Spatiotemporal Behavior of High Dominant Frequency During Paroxysmal and Persistent Atrial Fibrillation in the Human Left Atrium

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Background—Sites of high dominant frequency (DF_{peak}) are thought to indicate the location of drivers of atrial fibrillation (AF), but characterization of their spatiotemporal distribution and stability, critical to their relevance as targets for catheter ablation, requires simultaneous global mapping of the left atrium.

Methods and Results—Noncontact electrograms recorded simultaneously from 256 left atrial sites during spontaneous AF were analyzed. After subtraction of the ventricular component, fast Fourier transform identified the DF at each site. Focal areas of DF_{peak} were defined as those having a DF >20% above all neighboring sites. Twenty-four patients with spontaneous AF (11 paroxysmal and 13 persistent) were studied. In paroxysmal AF, sites of DF_{peak} (mean DF, 11.6±2.9 Hz) were observed in 100% of patients (present during 65% of the mapping period). In contrast, DF_{peak} was detected in only 31% of patients with persistent AF (P<0.001) and for only 5% of the mapping period (P<0.001). In both groups, locations of DF_{peak} varied widely in both consecutive and separated segments of AF (κ coefficient range, -0.07–0.22). Activation sequences around sites of DF_{peak} did not demonstrate centrifugal activation that would be expected from focal drivers.

Conclusions—Focal areas of high DF are more frequent in paroxysmal than persistent AF, are spatiotemporally unstable, are not the source of centrifugal activation, and are not, therefore, indicative of fixed drivers of AF. In the absence of spatiotemporal stability, the success of ablation at sites of DF_{peak} cannot be explained by elimination of fixed drivers. (***Circ Arrhythm Electrophysiol*. 2012;5:650-658.**)

Key Words: arrhythmia ■ atrial fibrillation ■ atrium ■ electrophysiology mapping ■ spectral analysis

Although the importance of pulmonary venous ectopy in initiating human atrial fibrillation (AF) is beyond doubt, the extent to which other focal areas of high-frequency activity persist to maintain AF remains uncertain.[1,2] In a cholinergic sheep model of AF, localized microreentrant sources at the posterior left atria (LA) maintained fibrillation by periodic high-frequency activation, which, in turn, fractionated in the surrounding tissue into multiple electrical wavefronts, activating the rest of the atrial mass with fibrillatory conduction.[3,4] Limited evidence exists that this phenomenon also occurs during human AF.[5] As a consequence, areas of high-frequency activation have been proposed as potential targets during AF ablation, and this, in turn, has led to the adoption of techniques to systematically identify high-frequency activity. Spectral analysis is a powerful signal processing algorithm that can identify regular contributions within complex and irregular electrical signals. These contributions are displayed in a power frequency spectrum, and the frequency with the highest power, termed the dominant frequency (DF), has been shown to correspond to the oscillating cycle lengths of underlying drivers.[4]

Clinical Perspective on p 658

Spectral analyses of human AF have been limited to recordings acquired sequentially over several minutes or confined to a limited area of the atrium and have, therefore, provided data of limited temporal and spatial comparability or stability. These methodological limitations have imposed important constraints in assessing the spatiotemporal behavior of high-frequency areas. Noncontact mapping (EnSite Array; St. Jude Medical, St. Paul, MN) is a unique tool for simultaneous, high-density global mapping, and we and others have validated its use in the ventricle and atrium.[6–10]

To address the critical question of spatiotemporal stability underlying the rationale for targeting high-frequency areas for ablation in AF and to address the hypothesis that such regions are spatiotemporally stable, we have combined the 2 techniques of spectral analysis and noncontact mapping to characterize simultaneous, global LA DF distribution during spontaneous human paroxysmal and persistent AF.

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Methods

Patients

Consecutive patients with symptomatic AF who had episodes of spontaneous AF recorded during EnSite noncontact system–guided LA ablation were included in the present study. All antiarrhythmic drugs were stopped at least 5 half-lives before the procedure, and no patient was on amiodarone. The study protocol was approved by the St Mary's Hospital ethics committee, and all procedures were carried out after obtaining written informed consent.

Noncontact Mapping

A noncontact multielectrode array (EnSite 3000; Endocardial Solutions Inc, St. Paul, MN) and a conventional mapping catheter (Biosense Webster, Diamond Bar, CA) were deployed transseptally into the LA. The details of the noncontact system have been described previously.[6,7] Patients were anticoagulated with heparin, and the activated clotting time was maintained >300 seconds. A detailed LA geometry was acquired with the mapping catheter, and anatomical landmarks, including mitral valve annulus, pulmonary vein ostia, LA appendage, roof, and septal, anterior, and posterior walls, were identified and labeled. All spontaneous episodes of paroxysmal AF (not initiated by catheter manipulation), along with randomly selected periods of persistent AF, were recorded before performing any ablation and were subsequently analyzed. The filter setting of the noncontact electrograms was 1 to 150 Hz.

Signal Processing and Spectral Analysis of Noncontact Electrograms

Of the 3360 noncontact electrograms reconstructed, those from 256 evenly distributed LA points were analyzed in 6.8-second-long segments. Off-line analysis was performed using customized software programmed in the MATLAB (Mathworks, Natick, MA) environment. The software was specifically designed to process the noncontact LA electrograms through 3 main steps: (1) to subject the unipolar raw electrograms to ventricular signal subtraction using a novel algorithm that avoids the limitation of loss of atrial data by simply rejecting segments contaminated by far-field ventricular signal, (2) to filter the subtracted electrograms using a Hanning window to minimize the impact of discontinuities at the beginning and end of the segment on the spectrum, and (3) to analyze the processed electrograms using fast Fourier transform algorithm. The details of each step are described below.

Subtraction of the Ventricular Components

The far-field ventricular components of the unipolar noncontact electrograms from each of the 256 sites were subtracted using a 4-stage stepwise semiautomated subtraction algorithm as illustrated in Figure 1. First, the timing of the peak of far-field ventricular depolarization was identified automatically from a reference noncontact electrogram (the electrogram from the LA site with the clearest ventricular depolarization defined by the largest skew) as shown in Figure 1A. Second, all the ventricular components from the segment at that site were overlaid and time aligned by the peak ventricular depolarization (Figure 1B) to obtain a mean (Figure 1C and 1D). Segments with clear variation in QRS morphology on visual inspection (n=0) were rejected. Third, the mean ventricular complex was used as a template for the individual site for the subtraction of the ventricular component of the electrogram at that site (Figure 1E and 1F). Fourth, this process was repeated automatically on the electrograms from all 256 individual LA sites, with the timing of the ventricular component referenced from the reference electrogram in each case. The disparity in DF value before and after ventricular subtraction is illustrated in Figure 1G and 1H, respectively.

Filtering and Spectral Analysis

A Hanning window was applied to the ventricular subtracted atrial fibrillatory electrograms to minimize spectral leakage effects and to improve the sharpness of the spectral peak. Eight thousand one hundred ninety-two filtered data points (6.8 seconds at 1.2 kHz) from each of the 256 LA sites were subjected to fast Fourier transform algorithm. The power frequency spectra after Fourier transformation between 3 and 20 Hz (physiologically relevant to fibrillatory activity in the human atrium) were analyzed. The frequency with the greatest power was taken as the DF. From the location in x, y, and z axis of the 256 sites of the LA, a color-scaled map of DF distribution across the LA was constructed, with the DF from each site displayed on the 3-dimensional LA geometry (Figure 2).

Validation of the Noncontact Electrograms and the Frequency Spectra

Noncontact mapping and electrogram reconstruction in the atria during AF using the EnSite system have previously been validated in animals[8] and humans,[7,9,10] including in the frequency domain.[8,10] In the present study, further validation of noncontact electrograms during AF in the LA was performed by comparison with the corresponding contact electrograms from 62 randomly distributed LA locations in 4 patients with persistent AF. Unipolar signals were recorded by the 4-mm-tip mapping catheter and were directly compared with the simultaneously acquired noncontact electrograms. The dominant frequencies from each site from the contact and noncontact electrograms were also compared.

Definitions

The DF at each site was defined as the frequency with the highest power in the range of 3 to 20 Hz. A focal area of high DF (DF_{peak}) was defined as having a DF of at least 20% higher than any of its immediately neighboring points during each 6.8-second recording. This level of 20% was selected to ensure the presence of a DF gradient in keeping with previous investigations. For localization of each site of DF_{peak}, the LA was divided into 7 anatomical regions: pulmonary vein orifices, remaining intervenous posterior wall, lateral wall, LA appendage, anterior wall, septum, and roof. The presence or absence of focal DF_{peak} within each anatomical region was noted for each sequential 6.8-second recording of AF, thus allowing temporal stability of focal DF_{peak} to be calculated at each anatomical region, with the composite of the data for all regions allowing spatiotemporal stability to be assessed.

Analysis of Wavefront Propagation Around DF_{peak}

At sites of DF_{peak}, localized wavefront propagation was analyzed during gaps between QRS complexes. With bandwidth filtering from 1 to 150 Hz, a threshold voltage between −0.25 and −0.75 mV was defined to differentiate depolarized from repolarized myocardium, and wavefront propagation around DF_{peak} for each segment was examined.

Statistical Analysis

Continuous data are expressed as mean±SD where normally distributed or median and interquartile range otherwise. Comparison between groups was performed with the unpaired Student t test or ANOVA where normally distributed or with the Mann-Whitney test otherwise. Categorical variables were compared using the Fisher exact test. The correlation of each of the 62 segments was calculated using Spearman rank correlation, with the average values of the correlations presented. Because the 62 segments came from 4 different patients, the correlation of, and differences between, the dominant frequencies were analyzed using a mixed model regression analysis, with patient entered as a random effect to adjust for within-patient variability. The temporal stability of DF_{peak} at each anatomical region was calculated with the κ coefficient to assess the level of agreement in the presence and location of DF_{peak} between consecutive segments of AF. $\kappa>0.60$ at each location would be considered to indicate that DF_{peak} was stable in space and time. Two-sided $P<0.05$ was considered significant.

Results

Patient Characteristics

Twenty-four patients (age, 53±4 years; 19 men) with AF refractory to at least 1 antiarrhythmic agent (median, 2; interquartile

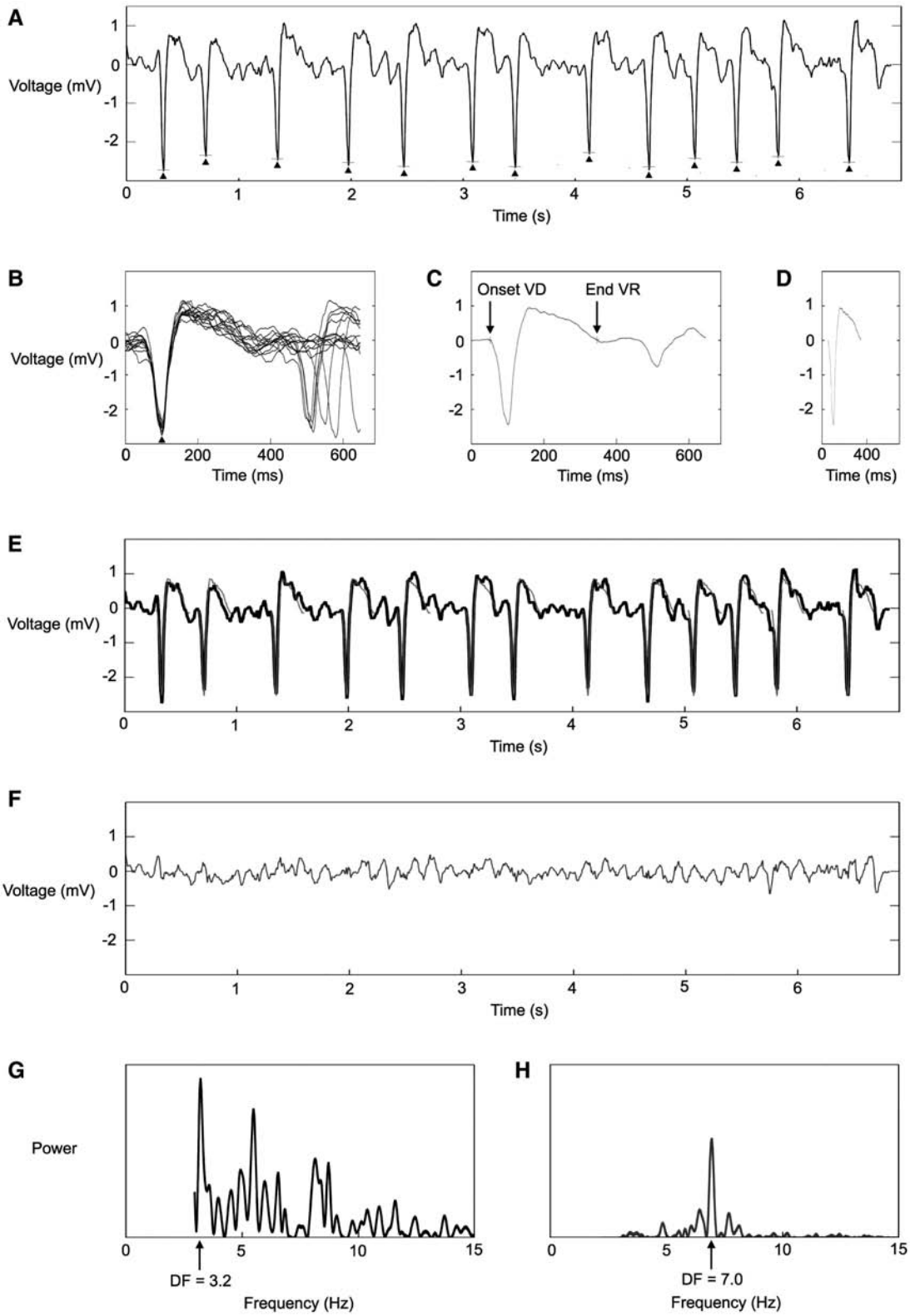

Figure 1. A–H, Subtraction of ventricular components. Please refer to the article text. DF indicates dominant frequency.

range, 1–3 agents) completed the protocol. Eleven patients had paroxysmal AF, and 13 had persistent AF. The clinical characteristics of the 2 groups are summarized in Table 1. The LA dimensions were larger in the persistent (5.0±0.8 cm) compared with the paroxysmal (3.9±0.4 cm) AF subgroup. Two of the 13 patients who had persistent AF also had left ventricular abnormality (hypertrophy and impaired systolic function, respectively).

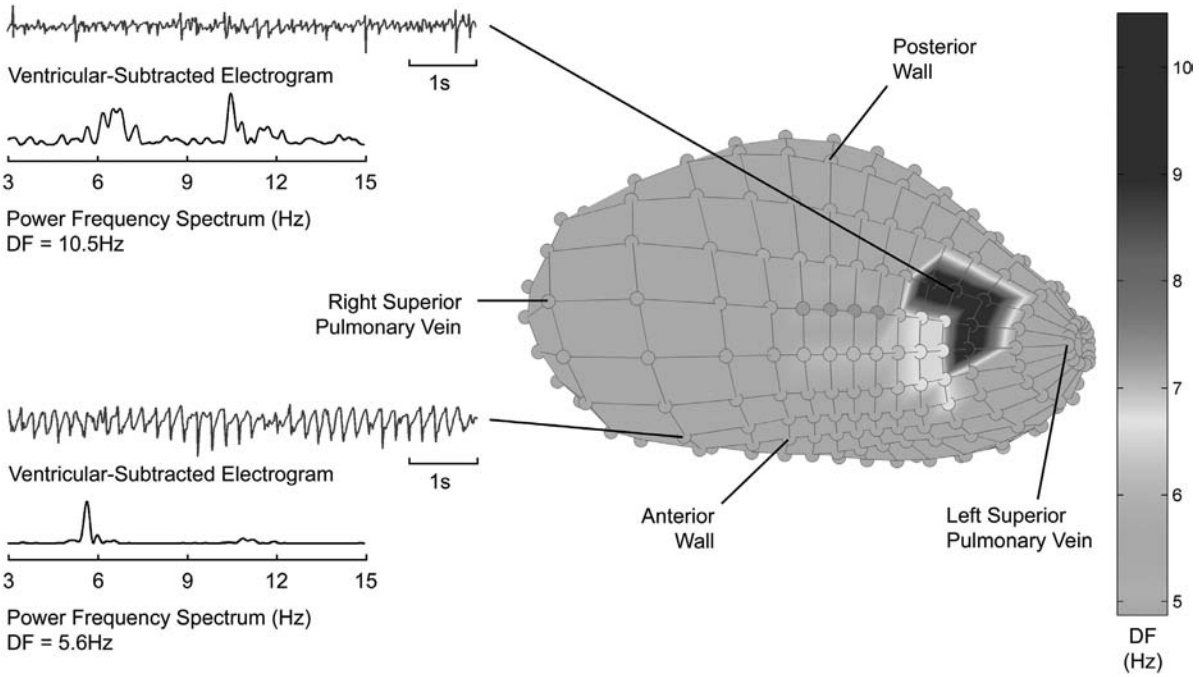

Figure 2. Dominant frequency (DF) map of the left atrium. Roof view in a paroxysmal atrial fibrillation subject. **Circles** represent 256 noncontact electrogram recording sites. The color spectrum is illustrated on the right, from **light** (4.8 Hz) to **dark** (10.5 Hz). A **dark** high DF (DF_{peak}) is seen near the left superior pulmonary vein. Typical noncontact electrograms, after ventricular signal subtraction, from virtual electrodes within DF_{peak} (upper electrogram) and outside DF_{peak}. Power frequency spectrum for each electrode (3–15 Hz range) is shown below it. Note the high-frequency activity at the electrode within DF_{peak}.

A total of 83 episodes (229 segments; median, 2 segments per episode [interquartile range, 1–3]) of spontaneous onset of AF recorded by the noncontact system were analyzed in patients with paroxysmal AF. One hundred ninety-three segments were randomly selected from 13 persistent AF patients.

Validation of Noncontact Data

The mean correlation coefficient between the voltages of unipolar contact and noncontact electrograms over 6.8 seconds for all 62 randomly selected sites was 0.70±0.15 (range, 0.29–0.94; interquartile range, 0.63–0.81; Figure 3) There was no difference in mean DF from all 62 sites between the noncontact and contact electrograms (6.9±1.5 Hz versus 7.0±1.7 Hz). The contact and noncontact signals were significantly related, with a regression coefficient (95% CI) for the noncontact signal of 1.00 (0.87–1.14); $P<0.001$.

Table 1. Clinical Characteristics of Patients

	Paroxysmal AF (n=11)	Persistent AF (n=13)	*P* Value
Male, %	9 (81.8)	10 (76.9)	1.000
Age, y	54.5±11.9	56.6±9.9	0.646
AF duration, mo	68.0±55.8	68.4±36.1	0.621
Failed AAD (no.)	1 (1–3)	2 (1–5)	0.059
LA dimension, cm	3.9±0.4	5.0±0.8	0.02
LVEF, %	57±12	49±17	0.2
Comorbidities	0	1 LVH, 1 impaired LV function	0.482

AF indicates atrial fibrillation; AAD, antiarrhythmic drugs; LA, left atrial; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LV, left ventricle.

Paroxysmal AF

Sites of DF_{peak} (DF >20% above the neighboring points) showed dominant frequencies of 11.6±2.9 Hz and were evident in all 11 (100%) patients with spontaneous onset of paroxysmal AF and in 64 of the total of 83 (77%) AF episodes. Of the 229 segments of paroxysmal AF, 149 (65%) showed at least 1 DF_{peak} (1.3±0.6 foci per segment; Figure 4): in the pulmonary venous region 33% (local DF_{peak} 11.6±3.1 Hz), remaining intervenous posterior wall 10% (11.0±3.0 Hz), anterior wall 19% (12.0±2.7 Hz), appendage 11% (12.1±2.2Hz), lateral wall 9% (11.6±2.7 Hz), septum 9% (10.9±3.3 Hz), and roof 8% (11.1±2.6 Hz: difference in local DF_{peak} between LA locations; $P=0.72$; Figure 5). Simultaneously occurring DF_{peak} were observed during 34 segments (15%) among 21 episodes (25%).

Figure 2 shows examples of noncontact electrograms from DF_{peak} and surrounding areas, examination of activation patterns of which showed no consistent centrifugal pattern of activation propagating from the sites of DF_{peak}. Any pattern suggestive of activation arising from a site of DF_{peak} was exceptional and never occurred for >1 cycle within a 6.8-second segment (Figure 6).

Spatiotemporal Stability of DF_{peak} in Paroxysmal AF

In all paroxysmal AF subjects, the presence of DF_{peak} in individual anatomical regions was spatiotemporally unstable. This is reflected by the low κ values for individual anatomical regions (range, -0.07–0.22) expressing the lack of agreement between consecutive 6.8-second segments with respect to the presence or absence of DF_{peak} at each location (Table 2). $\kappa>0.60$ at each location would be considered to indicate that the DF_{peak} was stable in space and time.

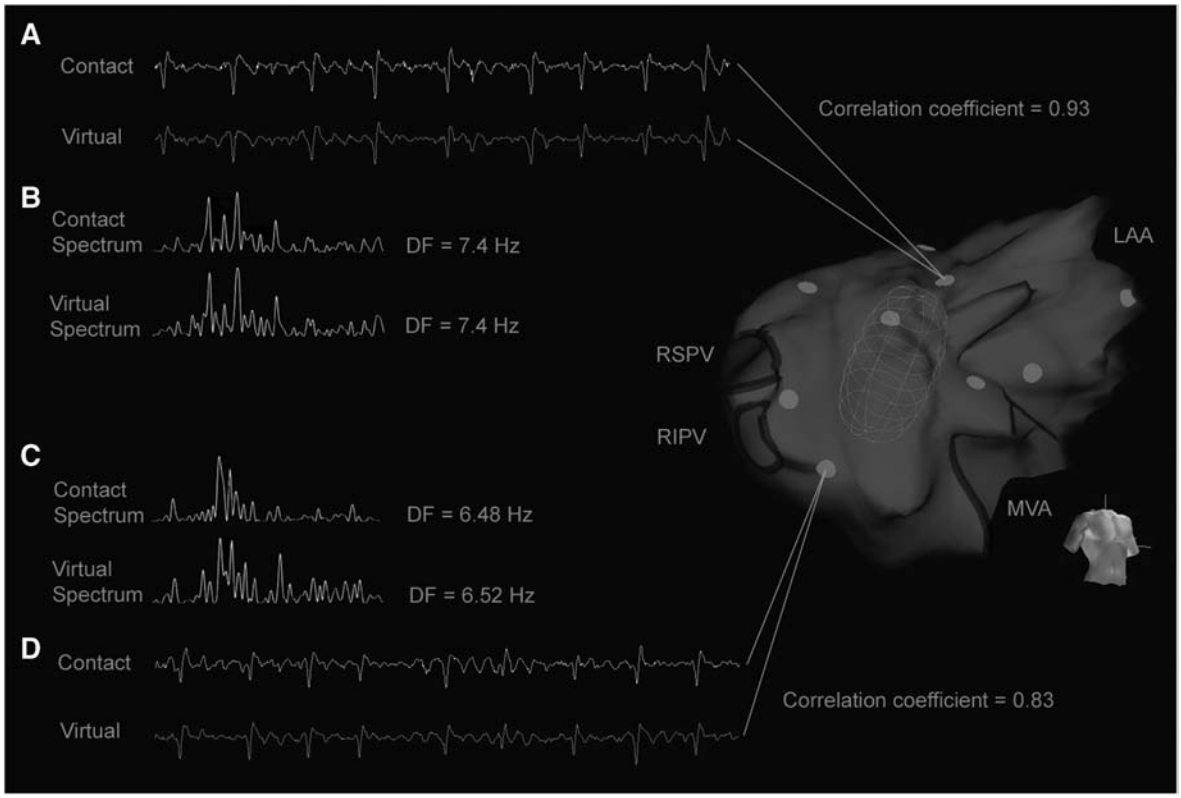

Figure 3. Validation of noncontact electrograms and frequency spectra. Left atrial (LA) geometry of a persistent atrial fibrillation subject in right anterior oblique projection. Points where validation data were gathered are marked with **lighter dots**. Contact and virtual noncontact electrograms from 1 location are displayed together (**A**); the correlation coefficient between them is 0.93. Power frequency spectra after Fourier transformation for the signals are also displayed over a 3 to 15 Hz range of frequencies on the *x* axis (**B**), demonstrating that the highest peak dominant frequency (DF) occurs at the same frequency in both cases. The same data for an alternative LA location are also displayed (**C**, **D**). LAA indicates LA appendage; MVA, mitral valve annulus; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

Three patterns of spatiotemporal instability were discerned. In the first (33% of cases), DF_{peak} would appear, disappear, and then reappear at the same location at a later time (median duration of disappearance was a 6.8-second segment and maximum was three 6.8-second segments). In the second (31%), DF_{peak} was seen to disappear from one region and appear in an adjacent region in the next successive time segment. In the third (36%), DF_{peak} would both disappear from a region without subsequently recurring and appear in a nonadjacent region without having previously been seen there.

Persistent AF

DF_{peak} (DF >20% above the neighboring points) was evident in only 4 of 13 (31%) patients with persistent AF compared

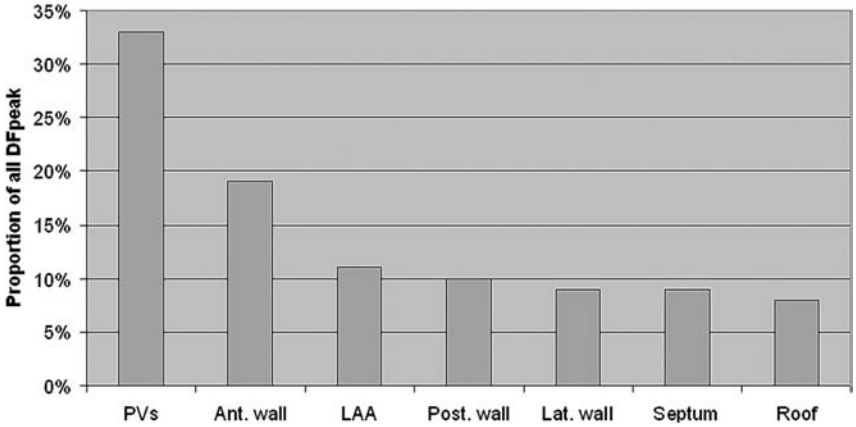

Figure 4. Location of high dominant frequency (DF_{peak}). Among paroxysmal atrial fibrillation subjects, the proportion of all DF_{peak} located at the 7 left atrial (LA) regions is shown. PVs indicate pulmonary venous region; Ant. wall, anterior wall; LAA, LA appendage; Post. wall, intervenous posterior wall; Lat. wall, lateral wall.

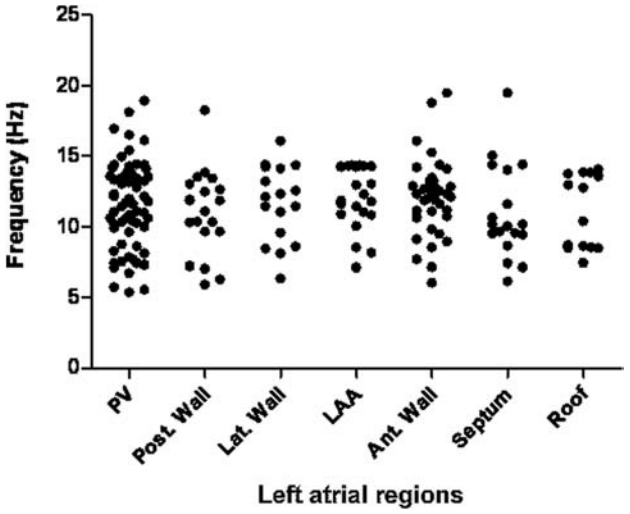

Figure 5. Distribution of maximum dominant frequency (DF) values of high DF (DF_{peak}). Within the 7 left atrial (LA) regions of paroxysmal atrial fibrillation subjects, values of maximum DF for each DF_{peak} are plotted. Ant. wall indicates anterior wall; LAA, LA appendage; Lat. wall, lateral wall; Post. wall, intervenous posterior wall; PVs, pulmonary venous region.

with 100% with paroxysmal AF (P<0.001). Similarly, DF_{peak} was rarely seen, occurring in only 9 of 193 (5%) persistent AF segments analyzed compared with 65% of paroxysmal AF segments (P<0.001). Although the mean DF of all 256 LA sites did not differ between persistent and paroxysmal AF (5.7±0.9 versus 5.7±0.9Hz; P=0.77), the highest DF at any one LA site in persistent AF (mean of the values for all segments in all persistent AF patients) was lower than that during paroxysmal AF (7.2±1.4 versus 9.6±3.6 Hz; P<0.001).

Discussion

In the present study, focal areas of DF_{peak} in the LA during fibrillation were present in 100% of patients (65% of segments) with paroxysmal AF compared with 31% of patients (5% of segments) with persistent AF. Although 43% of focal areas of DF_{peak} during paroxysmal AF were located in the pulmonary veins and posterior LA region, 57% were located in other regions. Importantly, we have shown that the locations of DF_{peak} were highly variable with time.

Putative Mechanisms of AF Maintenance

There is still much debate as to the mechanisms by which AF is maintained. One hypothesis is that fibrillation can be maintained as long as the number of electrical wavelets circulating randomly within the atria exceeds a critical number, such that mutual extinction of all wavelets does not occur and a steady state of random propagation exists.[11] However, the demonstration of spatial gradients in AF behavior[4] would contradict this concept as being the sole explanation for the maintenance of AF.

An alternative hypothesis is supported by the experimental data from cholinergic stimulation of sheep atria, during which high-frequency localized vortex-like microreentry circuits can be demonstrated with high-resolution optical mapping.[4] The cycle lengths at which these rotors oscillated correlated with the local DF as determined by spectral analysis. At the peripheries of these rotors, wavefront fractionation occurs, resulting in the outward propagation of multiple fibrillating wavelets toward the rest of the atria producing atrial frequency gradients.[12]

Previous mapping studies in humans have applied spectral analysis to demonstrate that frequency gradients also characterize paroxysmal and persistent AF in humans.[5,13] However, the key question is not whether they exist but their spatiotemporal stability in the rationale for targeting high-frequency areas for ablation in AF. By combining the techniques of spectral analysis with simultaneous global mapping, we have demonstrated that, although frequency gradients exist around localized peaks of DF throughout the LA in spontaneously occurring human AF, these DF_{peak} are spatiotemporally unstable. Although not previously characterized at high density with global and simultaneous data, the findings of the present study are supported by a growing body of evidence showing DF values to be temporally variable, provoking considerable current debate on this point that is critical to one of the prevailing ablative strategies in the evolution of AF ablation.[14,15]

Spatiotemporal Behavior of DF in Paroxysmal AF

It is notable in the present study, as well as in previous DF mapping studies of human AF,[13,16] that DFs >10 Hz occur. If the DF value equates to the underlying atrial activation rate, these values would represent cycle lengths <100 ms. The mean DF of DF_{peak} in our study (11.6 Hz) would equate to cycle length of 86 ms, and we observed DFs that would equate to cycle lengths <70 ms in 9% of DF_{peak}, including at nonpulmonary vein sites. Importantly, as in previous reports, these findings from noncontact data were validated by contact electrograms. A mechanistic explanation of DF_{peak} based on the presence of microreentrant rotors implies effective refractory periods of the underlying atrial tissue below these values. However, studies of effective refractory periods of human LA myocardium in patients with AF consistently find mean values >180 ms and lowest values >120 ms, outside the pulmonary veins in either atrium.[17–19] Action potential duration at the core of a rotor may be significantly shorter than at the periphery; however, to uphold the hypothesis that measured cycle lengths of the order of half of the effective refractory period of normal atrial tissue, derived from summated electrical activity measured in a unipolar fashion, are because the presence of rotor activity would require that localized areas of tissue with exceptional electrophysiological properties exist, capable of short refractory periods, possibly because of atypical cellular or architectural properties or the presence of high cholinergic activity, and most explanations of this nature would imply a fixed location.

For these reasons, our finding of spatiotemporal instability has particular significance in the interpretation of high-frequency phenomena, both in this and other studies. Although locally meandering reentrant activation or intermittency of rotor activity at multiple locations, possibly because of surges of cholinergic activity, could give rise to an appearance of spatiotemporal instability, the pattern of drift over several centimeters sometimes observed in our study is inconsistent with these mechanisms and argues against fixed and highly localized rotors being the sole explanation for DF_{peak}, even if only intermittently active. Furthermore, no consistent sequences in keeping with centrifugal activation centered around DF_{peak}

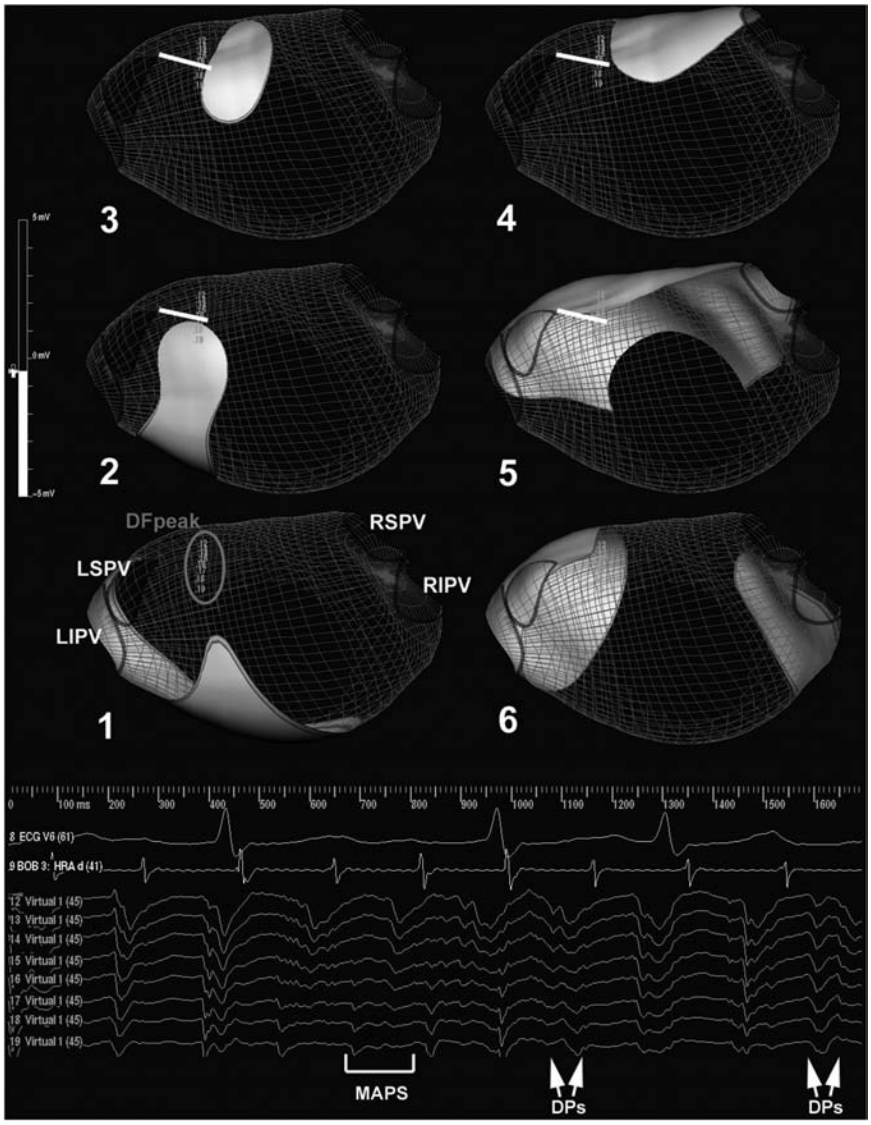

Figure 6. Wavefront propagation at the site of high DF (DF_{peak}). Six sequential posteroanterior views of left atrium (LA). DF_{peak} with DF 10.5 Hz indicated by the **oval** with virtual electrogram sample points overlying. Most of remaining LA has DF between 5 and 6 Hz. Wavefront of depolarization (**white**) is seen to pivot around line of block highlighted in **white** on maps 2 to 5. Virtual electrograms (**lower 8 electrograms**) exhibit frequent double potentials (DPs): region corresponding to maps indicated (MAPS). High right atrial electrogram (**second from top**) has frequency just >5 Hz. LIPV indicates left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

were seen during detailed off-line examination of noncontact mapping data, suggesting that these phenomena do not represent microreentrant circuits driving activation elsewhere.

Table 2. Temporal Stability of DF_{peak} in Paroxysmal Atrial Fibrillation

	κ Coefficient	Strength of Agreement	*P* Value
Pulmonary venous region	0.05	Poor	0.168
Posterior wall	−0.02	Poor	0.647
Lateral wall	0.04	Poor	0.285
LA appendage	0.19	Poor	0.001
Anterior wall	0.22	Fair	<0.001
Septum	−0.07	Poor	0.856
Roof	0.20	Fair	0.002

DF_{peak} indicates high dominant frequency; LA, left atrial.

An Alternative Explanation for DF_{peak}

An alternative explanation is that DF_{peak} represents sites of fibrillatory wavefront interruption, turning, or collision because of the development of functional lines of block. As is widely recognized in reentrant arrhythmias, electrograms at or near lines of block or turning points may show multiple or fractionated potentials, and this phenomenon has been shown to cause an increase in the measured DF at these sites, often causing it to double at sites where double potentials are recorded.[20] Other factors, such as electrogram morphology and amplitude, may also cause the measured DF of bipolar or unipolar electrograms to inaccurately represent underlying tissue activation rates.[20–22] On this background, our observation that DF_{peak} is not spatiotemporally stable suggests that the underlying mechanism is not always dependent on a fixed anatomical feature, but rather that DF_{peak} may often be functionally

determined electrophysiological phenomena, such as localized formation of functional block which may be transient and may occur or recur preferentially at some locations (Figure 6).

Differences in Behavior Between Paroxysmal and Persistent AF

It is notable that discrete areas of DF_{peak} were rarely observed during persistent AF compared with paroxysmal AF. If regions of DF_{peak} are functionally determined, whether by wavebreak surrounding microreentrant rotors or by wavefront collision or turning at lines of functional block, it is possible that these phenomena would be observed less frequently in the presence of the shorter refractory periods consequent upon the electrical remodeling of persistent AF.[23,24] However, these explanations cannot be proven with these data and require further investigation.

Is a Frequency-Map–Guided Ablation Strategy Rational?

Sites of high-frequency activation, displaying a frequency gradient to surrounding sites, have been proposed as possible locations of drivers maintaining AF and thus as potential targets for ablation.[13,25] In the present study, we did not use DF for targeting ablation. However, 2 studies to date have assessed the effect of prospective ablation at such sites, with differing results. Atienza et al[26] performed DF ablation in addition to circumferential pulmonary vein isolation (CPVI) in patients with paroxysmal and persistent AF and concluded that DF ablation predicted a successful outcome. The study lacked a control group without DF ablation, and the results achieved with their combined technique were not superior to those widely reported using CPVI alone.[27–29] Among patients with persistent AF, Verma et al[27] combined DF ablation with CPVI. Despite ablating all LA sites with a DF greater than the mean, there was minimal impact on AF cycle length, and long-term outcomes were not different from those in a control group that underwent CPVI alone.

The absence of convincing data to demonstrate clinical benefit from a DF-guided ablation strategy is consistent with our findings of spatiotemporal instability, drift, and absence of centrifugal activation from DF_{peak} in spontaneous AF. Taken together, all these findings call into question the concept of targeting DF_{peak} with ablation and indicate that (1) high-frequency activation per se is not necessarily an important site for ablation therapy, and (2) DF_{peak} is not typically anchored and may instead be functionally and, therefore, variably determined. Anatomy may be a determinant of preferential locations for this otherwise transient phenomenon. In summary, although high-frequency activation may be caused by intermittently active localized sources driving AF, as provides the theoretical rationale for ablating them, they are more likely to be sites of summated complex activation, resulting from complex incident activation and not source activity.

Although frequency mapping may, therefore, identify potentially important areas for maintaining AF, in the absence of consistent location of DF_{peak} and frequency gradient over time a strategy of targeting sites of high DF cannot be justified by the concept of ablating fixed driver sites, is unlikely to prove effective as the sole intervention, and will result in excessive atrial myocardial destruction.

Recent intriguing preliminary reports indicate how more sophisticated spectral analysis techniques, beyond identification of sites of high DF, may, however, fulfill the early promise of spectral analysis as a useful tool to guide AF ablation procedures. High-density contact mapping combined with the Hilbert transform and wave similarity analysis identifies sites for ablation reported to improve the success of wide-area CPVI.[30]

Limitations

Although the sample size in the present study was small, novel and meaningful findings of statistical significance were obtained. With respect to the ventricular subtraction process, variations in ventricular signal morphology could lead to incomplete cancellation. However, all segments were visually inspected and none needed to be rejected on grounds of major variations in QRS morphology. Although the accuracy of noncontact mapping signals has previously been demonstrated in the LA during human AF, it was found to decrease at sites distant (>4 cm) from the multielectrode array.[9] In the present study, 84% of all data were acquired at distances <4 cm from the center of the array, and the mean correlation coefficient between contact and noncontact signals in our validation data was high. Although validation of the accuracy of electrogram reconstruction was limited in the present study, the correlation findings are in keeping with those obtained in previous studies validating the system. The resolution of noncontact mapping technology, like that of contact unipolar or bipolar electrograms, is limited by several factors, including the effects of summating extracellular potentials from several cubic millimeters of myocardium, and has prevented elucidation of the exact local pathophysiology underlying these phenomena, which we have observed in the frequency domain.

Conclusions

Localized regions of high DF can be identified in humans by noncontact spectral analysis of the LA. They are not confined to the posterior LA and are seen in all patients with paroxysmal AF but only a minority of those with persistent AF. These areas exhibit significant spatiotemporal instability, and although DF-guided ablation is feasible, it cannot be advocated on the basis of the concept of ablating critical fixed drivers of AF. In attempts to improve outcomes in AF ablation, better identification of regions of the atria critical to maintaining fibrillation is needed.

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Disclosures

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CLINICAL PERSPECTIVE

Spectral analysis of atrial fibrillation (AF), using the fast Fourier transform, has been one of the most significant innovations in recent years in the search to understand the mechanisms maintaining AF and develop new targets for ablation therapy. Regions of high dominant frequency have been postulated to indicate the location of so-called drivers of AF, based, in part, on the observation of localized microreentrant sources in animal models exhibiting periodic high-frequency activation. Based on these theories, dominant frequency analysis software has been incorporated into major commercial electroanatomic mapping systems to guide AF ablation. Our research indicates that high dominant frequency areas are highly unstable in their location and, therefore, seem not to be associated with the location of fixed drivers of AF and are unlikely to be suitable targets for ablation. This finding has important clinical implications in view of the widespread dissemination of this mapping technology and contributes importantly to a currently polarized debate on its validity. Despite our finding that high dominant frequency seems not to be a useful marker for the presence of drivers, it is possible that other spectral characteristics of reentrant sources, such as high organizational index, may provide better means for identifying such sites.