Published in final edited form as:

IEEE Trans Biomed Eng. 2016 June ; 63(6): 1333–1340. doi:10.1109/TBME.2016.2553641.

Noninvasive Imaging of High Frequency Drivers and Reconstruction of Global Dominant Frequency Maps in Patients with Paroxysmal and Persistent Atrial Fibrillation

Zhaoye Zhou,

Department of Biomedical Engineering, University of Minnesota, Minneapolis, MN 55455 USA

Qi Jin,

Department of Cardiology, Ruijin Hospital Affiliated to Shanghai Jiaotong University, Shanghai, China

Lin Yee Chen,

Cardiovascular Division, Department of Medicine, University of Minnesota, MN 55455 USA

Long Yu,

Department of Biomedical Engineering, University of Minnesota, Minneapolis, MN 55455 USA

Liqun Wu, and

Department of Cardiology, Ruijin Hospital Affiliated to Shanghai Jiaotong University, Shanghai, China

Bin He [Fellow, IEEE]

Department of Biomedical Engineering and the Institute for Engineering in Medicine, University of Minnesota, Minneapolis, MN 55455, USA

Abstract

Objective—Highest dominant-frequency (DF) drivers maintaining atrial fibrillation (AF) activities are effective ablation targets for restoring sinus rhythms in patients. This study aims to investigate whether AF drivers with highest activation rate can be noninvasively localized by means of a frequency-based cardiac electrical imaging (CEI) technique, which may aid in the planning of ablation strategy and the investigation of the underlying mechanisms of AF.

Method—A total of 7 out of 13 patients were recorded with spontaneous paroxysmal or persistent AF and analyzed. The bi-atrial DF maps were reconstructed by coupling 5-second BSPM with CT-determined patient geometry. The CEI results were compared with ablation sites and DFs found from BSPMs.

Results—CEI imaged left-to-right maximal frequency gradient (7.42 ± 0.66 Hz vs. 5.85 ± 1.2 Hz, LA vs. RA, $p < 0.05$) in paroxysmal AF patients. Patients with persistent AF were imaged with a loss of the intra-chamber frequency gradient and a dispersion of the fast sources in both chambers. CEI was able to capture the AF behaviors, which were characterized by short-term

stability, dynamic transition, and spatial repetition of the highest DF sites. The imaged highest DF sites were consistent with ablation sites in patients studied.

Conclusions—The frequency-based CEI allows localization of AF drivers with highest DF and characterization of the spatiotemporal frequency behaviors, suggesting the possibility for individualizing treatment strategy and advancing understanding of the underlying AF mechanisms.

Significance: The establishment of noninvasive imaging techniques localizing AF drivers would facilitate management of this significant cardiac arrhythmia.

Index Terms

Atrial fibrillation; Cardiac electrical source imaging; Dominant frequency; Body surface potential mapping; Catheter ablation

I. Introduction

The mechanism of atrial fibrillation (AF) is complex and not yet fully understood. Contemporary studies suggested that disorganized electrical activations during AF might be maintained by drivers with exceedingly high activation rate, namely the highest dominant frequency (DF) [1–3]. Previous study have shown that ablation of these drivers with successful elimination of the bi-atrial frequency gradient could predict long-term freedom of fibrillation [4]. Therefore, it is postulated that such high-frequency drivers are effective targets for AF ablation. The localization of the drivers with highest DF is important for guiding ablation treatment as their locations can be found in both left and right atria, especially for patients with persistent and non-pulmonary-vein-foci paroxysmal AF. However, intracardiac mapping has limitations in identifying the locations due to the challenge of generating precise spatial-temporal maps within limited procedure time. Therefore, an alternative noninvasive technique to reconstruct atrial DF maps is needed for treatment individualization.

Noninvasive cardiac electrical source imaging techniques reconstruct cardiac electrical activities based upon body surface ECGs and patient's heart-torso geometry [5–16]. Unlike body surface potential maps (BSPMs) which represent a body surface manifestation of overall cardiac electrical activities, cardiac electrical source imaging reconstructs myocardial activation by mapping BSPM onto the source domain - the heart, thus allowing direct interpretation on cardiac activities. Cardiac electric imaging has previously been utilized for imaging atrial activities in terms of atrial activation sequences and AF rotor behavior [17–21]. However, none of the previous studies has examined whether frequency domain features can be imaged from the BSPMs. In the present study, we have proposed a frequency-based noninvasive cardiac electrical imaging (CEI) approach, which integrates spectral analysis with source imaging to reconstruct DF maps during AF. The goal of the study is to evaluate whether CEI is capable of identifying highest-DF drivers and recovering frequency features in AF patients.

II. Methods

A. Subjects

BSPMs were measured on 13 patients (Female=8, Male=5, averaged age = 58.5 ± 9.3) with paroxysmal AF and persistent AF. Subjects' clinical characteristics are summarized in Table 1. Among the 13 patients, a total of 7 of them underwent spontaneous AF and the AF episodes during BSPM recordings were analyzed by using the CEI method. All protocols were approved by the Institutional Review Board (IRB) of the Shanghai Ruijin Hospital (affiliated with Shanghai Jiao Tong University School of Medicine, Shanghai, China) and the IRB of the University of Minnesota. Data collection was performed after the signed informed consents were obtained from patients. See Fig. 1 for the study design.

B. Body surface potential mapping

The BSPMs were recorded when patients were at resting state (supine position with smooth breath). Before the BSPM recording session, a total of 208 Ag-AgCl carbon electrodes (BioSemi Active-Two) were placed on the anterior-lateral chest ($n=144$) and the posterior trunk ($n=64$). The electrodes were connected to BioSemi Active-Two measurement system with a sampling rate of 2048 Hz (with 400 Hz cutoff frequency for the low pass filter) and a 24 bit analog-to-digital converter. During the BSPM recording, patients were told to keep still with slow respiration in order to minimize baseline wandering and motion artifacts. After the BSPM measurement, the locations of electrodes were recorded by using a radio frequency digitizer (Fastrak, Polhemus Inc., Vermont).

C. Anatomical data acquisition

Computer Tomography (CT) was performed on each subject to obtain subject-specific heart-torso geometry. The heart geometries were obtained by continuous volume scanning from the great vessel level down to the diaphragm with intravenous (IV) contrast. The slice thickness was 0.4 mm and was fine enough for the segmentation of a refined heart model. Additional torso scans were performed with a slice thickness of 6 mm from the level of collar bone down to the lower abdomen, and were used to build a complete torso model. The in-plane resolution of the CT scan was fixed at 512×512 pixels. In order to avoid respiratory artifact, patients were alerted before the scanning to hold respirations. Continuous ECG was monitored and used for gating the CT scanner. The CT images were further processed by commercial software (Curry 6.0, Neuroscan, North Carolina) to obtain the individual heart-torso geometry. The heart and torso CT images were coupled based on important cardiac anatomical landmarks, such as the apex, and the co-registration errors were minimized with the assistance of Curry 6.0. Detailed anatomy structures including the atria, the ventricles, the lung and the torso were segmented. For the segmentation of the atria, important anatomical structures, like the pulmonary veins (PV), superior vena cava (SVC), inferior vena cava (IVC), tricuspid annulus (TA) and mitral annulus (MA), were identified and marked.

D. Signal processing

BSPMs were grounded with Wilson central terminal (WCT) and filtered with either 50-Hz or 60-Hz second-order infinite impulse response notch filter to remove the utility frequency component. BSPMs contained ventricular signals which would affect the atrial DF reconstruction, hence a classic and validated QRS-T template subtraction technique was applied to remove ventricular activities [22]. As ventricular components are independent from the atrial activities during AF [23], the Independent Component Analysis was further utilized following the template subtraction to remove any presented QRS residuals. BSPMs were then further low-pass filtered by a 10th order Butterworth filter with a cut-off frequency of 40 Hz.

E. Equivalent current density modeling

Based on the bi-domain theory, for a given point r in the myocardium, the equivalent cardiac source $\vec{j}_{eq}(r, t)$ representing the cardiac electrical activities can be derived as

$$\vec{j}_{eq}(r, t) = -\sigma_i(r) \nabla \phi_m(r, t) \quad (1)$$

where $\sigma(r)$ is the intracellular conductivity tensor, and $\phi_m(r, t)$ is the transmembrane potential (TMP) at location r and time t . Equation (1) defines $\vec{j}_{eq}(r, t)$ to be proportional to the spatial gradient of TMP. The depolarization phase of action potential is featured by an instantaneous rise from the resting potential to the plateau phase. The propagation of cardiac activation wavefront separates the myocardium into depolarized and non-depolarized regions.

Note that the widely-used intracardiac mapping technique using bipolar electrograms (EGM), is approximately a directional component of the spatial gradient of TMP [12]. The relationship between $\vec{j}_{eq}(r, t)$ and $\nabla \phi_m(r, t)$ in equation (1) tells that, similarly, the bipolar EGM can also be considered as a directional component of the local current density $\vec{j}_{eq}(r, t)$, that is, $|\vec{j}_{eq}(r, t)|$ provides an alternative and equivalent feature as bipolar EGMs for deriving the local activation rates.

F. Frequency analysis of cardiac sources

Clinical EP studies based on bipolar EGMs reported that the AF drivers with the highest DF served as potential ablation targets for AF treatment. As discussed above, local current density provides equally effective characteristics as the bipolar EGMs for frequency analysis, which enables us to implement the concept of DF into noninvasive cardiac source imaging technique.

Considering the local current density $|\vec{j}_{eq}(r, t)|$ at myocardium point r , which are sampled into T discrete samples j_m , $n=0, 1, 2, \dots, T-1$. The local excitation frequency can be determined by using Discrete Fourier transform (DFT) to transform j_n from time domain to $J_{eq}(k)$ in the frequency domain:

$$J_{eq}(k) = \sum_{n=0}^{T-1} j_n e^{-i2\pi kn/T} \quad (2)$$

where T is the number of samples, n is the current sample being considered, k is the index of frequency. The actual frequencies of periodic sequences depend on the sampling rate f_s and can be expressed by $f = f_s k/T$. The DF of atrial electrical activities for a given location r is corresponding to the frequency at which the power spectrum reaches maximal amplitude:

$$DF(r) = \frac{f_s}{T} \arg\max_k \left(\frac{|J_{eq}(k)|^2}{T} \right) \quad (3)$$

The time to frequency domain transform of cardiac sources allows us to investigate the spectral features of AF and identify high-frequency drivers for catheter ablation in a noninvasive way.

G. Forward and inverse solutions

The CEI technique was previously used to reconstruct 3-D ventricular cardiac activation patterns from BSPM, and has been validated with animal studies [11–13, 24, 25]. In the present study, CEI was used to image atrial electrical activity. As mentioned in the previous section, the equivalent cardiac electrical sources were represented by the equivalent current density (ECD) distribution. Given a tessellated geometrical heart-thorax model and the prior knowledge of the electrical conductivities of relevant tissues and organs [26, 27], the relationship between the ECD distribution and the extracellular potentials measurable on the body surface can be described by the following linear equation:

$$\Phi(t) = LJ(t) \quad (4)$$

Where $\Phi(t)$ is a $M \times 1$ column vector of body surface potentials measured from M body surface electrodes at time t , $J(t)$ is a $3N \times 1$ column vector of ECD distribution from N myocardial grid points, and L is the $M \times 3N$ source-to-field transfer matrix relating the ECD distribution to the body surface potentials. This linear inverse problem was solved using the weighted minimum norm (WMN) estimation [11, 28, 29], which minimizes the following objective function:

$$\min_{J(t)} (\|\Phi(t) - LJ(t)\|_2^2 + \lambda \|WJ(t)\|_2^2) \quad (5)$$

Where W is the Kronecker product of a 3×3 identity matrix I and a $N \times N$ diagonal matrix Ω . λ is the regularization parameter, which can be chosen by using the L-curve method [30].

H. Data Analysis

In the present study, a 2-dimensional (2-D) atrial surface source model was used to equivalently represent atrial electrical activity, ignoring the thickness of atria. The LA and RA were discretized into 2282 ± 576 grid points with a spatial resolution of 3mm. The 2-D atrial ECD distributions were then reconstructed from the BSPM with the aid of the patient-specific heart-torso boundary element geometry model obtained from subjects' CT images [11–13]. In order to image AF drivers exciting at relatively stable high frequency, a fixed 5-seconds length of BSPMs was used for analysis to ensure the capture of reliable high-frequency source.

Following ECD reconstruction, the ECD waveforms were then tapered with Hanning window to set the edge value to zero, and processed with a 3 Hz – 15 Hz band-pass filter. The ECD waveform of 5 seconds was zero-padded to 20 seconds in order to obtain higher spectral resolutions. FFT was then performed on the ECD waveform at each given atrial location using the commercial MATLAB package (MATLAB R2012b, Mathworks, Massachusetts). The bi-atrial DF map was computed from the frequency corresponding to the highest peak in the power spectrum. The regularity index (RI) was defined as the ratio of the power at the DF and its neighboring 0.75 Hz frequency band to the power of the 3–15 Hz band [2], and was used here to guarantee the reliability of the reconstructed DF. Only points with $RI > 0.2$ were selected in the reconstruction of DF map. The maximal DF site was defined as the highest DF surrounded by a 20% decreasing frequency gradient.

I. BSPM DF maps

CEI reconstructs the spatial distribution of atrial electrical activities at each time instant, from the potential map on the torso at the corresponding time point. It is necessary to evaluate whether it can also reliably recover the frequency features in the atria based on what is spatially observed from BSPM. Therefore, the DF distribution on the torso was computed by performing the same FFT analysis procedure on the BSPM and compared with the reconstructed atrial DF map. After removal of ventricular components, the surface ECG waveforms were tapered with Hanning window and filtered by 3 Hz – 15 Hz band-pass filter. The BSPM DF map was then computed by applying FFT analysis to 5-second surface ECGs and selecting the frequency with highest peak in the power spectrum.

J. Statistical Analysis

To further investigate the dispersion and coherence of the results, statistical analysis was applied to compare the variability of frequency features in different groups of patients. Paired student's t test was applied in the comparison for maximal DFs in RA and LA within each group (paroxysmal group vs. persistent group) in order to evaluate the LA-to-RA frequency difference. The result was considered to be statistically significant when the p-value was found to be < 0.05 . Repeating variables, like the maximal DFs observed in patients from different time intervals, were reported in the form of mean $\pm$ standard deviation (SD).

III. Results

A total of 7 patients had spontaneous AF during BSPM recording (n=3 for paroxysmal patients, n=4 for persistent patients) and were analyzed by using the CEI technique. In paroxysmal AF patients, atrial enlargements were found in two of the four analyzed patients. All persistent AF patients had atrial enlargements (LA=3, RA=1), which might indicate more risks of structural heart disease. Patients without spontaneous AF were recorded with sinus rhythm and therefore no high-frequency drivers could be observed.

Fig. 2 shows successive DF maps obtained from a 60-year old male paroxysmal AF patient. The patient had AF recurrence 22 months after the first ablation procedure. Spontaneous AF was recorded one day prior to the second procedure. On this patient, CEI repeatedly showed: (1) focal maximal DF sites at the inferior area of the right inferior PV (RIPV), the superior area of the left superior PV (LSPV), and the LA roof; and (2) a persistent LA-to-RA frequency gradient (maximal DFs in LA vs. maximal DFs in RA: 7.2 ± 0.4 vs. 6.6 ± 0.2 , $p < 0.05$). CEI was able to image the persistent maintenance as well as transition of maximal DF sites over time. At time window A, the maximal DF sites were observed at superior LSPV (7.4Hz) and LA roof (7.4 Hz) (Fig. 2A). Later on, the maximal DF at superior LSPV persists (7.8 Hz) while the high frequency activity at LA roof vanishes, and the inferior area of the RIPV begins to activate as the secondary highest DF site (7.4 Hz) (Fig. 2B). In the following time window C, the superior LA completely degenerates into low frequency activity, and the inferior area of the RIPV takes the role of dominant driver (6.8Hz). Note that the temporal transition of highest DF sites appeared to be spatially stable, namely highest DF sites were only found in certain locations. The time window for observation was shown by lead V1, each with a fixed 5-second interval. A sustaining LA-to-RA frequency gradient was observed over time regardless of the change of the maximal DF sites. The imaged maximal DF site corresponded well with the ablation sites (Fig. 2, red balls, superior LSPV, LA roof and the inferior area of RIPV), and the variation of the highest DF was confined to the sites of ablation.

Fig. 3 shows the examples of DF maps reconstructed from a 59-year old patient with persistent AF, the time windows for imaging were shown by ECG lead V1. In a sequential time series, CEI repeatedly found: (1) Maximal DF sites localized at the left inferior PV (LIPV), RIPV, right superior PV (RSPV) and right atrial appendage (RAA); (2) the absence of significant hierarchical LA-to-RA DF gradient and a spatial disorganization of frequency distribution; (3) a bi-atrial dispersion of high-frequency activities as compared with the paroxysmal patient; and (4) the maximal DF sites migrated over time yet were restricted in a confined region and can be repeatedly imaged from independent AF segments. The results show stationary maintenance, dynamic transition, and spatial repetition of maximal DF sites over time: a sustaining maximal DF was observed to be harboring at the RAA over time (the lower panels of Fig. 3, A–D), the maximal DF located at LIPV was stable during time window A–B (purple red area in white dotted line, the upper panels of Fig. 3, A–B), yet degenerated at time window C, and RSPV and RIPV have become the sites with maximal DF (Fig. 3, C and D). This patient underwent circumferential pulmonary isolation (CPVI) and AF re-occurred at day 2 after ablation. The un-ablated persistent highest DF site at RAA might possibly associate with the remaining drivers leading to the recurrence of AF episode.

The highest DF sites found in all patients were summarized and compared with ablation sites in Table II. AF drivers were also found around PVs in the other 2 paroxysmal patients who underwent circumferential PV isolation (7.48 ± 0.8 Hz). In all paroxysmal patients, a significant left-to-right frequency gradient was found (7.42 ± 0.66 Hz vs. 5.85 ± 1.2 Hz, LA vs. RA, $p < 0.05$). The imaged drivers were consistent with ablation sites in paroxysmal AF patients. All persistent AF patients underwent circumferential PV isolation, but AF was not terminated by the ablation (Table II). High frequency drivers were identified in all persistent AF patients. In three out of the four persistent AF patients, non-PV drivers were found at LAA and RAA, suggesting the existence of un-ablated sources likely to maintain AF. Compared with paroxysmal AF, a loss in LA-to-RA frequency order was observed from persistent AF patients (8.09 ± 1.06 Hz vs. 7.6 ± 1.03 Hz, LA vs. RA, $p = 0.2$).

We also evaluated the correlation between the body surface DFs and the imaged atrial DF. Fig. 4 shows the DF map on the torso determined from 5-s BSPM in Fig. 3C. The body surface DF map shows similar frequency ranges (6.0 – 8.5 Hz) with the imaged atrial DF map (5.8 – 8.6 Hz). Highest DF sites on the torso were located at right anterior chest and medial to right posterior trunk, which may represent the projections of highest intracardial DF from RAA and left pulmonary veins. The mean DF was 6.4 Hz for body surface and 6.5 Hz for the atrium.

IV. Discussions

We report for the first time an investigation of noninvasive imaging AF spectral characteristics from BSPM in a group of patients by integrating the cardiac electric imaging (CEI) with clinical dominant frequency (DF) concept. The frequency-based CEI technique is capable of imaging the spatiotemporal behavior of DF and pinpointing the drivers with highest activation frequency during AF. On paroxysmal AF patients, the hierarchical spectral patterns featured by LA-to-RA maximal frequency gradient were observed. In persistent AF patients, the DF behavior was characterized by the loss of the hierarchical pattern and the dispersion of AF drivers in both atriums. Although the DF maps were reported previously [3] from intracardiac recordings, our results indicate, for the first time, that similar findings can be obtained noninvasively from the frequency-based CEI. For patients with both paroxysmal and persistent AF, the CEI captured the temporal dynamic transition as well as repetition of highest-DF drivers. Therefore, for AF patients with significant spatial and temporal variability, the CEI may assist in the planning of ablation strategy by identifying drivers with high-occurrence rate as effective targets for AF termination. The present imaging results were retrospectively evaluated with clinical outcome and the DF sites found from paroxysmal patients were consistent with ablation sites. The CEI also identified untargated high-frequency sources, which might be a reason of AF maintenance in persistent AF cases. Our findings suggest that the CEI is able to image AF triggers and substrates featured by high-frequency activities during AF.

A recent study, using a sheep model, has demonstrated that DF increased with the progression from paroxysmal to persistent AF, and that the speed of DF change was strongly correlated with the time of AF transition [31]. The dynamic transition of DF reflects altered activation frequency resulting from the complex atrial remodeling process; hence,

investigating spectral variation may yield insights into novel AF mechanisms. Since there are limitations in extrapolating from animal models, and spontaneous AF are likely to have different mechanisms, it is important to study how electrical activity behaves as AF evolves in human subjects in real-life settings. The CEI technique enables noninvasive electrical imaging from body surface recording; hence it provides the potential to investigate AF mechanism in intact human hearts and gives insights into the realistic electrical remodeling process.

The paroxysmal AF data presented here reveals the underlying AF mechanisms. Specifically, the existence of sustaining left-to-right DF gradients is consistent with the spatiotemporal organization of paroxysmal AF [1–3]. The single or multiple highest DF sites featured by high-frequency periodical electrical activities are in good agreement with ablation sites. The observation of temporal variation as well as spatial repeatability of the highest DF sites are consistent with the spatio-temporal complexity of AF itself and is further supported by previous findings [32, 33]. The above-mentioned observations suggest localized sites of high-frequency electrical activities with a corresponding frequency hierarchy as the mechanism of AF in patients.

The CEI method also offers the potential to further aid in clinical intervention of paroxysmal AF. Patients with paroxysmal AF may have non-PV triggers [34]. The locations of AF triggers in these patients were found to be dispersive over LA and RA. Therefore, it is of clinical significance to distinguish between PV and non-PV initiated paroxysmal AF and to further predict the location of the non-PV triggers. As the highest DF is closely associated with such underlying source maintaining AF, the CEI may characterize locations of the high-frequency sources and optimize the ablation strategy pre-operatively.

Our technique also has important clinical implications for assisting the ablation of persistent and long standing persistent AF, which has much lower success rates than paroxysmal AF. Compared with the paroxysmal AF, it is characterized by spatiotemporal disorganization, a loss of the hierarchical frequency gradient, and a biatrial dispersion of the highest DFs [2, 3]. It has also been suggested that failure of termination might be due to the untargeted critical highest DF dispersed at both atria [2–4]. The temporal complexity of persistent and long-standing persistent AF results in the challenge of intraoperative mapping [35]. Knowledge regarding the spatio-temporal distributions of these underlying substrates is important and might help improve the ablation outcome. While clinical sequential mapping is limited in this aspect [35], the CEI technique offers the potential to localize these critical DF sites, image the spatiotemporal variation of highest DF before clinical intervention and assist in individualizing the ablation strategy.

We have used a 2D equivalent current density source model to represent atrial electrical activity. Due to the very thin nature of atria over most areas, such approximation is deemed appropriate and supported by our promising clinical results. In a more accurate source model, one would need to account for the volume nature of atria by expanding the 2D atrial surface current density source model to a 3D atrial current density source model (see [7]–[13], e.g.).

The current density distribution, as the output of the source model adopted in this study, maybe interpreted as the spatial gradient of the transmembrane potential. Therefore, its components are dependent to the direction of the activation wavefront, e.g., the directional component will be zero if it is parallel with the activation wavefront. It has similar biophysical indication to intracardiac bipolar EGMs which have already been used for clinical DF maps – both are scalars due to the propagation of activation wavefront and reflect local excitation frequency. For these considerations, we have performed the spectral analysis on the norm of the current density vector. Alternatively one may perform FFT on individual directional components which maybe computationally more efficient, but there maybe challenges in its biophysical interpretation.

To our knowledge, this study represents the first report to noninvasively imaging the frequency feature of AF from BSPM by coupling the cardiac electric imaging technique with dominant frequency concept. This technique has important clinical implication for assisting catheter ablation, individualizing ablation strategy, and facilitating the study of AF mechanism in real-life setting. The scope of the present study is to evaluate the feasibility of CEI to imaging DF behaviors during AF, thus a relatively limited number of patients was included. A large-scale patient study including paroxysmal, persistent and long-standing persistent AF patients is needed for further rigorous evaluation.

In the present study, direct intracardiac DF map is not available due to the fact that the acquisition of bi-chamber electrograms is not a standard clinical routine. We evaluated the frequency-based CEI by 1) comparing the highest DF sites with ablation sites and 2) comparing the overall spectral characteristics with literatures of intracardiac DFs. Multiple studies with intracardiac AF electrograms and body surface potential maps [36–39], reported that the DFs presented in atria were correlated with DFs presented on the body surface: 1) high frequency sites on the torso are correlated with high frequency sites in the closest chamber; 2) the LA-to-RA DF gradient in atria can also be observed on the body surface; 3) regions of maximal DF can be reflected on the body surface. Therefore, although DF map from intracardiac recording is not available in current study, comparing simultaneous BSPM DF with imaged DF suggests the qualitative concordance between these two measures.

V. Conclusions

We have developed a new approach integrating cardiac electric imaging with spectral analysis, and evaluated the method in a group of patients suffering from AF. The present study reports for the first time a noninvasive investigation of the spatial distribution of dominant frequency and identifying high-frequency drivers that maintain AF. The frequency based cardiac electric imaging revealed high frequency drivers consistent with ablation sites in the patients studied. The present results indicate noninvasive frequency analysis of AF is feasible and may give insight into the underlying mechanisms of AF in intact human hearts. Furthermore, a priori knowledge of the atrial substrate maintaining the fibrillation activity may help individualize ablation strategy, improve ablation outcome, and reduce procedural time.

Acknowledgments

This work was supported in part by NIH RO1HL080093 and NSF CBET-0756331, and a grant from the Institute of Engineering in Medicine from the University of Minnesota.

The author would like to thank Dr. Chengzong Han for useful discussions.

References

1. Skanes AC, et al. Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart. *Circulation*. Sep; 1998 98(12):1236–1248. [PubMed: 9743516]
2. Sanders P, et al. Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. *Circulation*. Aug; 2005 112(6):789–797. [PubMed: 16061740]
3. Lazar S, et al. Presence of left-to-right atrial frequency gradient in paroxysmal but not persistent atrial fibrillation in humans. *Circulation*. Nov; 2004 110(20):3181–3186. [PubMed: 15533867]
4. Atienza F, et al. Real-time dominant frequency mapping and ablation of dominant frequency sites in atrial fibrillation with left-to-right frequency gradients predicts long-term maintenance of sinus rhythm. *Heart Rhythm*. Jan; 2009 6(1):33–40. [PubMed: 19121797]
5. Greensite F, Huiskamp G. An improved method for estimating epicardial potentials from the body surface. *IEEE Trans Biomed Eng*. Jan; 1998 45(1):98–104. [PubMed: 9444844]
6. Armoundas AA, et al. A single equivalent moving dipole model: an efficient approach for localizing sites of origin of ventricular electrical activation. *Ann Biomed Eng*. May; 2003 31(5):564–576. [PubMed: 12757200]
7. He B, Wu D. Imaging and visualization of 3-D cardiac electric activity. *IEEE Trans Inf Technol Biomed*. Sep; 2001 5(3):181–186. [PubMed: 11550839]
8. Li G, He B. Localization of the site of origin of cardiac activation by means of a heart-model-based electrocardiographic imaging approach. *IEEE Trans Biomed Eng*. Jun; 2001 48(6):660–669. [PubMed: 11396596]
9. He B, et al. Noninvasive three-dimensional activation time imaging of ventricular excitation by means of a heart-excitation model. *Phys Med Biol*. Nov; 2002 47(22):4063–4078. [PubMed: 12476982]
10. Liu C, et al. Estimation of global ventricular activation sequences by noninvasive three-dimensional electrical imaging: validation studies in a Swine model during pacing. *J Cardiovasc Electrophysiol*. May; 2008 19(5):535–540. [PubMed: 18179521]
11. Liu Z, et al. Noninvasive reconstruction of three-dimensional ventricular activation sequence from the inverse solution of distributed equivalent current density. *IEEE Trans Med Imag*. Oct; 2006 25(10):1307–1318.
12. Han C, et al. Noninvasive three-dimensional cardiac activation imaging from body surface potential maps: a computational and experimental study on a rabbit model. *IEEE Trans Med Imag*. Nov; 2008 27(11):1622–1630.
13. Han C, et al. Noninvasive imaging of three-dimensional cardiac activation sequence during pacing and ventricular tachycardia. *Heart Rhythm*. Aug; 2011 8(8):1266–1272. [PubMed: 21397046]
14. Ohyu S, et al. Use of the ventricular propagated excitation model in the magnetocardiographic inverse problem for reconstruction of electrophysiological properties. *IEEE Trans Biomed Eng*. Jun; 2002 49(6):509–519. [PubMed: 12046695]
15. Wang L, et al. Physiological-model-constrained noninvasive reconstruction of volumetric myocardial transmembrane potentials. *IEEE Trans Biomed Eng*. Feb; 2010 57(2):296–315. [PubMed: 19535316]
16. Wang D, et al. Inverse electrocardiographic source localization of ischemia: an optimization framework and finite element solution. *J Comput Phys*. Oct.2013 250:403–424. [PubMed: 23913980]
17. Tilg B, et al. Imaging of electrical function within the human atrium and ventricle from Paced ECG mapping data. *Funct Imag Modeling Heart*. 2001; 2230:148–155.

18. Tilg B, et al. Electrocardiographic imaging of atrial and ventricular electrical activation. *Med Image Anal.* Sep; 2003 7(3):391–398. [PubMed: 12946477]
19. Seger M, et al. Non-invasive imaging of atrial flutter. *Comput Cardiol.* 2006; 33:601–604.
20. Cuculich PS, et al. Noninvasive characterization of epicardial activation in humans with diverse atrial fibrillation patterns. *Circulation.* Oct; 2010 122(14):1364–1372. [PubMed: 20855661]
21. Haissaguerre M, et al. Driver domains in persistent atrial fibrillation. *Circulation.* Aug; 2014 130(7):530–538. [PubMed: 25028391]
22. Xi Q, et al. The effect of QRS cancellation on atrial fibrillatory wave signal characteristics in the surface electrocardiogram. *J Electrocardiol.* Jul; 2003 36(3):243–249. [PubMed: 12942487]
23. Rieta JJ, et al. Atrial activity extraction for atrial fibrillation analysis using blind source separation. *IEEE Trans Biomed Eng.* Jul; 2004 51(7):1176–1786. [PubMed: 15248534]
24. Han C, et al. Noninvasive reconstruction of the three-dimensional ventricular activation sequence during pacing and ventricular tachycardia in the canine heart. *Am J Physiol Heart Circ Physiol.* Jan; 2012 302(1):H244–252. [PubMed: 21984548]
25. Han C, et al. Noninvasive cardiac activation imaging of ventricular arrhythmias during drug-induced QT prolongation in the rabbit heart. *Heart Rhythm.* Oct; 2013 10(10):1509–1515. [PubMed: 23773986]
26. Gabriel S, et al. The dielectric properties of biological tissues: II. Measurements in the frequency range 10 Hz to 20 GHz. *Phys Med Biol.* Nov; 1996 41(11):2251–2269. [PubMed: 8938025]
27. Malmivuo, J., Plonsey, R. *Bioelectromagnetism.* New York: Oxford Univ. Press; 1995.
28. Wang JZ, et al. Magnetic source images determined by a lead-field analysis: the unique minimum-norm least-squares estimation. *IEEE Trans Biomed Eng.* Jul; 1992 39(7):665–675. [PubMed: 1516933]
29. Pascual-Marqui RD. Reply to comments by Hamalainen, Ilmoniemi and Nunez. *ISBET Newslett.* Dec.1995 6:16–28.
30. Hansen PC. Analysis of discrete ill-posed problems by means of the L-curve. *SIAM Rev.* 1992; 34:561–580.
31. Martins RP, et al. Dominant frequency increase rate predicts transition from paroxysmal to long-term persistent atrial fibrillation. *Circulation.* Apr; 2014 129(14):1472–1482. [PubMed: 24463369]
32. Schuessler RB, et al. Spatial and temporal stability of the dominant frequency of activation in human atrial fibrillation. *J Electrocardiol.* Oct; 2006 39(4 Suppl):S7–12. [PubMed: 16920139]
33. Konings KT, et al. High-density mapping of electrically induced atrial fibrillation in humans. *Circulation.* Apr; 1994 89(4):1665–1680. [PubMed: 8149534]
34. Lin WS, et al. Catheter ablation of paroxysmal atrial fibrillation initiated by non-pulmonary vein ectopy. *Circulation.* Jul; 2003 107(25):3176–3183. [PubMed: 12821558]
35. Habel N, et al. The temporal variability of dominant frequency and complex fractionated atrial electrograms constrains the validity of sequential mapping in human atrial fibrillation. *Heart Rhythm.* May; 2010 7(5):586–593. [PubMed: 20156614]
36. Guillem MS, et al. Noninvasive localization of maximal frequency sites of atrial fibrillation by body surface potential mapping. *Circ Arrhythm Electrophysiol.* Apr; 2013 6(2):294–301. [PubMed: 23443619]
37. Petrutiu S, et al. Manifestation of left atrial events and interatrial frequency gradients in the surface electrocardiogram during atrial fibrillation: contributions from posterior leads. *J Cardiovasc Electrophysiol.* Nov; 2009 20(11):1231–1236. [PubMed: 19563359]
38. Bojarnejad M, et al. Non-invasive estimation of left atrial dominant frequency in atrial fibrillation from different electrode sites: insight from body surface potential mapping. *J Atr Fibrillation.* 2014; 7(3):6–10.
39. Bojarnejad M, et al. Comparing Power Spectral Density of the 64-Channel Surface ECG with Left Atrial Electrograms in Patients in Atrial Fibrillation. *Comput Cardiol.* 2012; 39:713–716.

Fig. 1.
Schematic diagram of the frequency based cardiac electric imaging and validation in patients with atrial fibrillation.

Fig. 2.

(A)–(C) Imaged DF maps from a selected paroxysmal AF patient. The corresponding BSPM time frames A–C were shown in lead V1 in the upper panel. The dark red balls show the ablation points in CARTO record. The DF value is color coded from red (low frequency) to purple (high frequency).

Fig. 3.

Imaged DF maps in one persistent AF patient. Lead V1 on the upper panel shows the time frames which were used for the DF reconstruction. (A) – (D): the DF maps obtained from time frame A – D with a fixed length of 5 seconds in lead V1, respectively. The dotted white line indicates the ablation zone to isolate the electrical activities from the pulmonary vein area.

Fig. 4.

(A) The DF distribution on the torso corresponding to the 5-s BSPM in Fig. 3C. (B) The signals on surface leads.

TABLE I

PATIENT CHARACTERISTICS AND MEDICAL HISTORIES

	Age	Gender	Diagnosis	Previous Ablation	Blood Pressure	BSPM Rhythm	Antiarrhythmic Medication	Medical History*	Atrial Size
1	59	M	Persistent	None	123/74	AF	Metoprolol Warfarin Valsartan Amlodipine	Hypertension, Tricuspid Regurgitation	LA Enlargement
2	60	M	Persistent	None	149/94	AF	Metoprolol Digoxin	Hypertension, Mitral Regurgitation	LA Enlargement
3	59	F	Persistent	None	116/84	AF	Bisoprolol Warfarin	Mitral Regurgitation, Tricuspid Regurgitation	LA Enlargement
4	62	M	Persistent	1	129/102	AF	Bisoprolol Fumarate	Hyperlipemia, Tricuspid regurgitation	RA Enlargement
5	60	M	Paroxysmal	1	103/62	AF	Warfarin Flecainide Diltiazem	Hyperlipemia, Mitral Regurgitation	Normal
6	64	F	Paroxysmal	1	90/52	AF	Warfarin, Dronedarone	Hypertension, Tricuspid Regurgitation, Mitral valve Disorders, Congestive Heart Failure	Normal
7	38	F	Paroxysmal	1	91/58	AF	Warfarin Lisopril Metoprolol	Restrictive Cardiomyopathy Hypertension	LA Enlargement
8	45	F	Paroxysmal PAC	None	120/71	Sinus	None	N/A	Normal
9	55	F	Paroxysmal	None	130/80	Sinus	Aspirin	Diabetes	LA Enlargement
10	56	F	Paroxysmal	None	137/76	Sinus	Metoprolol	N/A	Normal
11	68	F	Paroxysmal PAC	None	150/90	Sinus	Aspirin, Clopidogrel	Hypertension	LA and RA Enlargement
12	70	M	Paroxysmal	None	101/48	Sinus	Warfarin	Mitral Regurgitation	Normal
13	65	F	Paroxysmal AFL	None	126/65	Sinus	Cordarone	N/A	Normal

* Selective cardiovascular related medical history; F = female, M=male, BSPM=body surface potential map, PAC=premature atrial contraction, AFL=atrial flutter.

TABLE II

Highest-DF sites found on patients by using the CEI technique in comparison with patients' clinical outcome.

#	AF Type	Locations of Highest DF	Ablation	Other Procedure	Un-ablated DF Sites *	Termination after Ablation
1	ParoAF	LSPV LA Roof Inferior RIPV	LSPV LA Roof Inferior RIPV	N/A	None	Y
2	ParoAF	LSPV LIPV RIPV	CPVI	N/A	None	Y
3	ParoAF	LIPV	N/A	MAZE	N/A	N/A
4	PerAF	LIPV RIPV RSPV RAA	CPVI	N/A	RAA	N
5	PerAF	LIPV LSPV RIPV RAA	CPVI	N/A	RAA	N
6	PerAF	RSPV LSPV	CPVI	N/A	None	N
7	PerAF	LSPV LAA	CPVI	N/A	LAA	N

* Atrial sites found with highest DF but were not ablated in radiofrequency ablation; CPVI = Circumferential pulmonary vein isolation; LSPV = Left superior pulmonary vein; LIPV = Left inferior pulmonary vein; RSPV = Right superior pulmonary vein; RIPV = Right inferior pulmonary vein; Y = Yes; N = No; N/A = Not applicable; ParoAF=Paroxysmal AF; PerAF=Persistent AF.