wall (POS), and another on the anterior ridge at the base of the LA appendage (ANT). The mapping catheter was navigated in these prespecified areas until a CFAE site was identified. In 1 patient with clinical paroxysmal AF, during acutely induced AF, no recording site outside the PVs with recordings satisfying CFAE criteria for at least 10 seconds could be detected. Therefore, data from this patient were not included in the following analysis. From each of the recordings mentioned above, when a CFAE sequence over 16.8s was recorded during AF, 2 consecutive 8.4s series were extracted and analyzed. Only sites at which the CFAE criteria were maintained during the recorded sequence were used for analysis. A total of 204 sequences—90 from paroxysmal and 114 from longstanding AF patients, all meeting the criteria for CFAE—were chosen for this study and included in the following analysis. As in the previous studies, to standardize the morphological characteristics, all CFAE signals were normalized to mean zero and unity variance (average level = 0 volts, standard deviation = 1).[11]

Generation of Ensemble Average Spectra

Ensemble average spectra were generated as described in detail previously.[9-11] The ensemble average spectrum is constructed by segmenting CFAE using a window width w. The n segments are summed and divided by n to form the ensemble average. The power in the ensemble average for each w is plotted versus the corresponding frequency:

$$f = \text{rate}/w \quad (1)$$

The method has been shown to be robust to phasic and random noise as compared with Fourier analysis.[10,11] The mathematical details of the spectral analysis and use of this method for signal reconstruction have been described.[11]

Spectral Measurements After Removal of Second Harmonic Interactions

To remove the second harmonic, which is usually the predominant sub- or superharmonic, an antisymmetry technique was applied to each ensemble average.

Antisymmetry is imparted by taking the average of x segments of the ensemble, and subtracting this average from each segment. For example, if the ensemble has a length of 100 points and x = 2, then the segment from 1 to 50 points is averaged with the segment from 51 to 100 points, and this average is subtracted from each segment. The result is that the power of the second harmonic is removed from this ensemble. We wanted to determine whether removal of second harmonic interactions could be used to enhance the distinguishing characteristics of CFAEs recorded during paroxysmal versus longstanding AF. Spectra were constructed from each CFAE recording with no harmonic removal and with second harmonic removal in the frequency range 3–12 Hz, which encompasses the range within which a DF might be present. Each spectrum was normalized by setting the maximum value to 1.0 and the minimum value to 0.0 so that characteristics between spectra could be compared. The relative spectral parameters that were compared were the mean and standard deviation in power spectral magnitude from 3 to 12 Hz (abbreviated as MPS and SPS, respectively). We also calculated the DF, which is defined as the frequency of the dominant (i.e., largest) fundamental peak in the power spectrum from 3 to 12 Hz, as described previously.[9,10] Finally, we recorded the amplitude of the dominant frequency peak (abbreviated ADF). In accord with prior comparisons for DF, the DF and ADF measurements were made for the 4 antral PV sites only, not the 2 FW sites.[10] Thus from the original 114 and 90 recordings used for analysis, for these measurements N = 76 and 60, respectively.

The unpaired *t*-test was used to determine significant differences in paroxysmal versus persistent CFAE for MPS and SPS (all recording sites), and DF and ADF (PV sites only).

Differences were considered significant at a level $P < 0.05$, and the statistical measurements were made using computer software (SigmaPlot 2004 for Windows Ver. 9.01, Systat Software, Chicago, IL, USA, and MedCalc Ver. 9.5, 2008, MedCalc Software bvba, Mariakerke, Belgium).

We then attempted to distinguish the 2 AF types by plotting MPS versus ADF for each patient (average from all recording sites for first 8s series) as an estimate of the spatial organization of activating wavefronts. The best linear discriminant function was drawn through the scatterplot to separate acute from longstanding AF patient values. This was repeated by plotting SPS versus DF. Furthermore, we determined the correlation between the number of months of uninterrupted AF prior to the catheter ablation procedure in longstanding AF patients, and LA volumes of all AF patients, versus MPS and versus ADF.

The LA volumes were calculated from computerized tomography (CT). CT images were obtained using a 32-MDCT GE scanner (GE Healthcare) within 1–2 weeks prior to electrophysiologic analysis and ablation. All 10 patients with longstanding AF had AF as their cardiac rhythm during the CT scan, whereas the paroxysmal AF patients were in sinus rhythm. After administration of contrast agent, helically acquired axial scans were made during AF. These scans were reconstructed as images with 1 mm spacing in the axial plane using algorithms developed at Columbia University Medical Center. Volumes were measured using the Volume Viewer 2 (AW Suite 2.0, GE Healthcare). Retrospective volumetric measurements were available for all but 2 AF patients (both having paroxysmal AF episodes).

The Spearman Rank Order Correlation statistic was used for determining correlation between the duration of uninterrupted persistent AF, and the LA volumes of all AF patients, to spectral parameters (Sigma Plot Ver. 9.0, 2004).

Results

An example of CFAE spectrum and harmonic relationships in a recording obtained at an antral site outside the left superior PV in a patient with longstanding AF is shown in Figure 1. In panels A–B are ensemble average spectra. In panel A there is no harmonic removal. The DF occurs at 6.6 Hz, and subharmonics are prominent. In panel B, the second harmonic has been removed by antisymmetry. This causes subharmonic peak 2 of the DF to be eliminated (peak at frequency of 3.3 Hz). In panel C the Fourier spectrum is shown. There is a high secondary peak near the main spectral peaks. The MPS and SPS are shown at top right in each panel. The effect of antisymmetry to the ensemble average spectral estimation is to reduce the MPS and SPS (compare panels A and B).

Based on prior studies, the spectral peaks generated from the CFAE of paroxysmal AF patients tend to appear more complex as compared with those of persistent AF patients.[9,10,12] To show how large versus small and complex spectral peaks quantitatively influence spectral profile parameters, an example spectral profile having DF of 6 Hz is shown in Figure 2A. The spectral profile parameters are shown at top right (MPS $\pm$ SPS). When peaks other than the DF are masked (panel B) the spectral profile mean value drops from 0.16 to 0.03 units. There is only a slight decrease in the standard deviation of spectral profile, from 0.13 to 0.12 units. When the DF is masked but the remaining spectrum is not normalized (panel C), it results in some decrease in both the MPS and SPS (compare panels A and C). The biggest change occurs when the spectrum with masked DF from panel C is normalized to a range of 0–1 (panel D). In this case, the MPS and SPS are considerably increased as compared with panel A. Thus when small irregular peaks are predominant in the spectral profile, as tend to occur in paroxysmal AF,[9,10] the MPS and SPS will be large.

An example of a CFAE recording obtained during acutely induced AF outside the ostium of the RSPV in a patient with paroxysmal AF is shown in Figure 3, panel A. The amplitude and timing of the larger deflections are uneven, and the average level varies. Overall, there is little reproducibility in the CFAE. This is reflected in the ensemble average frequency spectrum, which is shown in the range 3–12 Hz. For clarity, no harmonic interactions were removed prior to spectral estimation. The DF occurs at 5.58 Hz. The normalized spectral magnitude ranges between 0 and 1. Due to the large variability in spectral profile and a relatively high baseline level, the mean spectral profile is 0.41 units and the standard deviation is 0.18 units. For comparison, an example of a CFAE recording obtained outside the LSPV in a longstanding AF patient in shown in panel C. The deflections appear to be closer together as compared with panel A. Although there are differences in timing of the larger deflections, several of them have similar amplitude. The ensemble average frequency spectrum for this CFAE (no harmonic interactions removed) is shown in panel D. The DF occurs at 6.65 Hz. The spectral baseline is at a lower level (i.e., closer to zero) as compared to the spectrum in panel B. There are less spectral deflections in panel D. The profile has a mean value of 0.25 units and a standard deviation of 0.15 units. Thus, both the MPS and SPS are diminished for the persistent CFAE as compared with the paroxysmal CFAE.

Results of the measurements are shown in Table 1. For all parameters, there were no significant differences between the measurements obtained for the first 8-second series as compared with the second 8-second series. The means in 3–12 Hz spectral profile are tabulated for all recording sites for acutely induced and longstanding AF in Table 1A. All of the means in spectral profile are higher for paroxysmal AF as compared with persistent AF. Similarly, the standard deviations in spectral profile are also higher for paroxysmal AF as compared with persistent AF (Table 1B). This occurred for all measurement modes – Fourier analysis, and ensemble analysis with no harmonics removed (Ensemble0) and with harmonic 2 removed (Ensemble2). The significance of the difference in the means using the unpaired *t*-test is shown in Tables 1A and 1B. All of the means in acutely induced AF are greater than the longstanding AF means with significant differences $P < 0.0001$, except for Fourier analysis, second 8s series. For the standard deviations in spectral profile, the differences between the acutely induced and longstanding AF remain significant even after the second harmonic is removed using the antisymmetry technique.

Results for measurements of the amplitude and frequency of the dominant peak are shown in Tables 1C and 1D, respectively. Both amplitude and frequency of the dominant peak are significantly less in paroxysmal as compared with persistent CFAE. The most significant difference occurs when measuring the amplitude of the dominant peak by ensemble averaging ($P < 0.0001$, Table 1C). The DF measurement is

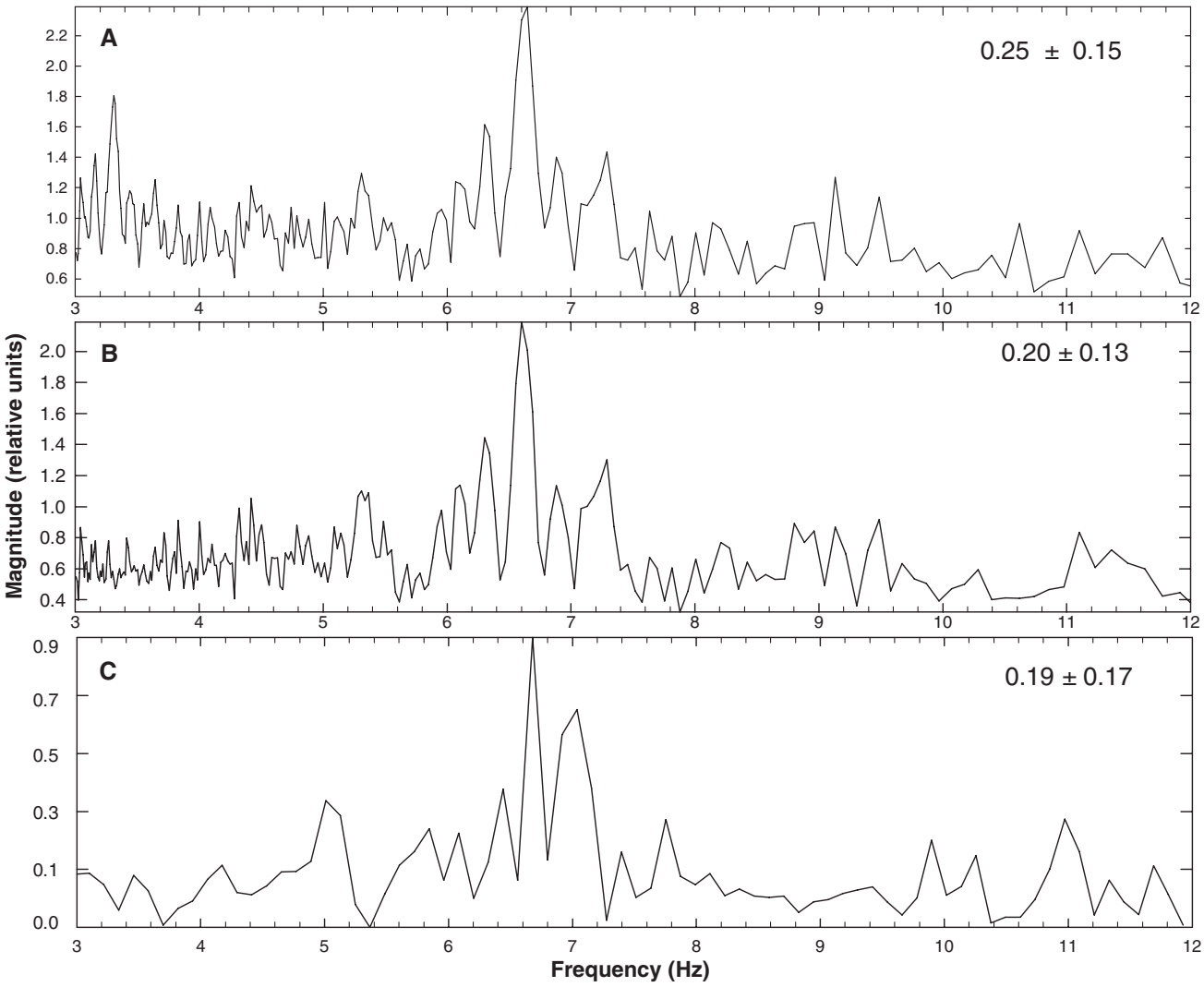

Figure 1. *An example of complex fractionated atrial electrogram spectrum and harmonic relationships in a recording from the right inferior pulmonary vein ostium in a longstanding, persistent atrial fibrillation patient. Panel A, no harmonic removal. Panel B, removal of harmonic 2. Panel C, the Fourier power spectrum for the same recording. The mean and standard deviation in the spectral profile is given at upper right in each panel. See text for further details.*

less significant, mainly due to its lesser stability over time (Table 1D).

Thus, the most significant parameters for discerning paroxysmal from persistent AF are the MPS (Table 1A) and the amplitude of the dominant peak (Table 1C) when ensemble averaging is used for spectral estimation ($P < 0.0001$). These measurement parameters also have very good temporal stability with almost no change to 2 significant digits from first to second 8s series (Table 1).

Scatterplots of the parameters used for measurement are shown in Figure 4. Each × represents a paroxysmal AF patient and each solid circle represents a persistent AF patient. The results for ensemble average analysis are shown in panels A–B, and for Fourier analysis in panels C–D. The plot of ADF versus MPS is shown in panel A. The best discriminating line, separating the 2 AF types, is noted. The averages for the 9 paroxysmal AF patients tend to cluster at higher MPS and lower ADF. The averages for the 10 persistent AF patients tend to cluster at lower MPS and higher ADF. The plot of DF versus SPS is shown in panel B. The best linear discriminant function is noted. The averages for the 9 paroxysmal AF patients tend to cluster at higher SPS and lower DF. The averages for the 10 persistent AF patients tend to cluster at lower SPS and higher DF. In panel A, of 7 of 9 paroxysmals and 10 of 10 persistents are classified correctly. In panel B, 8 of 9 paroxysmals and 9 of 10 persistents are classified correctly. Thus the mean sensitivity is 83.3% and the mean specificity is 95.0% using these measures. Similar results are achieved using Fourier analysis (panels C and D). Overall, for Fourier analysis, the mean sensitivity is 77.8% and the mean specificity is 80.0% using these measures.

The same plot as in Figure 4A with the time of uninterrupted AF in months prior to electrophysiologic study in longstanding AF patients is shown in Figure 5A for each longstanding AF patient. The number of months of uninterrupted AF (Fig. 5A) was found to be inversely correlated to the mean spectral profile ($\rho = -0.73$, $P = 0.013$) and trended toward significance with the amplitude of the dominant peak ($\rho = 0.58$, $P = 0.074$). The same plot, this time with the LA volumes prior to any ablation, is shown in Figure 5B for all AF patients, except for 2 patients with paroxysmal AF.

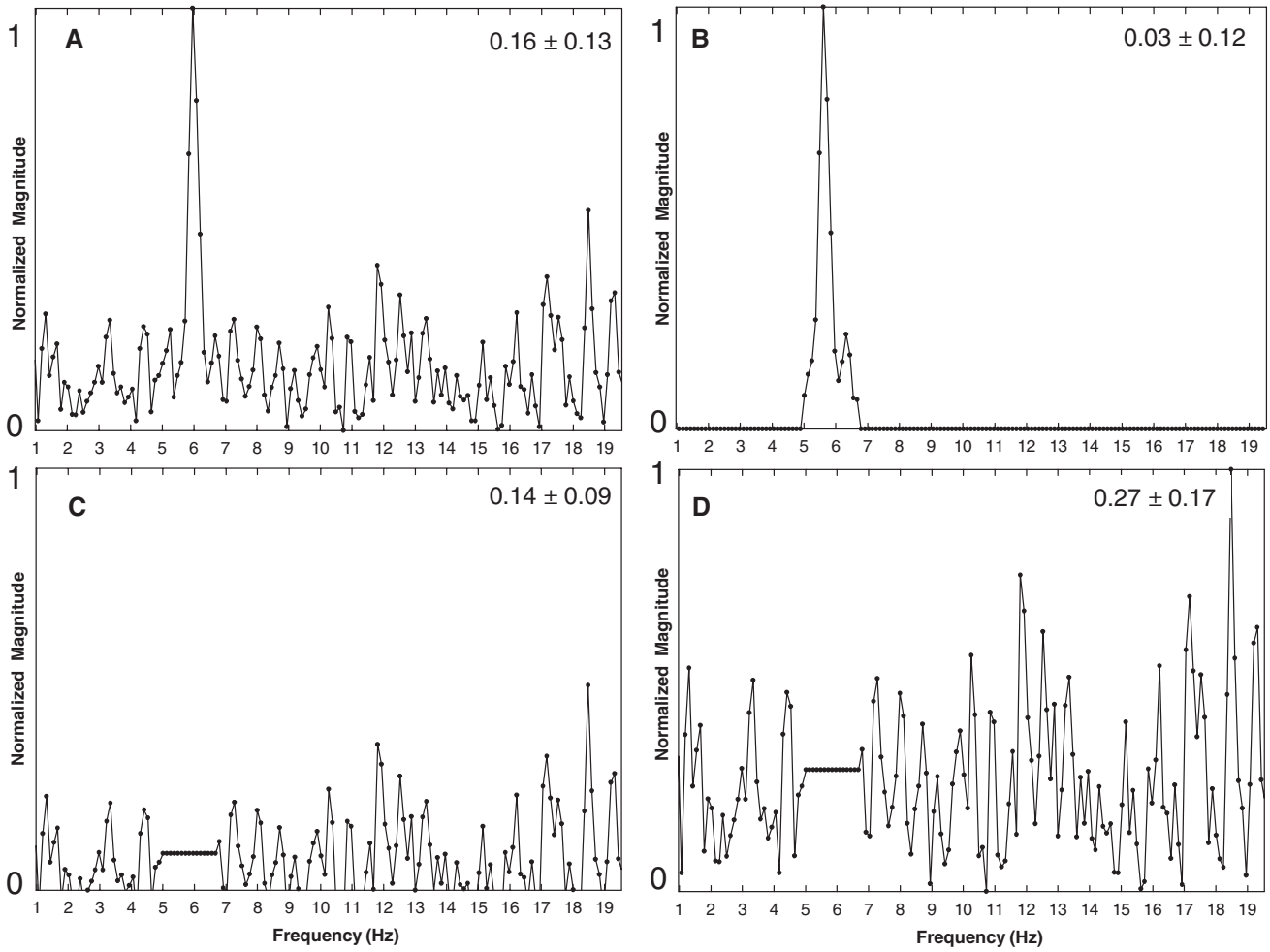

Figure 2. *An example of the complex fractionated atrial electrogram spectrum and harmonic relationships in a recording from the left superior pulmonary vein ostium obtained during acutely induced atrial fibrillation in a patient with paroxysmal atrial fibrillation is shown in panel A. The mean and standard deviation in the spectral profile is given at upper right. To show how these spectral profile parameters change, values are also shown when peaks away from the dominant frequency are masked (B), when the dominant frequency peak is masked (C), and when the remaining peaks are scaled to a range of 0–1 after masking the dominant frequency (D).*

LA volume is also inversely correlated to the mean spectral profile ($\rho = -0.51$, $P = 0.036$) and with the amplitude of the dominant peak ($\rho = 0.48$, $P = 0.047$).

Discussion

Summary

In this study, by normalizing the CFAE spectra, it was possible to compare the CFAE frequency patterns observed in longstanding, persistent AF to those present in acutely induced AF in patients whose arrhythmia is clinically paroxysmal and whose baseline rhythm was sinus. Our results show that the CFAE recordings during acute onset AF in patients with paroxysmal AF had significantly larger mean and standard deviation in the normalized power spectra, suggesting, but not proving, the presence of more randomly varying activation sources in general. By comparison, CFAE spectra from longstanding AF patients had lower mean value and standard deviation of spectral peaks, as would be expected if the peaks were generated by more stable and stationary sources present in the atrial substrate. Our results also show that the CFAE recordings during acute onset AF in patients with paroxysmal AF had significantly lower amplitude and frequency of the dominant peak. This suggests a greater complexity in the power spectral profile of paroxysmal patients, which is likely due to the presence of more peaks that are greatly varying in height, with no single predominant tall peak in the spectrum.

Motivation for Harmonic Removal by Introduction of Asymmetry

Although both ensemble average and Fourier power spectra can be used to analyze CFAE quantitatively, one potential drawback is the presence of spectral harmonics, which can mask independent spectral peaks.[3,5,6,9] This is undesirable because it is the independent components that provide information about distinct sources of electrical activation in the nearby substrate, potential distinct sites for catheter ablation targeting. Harmonics are multiples of a basic or fundamental frequency. They affect the shape of the fundamental frequency component in the CFAE and are dependent on it. After removal of harmonic interactions, the remaining spectral peaks would reasonably be expected to represent independent

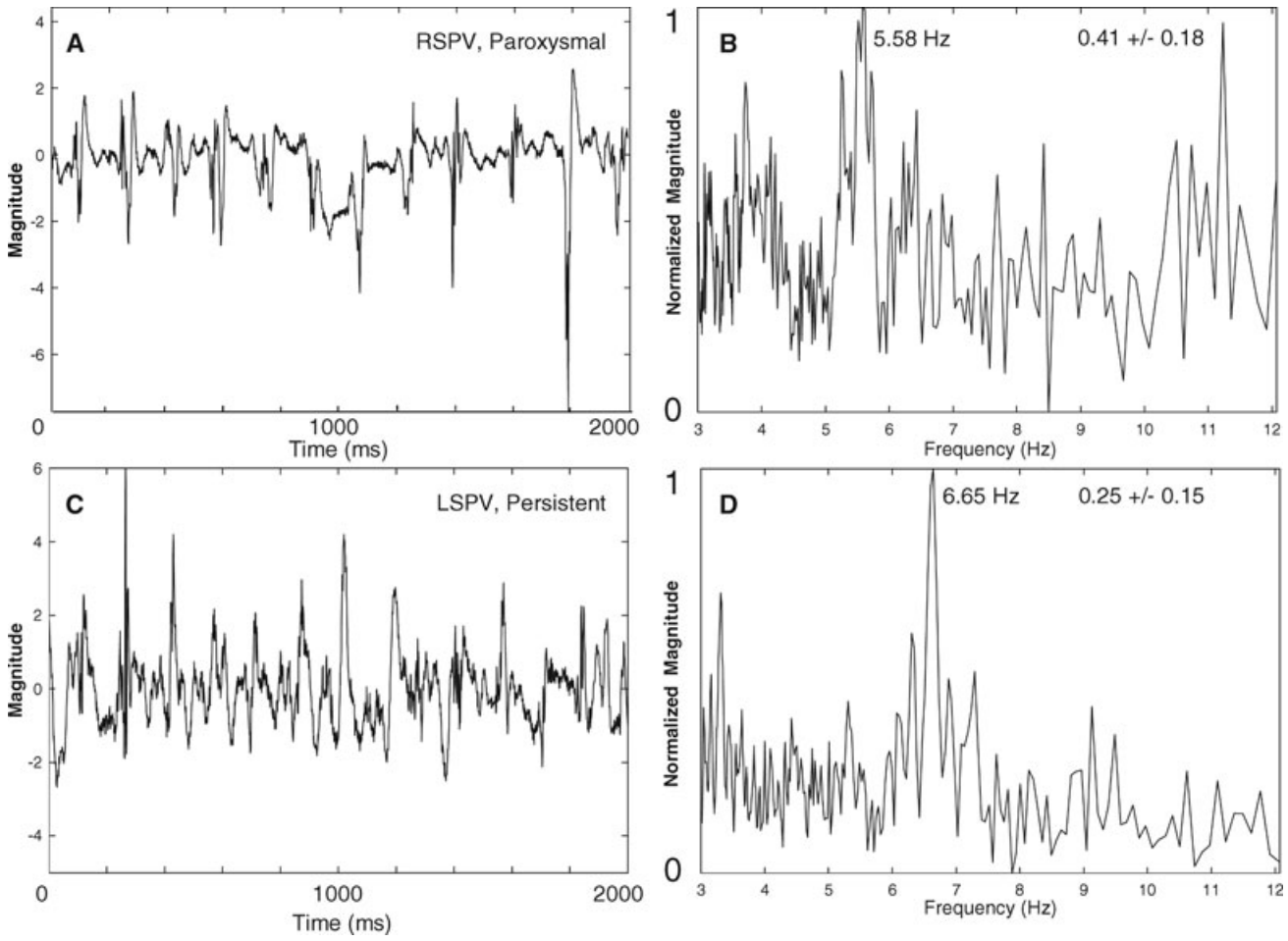

Figure 3. *An example of a complex fractionated atrial electrogram recording outside the right superior pulmonary vein in a patient with paroxysmal atrial fibrillation is shown in panel A. The ensemble average frequency spectrum for the recording in Panel A, in the range 3–12 Hz, is shown in Panel B (no harmonic interactions removed). An example of a complex fractionated atrial electrogram recording from the left superior pulmonary vein in persistent atrial fibrillation is shown in panel C. The ensemble average frequency spectrum for this complex fractionated atrial electrogram (no harmonic interactions removed) is shown in panel D. So that detail can be observed, only 2 seconds of recording time is shown in panels A and C. However, the spectra in panels B and D were generated from the entire 8.4 second sequence length.*

TABLE 1A

Mean of Spectral Profile (MPS)

per-1st 8s	par-1st 8s	Significance	Type	per-2nd 8s	par-2nd 8s	Significance
0.34 ± 0.10	0.40 ± 0.08	$P < 0.0001$	Ensemble0	0.34 ± 0.11	0.40 ± 0.07	$P < 0.0001$
0.31 ± 0.10	0.37 ± 0.08	$P < 0.0001$	Ensemble2	0.31 ± 0.10	0.38 ± 0.07	$P < 0.0001$
0.26 ± 0.07	0.31 ± 0.07	$P < 0.0001$	Fourier	0.26 ± 0.08	0.30 ± 0.07	$P = 0.0002$

TABLE 1B

Standard Deviation of Spectral Profile (SPS)

per-1st 8s	par-1st 8s	Significance	Type	per-2nd 8s	par-2nd 8s	Significance
0.16 ± 0.02	0.17 ± 0.02	$P = 0.0028$	Ensemble0	0.16 ± 0.03	0.17 ± 0.02	$P = 0.0204$
0.16 ± 0.03	0.17 ± 0.02	$P = 0.0052$	Ensemble2	0.16 ± 0.03	0.17 ± 0.02	$P = 0.0028$
0.20 ± 0.03	0.21 ± 0.03	$P = 0.0026$	Fourier	0.20 ± 0.03	0.21 ± 0.03	$P = 0.0242$

sources of electrical activity. The height and area of each independent peak could provide information about the distance to a particular source, and the volume of tissue that the source directly activates, both important parameters for characterizing catheter ablation targets.

Spectral Properties and the Underlying Mechanisms

Our selection of 3 Hz (333 ms) to 12 Hz (83 ms) as the physiologic range of atrial activation during AF is based on a long prior history in the literature.[13–15] This frequency range is conservative and reasonable since none of the atrial

TABLE 1C

Amplitude of Dominant Peak (ADF) in Relative Magnitude Units

per-1st 8s	par-1st 8s	Significance	Type	per-2nd 8s	par-2nd 8s	Significance
1.83 ± 0.59	1.46 ± 0.29	P < 0.0001	Ensemble0	1.83 ± 0.60	1.46 ± 0.24	P < 0.0001
1.50 ± 0.50	1.19 ± 0.29	P < 0.0001	Ensemble2	1.51 ± 0.46	1.17 ± 0.20	P < 0.0001
0.85 ± 0.37	0.70 ± 0.30	P = 0.0078	Fourier	0.89 ± 0.40	0.68 ± 0.26	P = 0.0007

TABLE 1D

Dominant Frequency (DF) in Hertz

per-1st 8s	par-1st 8s	Significance	Type	per-2nd 8s	par-2nd 8s	Significance
6.28 ± 0.96	5.38 ± 1.26	P < 0.0001	Ensemble0	6.28 ± 1.01	5.70 ± 1.16	P = 0.0018
6.26 ± 1.00	5.33 ± 1.30	P < 0.0001	Ensemble2	6.26 ± 1.07	5.72 ± 1.25	P = 0.0061
6.16 ± 1.05	5.51 ± 1.27	P = 0.0010	Fourier	6.14 ± 1.14	5.38 ± 1.15	P = 0.0002

Ensemble 0 = ensemble average method with no antisymmetry; Ensemble 2 = ensemble average method with antisymmetry implemented for the second harmonic; per-1st 8s = persistent AF, first 8 seconds; par-1st 8s = paroxysmal AF, first 8 seconds; per-2nd 8s = persistent AF, first 8 seconds; par-2nd 8s = paroxysmal AF, first 8 seconds.
Values are rounded to 2 decimal places for clarity.

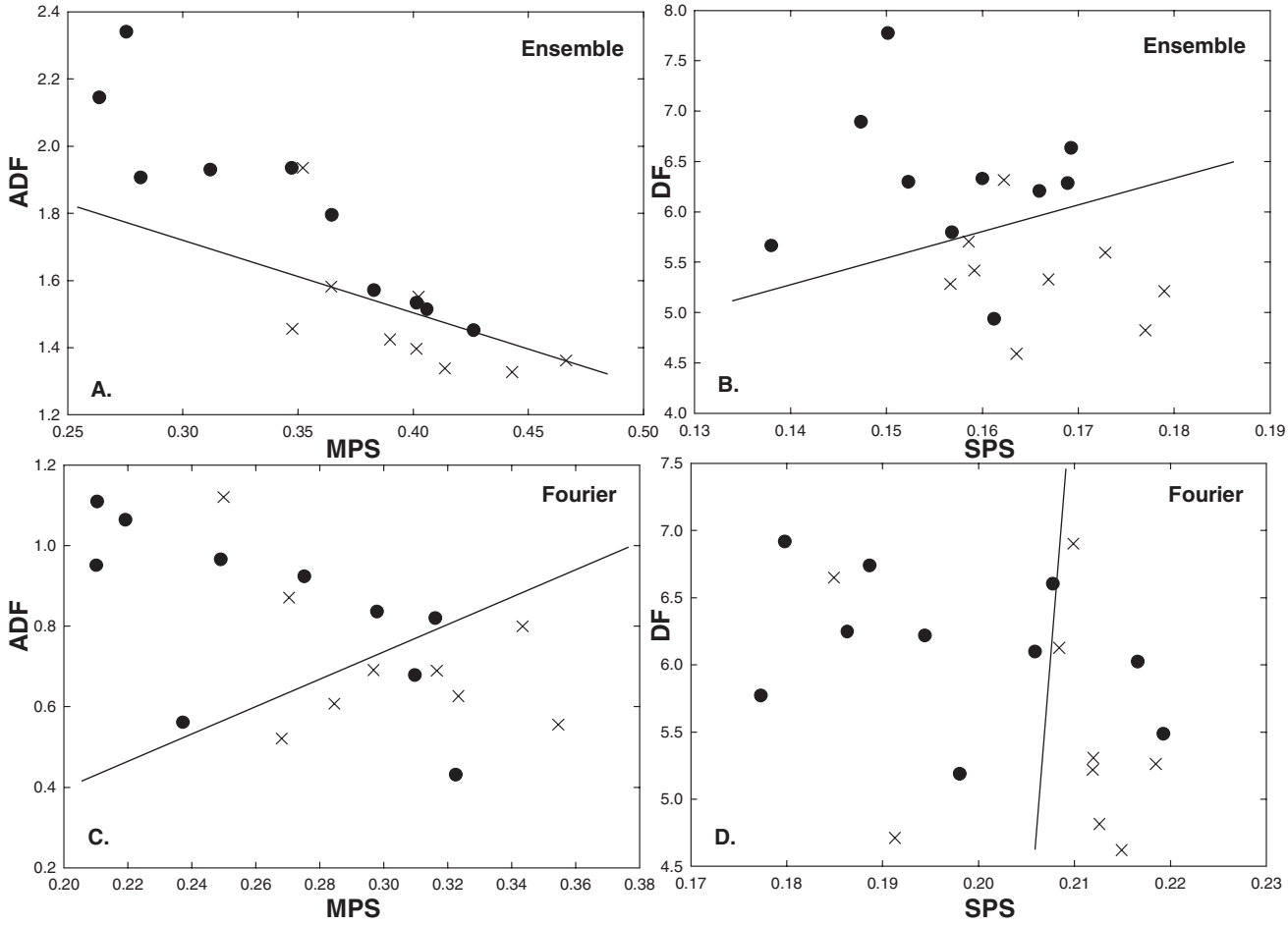

Figure 4. *Scatterplots of ADF versus MPS for each patient are graphed in panel A. Each solid black circle represents a persistent atrial fibrillation patient and each × represents a paroxysmal atrial fibrillation patient. Scatterplots of DF versus SPS for each patient are graphed in panel B. In panels C and D, the results are shown obtained using Fourier power spectral analysis. In each panel the best discriminating line is also shown for separating the 2 types of atrial fibrillation.*

arrhythmias was "mappable" flutter (longer cycle lengths), and on the other end of the spectrum, even with maximal electrical remodeling, it is probably not possible for local functional refractory periods to be significantly shorter than 90–100 ms. It is difficult to make firm conclusions about global phenomena based on local data collected at individual sites. With this limitation, it is quite possible that the differences observed between the paroxysmal and longstand-

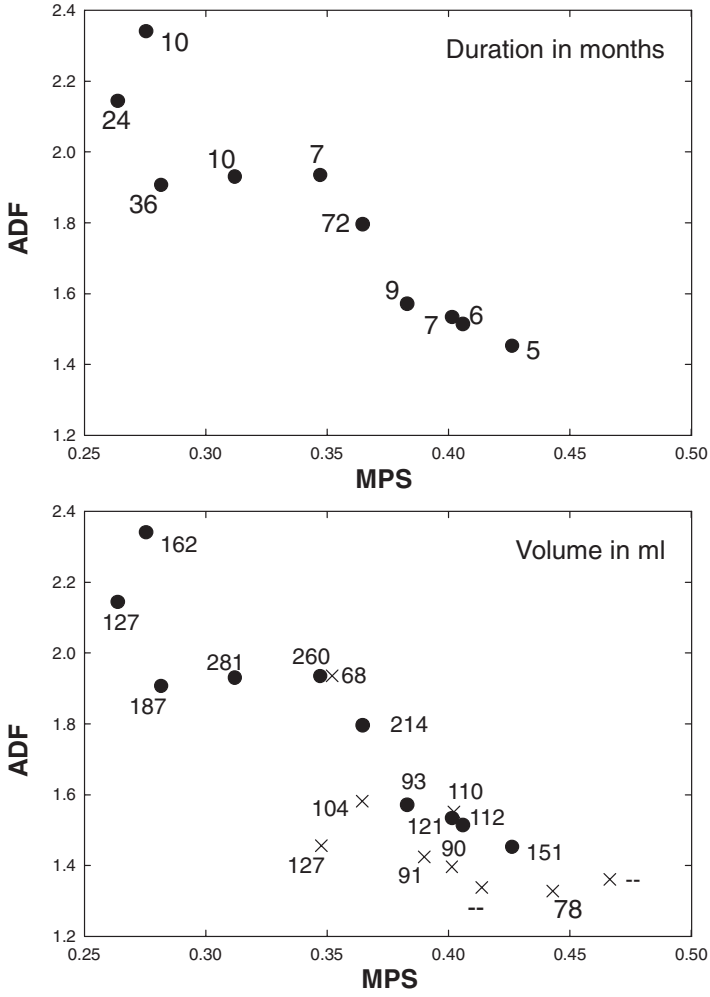

Figure 5. *In the top panel, a plot is shown of persistent atrial fibrillation patient data from Figure 4A, with the duration of uninterrupted atrial fibrillation prior to electrophysiologic study noted in number of months for longstanding patients. In the lower panel, all atrial fibrillation patient data from Figure 4A are plotted, with left atrial volume noted in milliliters in all 10 longstanding atrial fibrillation and 7 paroxysmal atrial fibrillation patients. Volumetric data were not obtained for 2 paroxysmal patients (noted by –).*

ing AF spectra, after the application of the antisymmetry technique, reflect the differences in their underlying mechanisms. Both structural and functional myocardial properties contribute to AF electrogram complexity.[16] Fractions of a DF may arise when a source of electrical activity fails to activate a substantial volume of atrial tissue at the same frequency as that of the driving source. For example, 2:1 entry block into a region surrounded by a tissue of increased relative refractoriness may result in $^1/_2$ the frequency of the source of the electrical activity. Multiples of the DF may also arise, for example, if the bipolar local electrograms record more than 1 component of a reentrant circuit during each revolution. This phenomenon may also partially explain the presence of peaks at higher frequencies outside our "physiologic" range. The frequencies that remain after the related harmonics are removed by antisymmetry are more likely to represent independent sources unrelated to the one generating the DF. If AF is driven by meandering rotors and wavefronts, in contrast to stationary drivers, a different spectrum than the one underlying the latter may result. First, the frequency of a meandering rotor may change from one site to the next, depending on the local tissue geometry, and the resulting frequencies may not necessarily be a ratio of the original frequency.[2] Furthermore, our findings are not incompatible even with a more stable rotor,[17] since the wavebreaks at the periphery of such a dominant rotor may be highly asymmetric and may result in different frequencies of local activation, resulting in nonuniformity and nonreproducibility. Due to this complexity, the amplitudes would be expected to have a high standard deviation about the mean. Our observations, therefore, while not constituting any direct proof whatsoever, are consistent with rotors with random wavebreaks as the underlying mechanism for new onset AF in patients with paroxysmal AF, not expected to have fibrosis and other chronic atrial tissue alterations. By contrast, site specific, stable sources, such as stable microreentry, may be the underlying mechanism for longstanding AF. Finally, needless to say, both of these mechanisms may be contributing to longstanding AF, but the site specific, stationary sources may be predominant.

Our study also showed a significant correlation between the duration of uninterrupted AF and the spectral characteristics of CFAE in patients with longstanding AF. The correlation with atrial volume was weaker for the MPS measurement. This is not surprising since factors other than AF, such as mitral regurgitation or left ventricular hypertrophy, may affect the LA volume, which may not be the best indicator of remodeling at the tissue level. Whatever tissue architectural remodeling occurs with prolonged AF, it is reasonable to suppose that the longer duration of AF, the greater the extent of remodeling. According to our data, longer periods of uninterrupted AF appear to promote the establishment of discrete extra-PV sources of relatively stable frequencies, none of

which is harmonically related to another and therefore likely to be independent drivers of persistent AF.

Limitations

The major limitation of this study is the small number of patients and also the small number of sampling sites per patient. The latter limitation was a consequence of the fact that data collection time was limited due to the nature of the long ablation procedures these patients were undergoing. Furthermore, limiting signal analysis to the CFAE sites may not be sufficient to describe the entire picture since this limitation misses other potentially critical sites such as those manifesting high frequency of activation but with discrete signals. Same or similar findings from the analysis of CFAE signals and non-CFAE electrograms recorded simultaneously at many more atrial sites will be needed for further validation and wider generalization of our results. It is possible to distinguish CFAE from non-CFAE automatically prior to further analysis.[18]

A technical limitation with introduction of antisymmetry is that the original morphologic information contained within each ensemble average is removed. This morphologic information can be useful to measure the characteristics of independent drivers.[11] Furthermore, after introduction of antisymmetry, ensemble average basis vectors may not be useful for signal reconstruction.[11] As described previously, differences in the CFAE reconstruction error were found in paroxysmal versus persistent AF patients using the Fourier method.[11] To use the ensemble average method for this purpose, antisymmetry should not be introduced.

Finally, the analysis of these data has been retrospective, and consequently the observations are hypothesis-generating only. Whether these differences observed between paroxysmal and longstanding AF can be used to perform catheter ablation more effectively in patients with either type of AF needs to be addressed by future studies. Despite its simplicity, calculation of mean spectral value is an indirect way of assessing periodicity, though more sophisticated algorithms such as regularity and organizational indices may be useful to further improve analysis of the spectral profile.[19]

Conclusions

Three new automated measures of power spectral profile were introduced to compare and contrast CFAE from paroxysmal and longstanding AF patients, and these were compared to the DF measurement. Our findings suggest that 2 of the 3 new measurements, the MPS and the ADF, are better indicators of AF type, particularly when using ensemble analysis for spectral estimation ($P < 0.0001$), as compared with the DF measurement. Since these new measurements were done automatically, they do not introduce user bias and can be implemented in real time. Moreover, it was found that the mean of the power spectral profile correlates well with the duration of uninterrupted AF in longstanding patients, and also correlated with the LA volume estimate in all AF patients. These observations are in accord with our previous work[9,10] that suggested a more complex content in the CFAE recordings of paroxysmal AF compared with similar data recorded during longstanding AF. Furthermore, introduction of antisymmetry was found useful to remove harmonic interactions in CFAE power spectra, and by this method of harmonics reduction, identifying peaks in the power spectrum unrelated to the DF, possibly representing other independent activation sources of AF.

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