A method for quantifying recurrent patterns of local wavefront direction during atrial fibrillation

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ABSTRACT

Introduction: Spiral wave reentry is a potential mechanism of atrial fibrillation (AF), but is difficult to differentiate clinically from multiple wavelet breakup using standard bipolar recordings. We developed a new methodology using bipolar recordings to estimate the direction of local activation wavefronts during AF by calculating the electrogram conformation (Egm-C). We subsequently used recurrence quantification analysis (RQA) of Egm-C to differentiate regions of spiral wave reentry from wavelet breakup.

Methods: A 2D computer simulation was created with regions containing a stable spiral wave and also regions of wavebreak. A grid of 40 × 40 unipolar electrodes was superimposed. At each site, the actual wavefront direction (WD) was determined by comparing relative activation timings of the local intracellular recordings, and the estimated wavefront direction (Egm-C) was determined from the morphology of the local bipolar electrogram. RQA of Egm-C was compared to RQA of actual WD in order to differentiate AF mechanisms.

Results: RQA of actual WD and Egm-C both distinguished regions of spiral wave reentry from wavelet breakup with high correlation between the two methods (recurrence rate, r = 0.96; determinism, r = 0.61; line max, r = 0.95; entropy, r = 0.84; p < 0.001 for all). In areas of stable spiral wave reentry, the recurrence plots of both Egm-C and actual WD demonstrated stable, periodic dynamics, while regions of wavebreak demonstrated chaotic behavior largely devoid of repetitive activation patterns.

Conclusion: Calculation of Egm-C allows RQA to be performed on bipolar electrograms during AF and differentiates regions of spiral wave reentry from multiple wavelet breakup.

1. Introduction

Atrial fibrillation is a dynamic, nonstationary system with multiple potential mechanisms including spiral wave reentry and multiple wavelet reentry [1–4]. Differentiation of areas exhibiting highly periodic or intermittently periodic behavior from regions of chaos could be important in identifying sources of AF which could be targeted for ablation. Recurrence quantification analysis (RQA) is a nonlinear tool that readily differentiates periodicity from chaos and quantifies stability, determinism and other features of dynamical systems, and thus could be helpful in this regard.

Analysis of the patterns of local wavefront direction may give insight into local dynamics and underlying mechanism of fibrillation. Bipolar electrogram morphology yields important information about the direction of wavefront propagation relative to the electrodes. It is not surprising that sources of AF have been shown to exhibit repetitive bipolar waveform morphology [5–7]. However, parameters such as similarity index, which generally measure the degree of self-similarity over short windows, in and of themselves provide limited information on system dynamics. RQA could potentially be performed on longer windows and quantify local dynamics over time.

RQA can be performed on either continuous or discrete time series. To maximize information from a dynamical system, the series should be embedded into a phase space of high enough dimension to allow complete unfolding of its attractor. When RQA has previously been applied to continuous AF voltage series using physiologically useful dimensions, much of the recurrence actually occurs in the relatively flat baselines in between activations, providing little information about local wavefront...
direction [8,9]. We have developed a novel technique where each activation can be reduced to a simple metric, electrogram conformation, which is a crude measure of wavefront direction. Transformation of the electrogram into a discrete series of electrogram conformations, allows the series to be embedded into a multi-dimensional phase space in a way that preserves information about the complex patterns of local wavefront direction. In this manuscript we describe our method for deriving electrogram conformation (Egm-C), and hypothesize that RQA of Egm-C will provide similar information about local dynamics to RQA of the series of actual local wavefront directions. Areas within a rotor are expected to display repetitive patterns of wavefront directionality and thus Egm-C. On the other hand, regions of unstable multiple wavelet reentry are expected to be affected by constantly changing multiple daughter wavelets and display chaotic dynamics. Areas with passive transient rotor formation may demonstrate unstable periodic behavior amid a background of chaos.

2. Methods

2.1. Myocyte action potential computer model

Atrial myocyte action potential was simulated using a modified Courtemanche detailed human atrial model [10]. This model calculates the membrane voltage as a function of time using the following formulation:

\[
\frac{dV}{dt} = \frac{1}{C_m} I_{ton} + I_{st}
\]

where

\[ I_{ton} = (I_{Na} + I_{Ca,L} + I_{L} + I_{K} + I_{K1} + I_{Ks} + I_{NCX} + I_{Nak} + I_{Ca} + I_{K,Ad}) \]

(1)

where \( I_{ton} \) represents the individual membrane currents, \( I_{st} \) represents the stimulus current, and \( C_m \) represents the membrane capacitance (1 μF/cm²). The following modifications were made to the model: 1) The maximum conductances of the L-type Ca current (\( I_{Ca,L} \)), the slow component of delayed rectifier K current (\( I_{Ks} \)), the transient outward K current (\( I_{Ko} \)), and the sodium-calcium exchanger current (\( I_{NCX} \)) were changed to 70%, 70%, 50%, and 145%, respectively, of the original values, to represent ionic remodeling in chronic heart failure [11]. 2) Cholinergic modulation was simulated with the addition of the ACh-activated K current, \( I_{K(ACH)} \), with the following formulation [12]:

\[
I_{K(ACH)} = \left( \frac{10}{1 + \exp \left[ \frac{[ACh] - 0.0172}{0.45116} \right]} \right) (V - E_K)
\]

(2)

where \([ACh]\) is the ionic concentration of acetylcholine (μmol/L).

2.2. Simulations of 2D wave propagation

2D wave propagation was simulated in a \( 800 \times 800 \) node (20 × 20 cm) monodomains tissue using the following reaction-diffusion equation using an adaptive time step [13–15]:

\[
\frac{\partial V}{\partial t} = \frac{1}{C_m} I_{ton} + I_{st} + V \cdot \nabla^2 V
\]

(3)

where \( \nabla^2 \) is the 2 × 2 diffusion tensor:

\[
\nabla^2 = \begin{pmatrix} D_{xx} & D_{xy} \\ D_{yx} & D_{yy} \end{pmatrix}
\]

(4)

with the following local to global transformation elements:

\[
D_{xx} = D_{L} \cos^2(\theta(x)) + D_{L} \sin^2(\theta(x))
\]

(5)

\[
D_{xy} = D_{L} \sin(\theta(x)) \cos(\theta(x))
\]

(6)

\[
D_{yx} = D_{L} \cos(\theta(x)) \sin(\theta(x))
\]

(7)

where \( D_{L} \) is the diffusion constant in the local fiber direction (0.001 cm²/ms) and \( D_{L} \) is the diffusion constant transverse to the local fiber direction (0.000454 cm²/ms). This corresponds to a local anisotropic ratio of 2.2 described in chronic AF [16]. (radian) is the local fiber angle. Changes in fiber orientation was introduced in the transverse direction [17]:

\[
\theta(x) = \left( \frac{\pi}{2} \right) \cos \left( \frac{\pi x}{L_x} \right)
\]

(8)

where \( L_x \) (cm) is the tissue length and \( x \) is the distance in transverse direction. All simulations were run for a duration of 20 s. The partial differential equations were solved using an operator-splitting method with a space step of 0.025 cm and an adaptive time step [14].

Regional differences in acetylcholine concentration ([ACh]) within the tissue were used to create action potential duration (APD) gradients and dispersion of refactoriness, with higher [ACh] in areas with stable reentry, and lower [ACh] in areas of active wavebreak [18–20]. Increasing [ACh] corresponded to APD shortening and flattening of the APD restitution which in turn resulted in rotor stabilization. A stable rotor was created by standard cross-field simulation in the left lower corner ([ACh] = 0.0172 μmol/L), with wavebreak elsewhere ([ACh] = 0.008 μmol/L). (Fig. 1 and Online Video 1).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.compbiomed.2017.08.027.

2.3. Electrogram simulation

Unipolar point electrograms were calculated using the following formula [21]:

\[
\phi_{x,y} = \iint -\left( \nabla V \right) \cdot \hat{r} \, dx \, dy
\]

(9)

\[
r = \sqrt{(x-x')^2 + (y-y')^2 + z^2}
\]

(10)

where \( \phi \) is the extracellular potential at source point \((x', y')\), \((x, y)\) is the field point, and \( z \) is the distance of the field point from the surface. To simulate spatial averaging, unipolar disk electrodes \( \phi_{x,y} \) were calculated by the spatial summation of all point electrograms \( \phi_{x,y} \) within a 0.5 mm radius of each grid point \((x', y')\). Disk electrograms of 1 mm diameter were generated from a grid of 40 × 40 oversampling the 2D.
tissue at distance of 0.25 mm. This corresponded to an edge-to-edge interelectrode distance of 4 mm in either transverse or longitudinal direction. The model was simulated for a duration of 20 s. After allowing AF to stabilize for 5 s, electrograms were calculated at each unipole over a 15 s window. Signals were recorded at a sampling frequency of 1 kHz and were filtered using a bandwidth of 30–300 Hz. Bipolar electrograms were then calculated by subtracting adjacent unipolar electrograms in the transverse direction. A still frame from the model and correlating 2 s sample of electrograms from the rotor and areas of multiple reentry are shown in Fig. 1.

Direct intracellular voltages were also recorded from the model from cells in an 80 × 80 grid, 2.5 mm apart. These cells were located at the center of each unipole and at all points midway between bipoles, and were used to derive local activation timings within the model and to calculate local wavefront directions.

2.4. Signal processing

2.4.1. Assessment of wavefront direction

All signal analysis was performed in Matlab (MathWorks, Inc., Natick, MA, USA). Activation times were determined for each event over the 15 s window at each point in the intracellular voltage matrix based on local maximal dV/dt. For each bipolar, wavefront direction was determined by evaluating the sequence of local activation times from nine cells covering a 5 mm square, the center of which was located at the midpoint between the bipole. For each activation at this central cell, wavefront direction was calculated as the direction which yielded the best fit of the temporal relation between the nine points in the square, assuming homogenous conduction velocity [22]. In this manner, a discrete series of wavefront directions (range 0–360°) was created for the areas covered by each bipolar (39 × 38 grid), the length of each series equal to the number of activations in the 15 s window at that site.

2.4.2. Calculation of Egm-C

2.4.2.1. Identification of electrogram onset. The threshold for voltage detection sensitivity (V1), i.e. the minimal stimulus that defined an event, was manually set. dV/dt was selected which separated the onset of an electrogram from background wander. Three potential states of the electrogram were possible: inactive, eligible, and activated. Starting from the beginning of the electrogram, an “inactive” state was defined until an isoelectric baseline was discovered (a window where |V| and |dV/dt| were consistently subthreshold), and then state was changed to “eligible”. During “eligible” states, activation was triggered if V > V1. The beginning of the complex was then identified by scanning backwards until consecutive dV/dt fell below slope threshold thus triggering “activation” state and annotation of t0onset. Following identification of t0onset, state returned to “inactive” and the next “eligible” state only occurred after expiration of refractory period (60 msec) and identification of another isoelectric interval.

2.4.2.2. Assignment of vector for Egm-C. Once all electrogram onsets are identified, a zc-dimensional vector can be created for each activation to grossly estimate initial wavefront direction across the bipole based on direction and timing between the first zc zero crosses in the activation. A short blanking period was assigned immediately after t0onset, during which zero crosses were ignored. This excluded any zero crosses immediately after t0onset simply due to baseline wander. Time and direction of first zc zero crosses (t0onset1, ..., t0onsetnc) were recorded and EGMCIj was assigned for each activation where

\[
\begin{align*}
\text{EGMC}_{ij} & = \text{t0onset}_{ij} - \text{t0onset}_c, & & \frac{dV}{dt} \text{ at } t = \text{t0onset}_{ij} > 0 \\
\text{EGMC}_{ij} & = -\left(\text{t0onset}_{ij} - \text{t0onset}_c\right), & & \frac{dV}{dt} \text{ at } t = \text{t0onset}_{ij} < 0
\end{align*}
\]

(11)

for i = 1, ..., N activations; j = 1, ..., zc zero crosses

Thus activations with initial upward deflections are assigned as opposite direction to signals with initial downward deflections. In this fashion, a discrete series of intervals with N x zc points for an electrogram with N activations (using zc zero crosses per activation) was created. Tagging of time points on the electrogram for creation of the discrete Egm-C time series is illustrated in Fig. 2.

To evaluate the relationship between Egm-C and actual wavefront direction, a separate simulation was performed in an isotropic tissue where single flat wavefronts traversed a bipole (1 mm disk and 4 mm interelectrode spacing), with wavefront direction covering every 5° from −90° (270°) to 90°. For analysis of the electrograms from the simulated rotor and area of multiple wavelet reentry: blanking period was set to 3 msec, and zc = 1,
2, and 3 zero crosses were used.

2.4.3. Recurrence quantification analysis

RQA was performed according to the previously described methods of Marwan et al. [23]. Time-delayed vectors \( x_i \) and \( x_j \) of length equal to the embedding dimension, \( m \), were constructed within these time series of length, \( N \), such that \( x_i = (x_i, x_i + 1, \ldots, x_i + m - 1) \) and \( x_j = (x_j, x_j + 1, \ldots, x_j + m - 1) \). \( x_i \) and \( x_j \) were defined as recurrent, \( R_{ij} = 1 \), if the Euclidean distance \( |x_i - x_j| < \varepsilon \), where \( \varepsilon \) is our radius. For non-recurrent vectors \( x_i \) and \( x_j \), \( R_{ij} = 0 \). Recurrence variables REC (recurrence rate), DET (determinism), ENT (Shannon entropy of diagonal line lengths), and Dmax (length of longest diagonal line) were then calculated according to the following equations [24]:

\[
REC = \frac{1}{N^2} \sum_{i,j=1}^{N} R_{ij} \tag{12}
\]

\[
DET = \frac{\sum_{i,j=1}^{N} P(l)}{\sum_{i,j=1}^{N} R_{ij}} \tag{13}
\]

where \( P(l) \) is the histogram of the lengths, \( l \), of the diagonal lines.

\[
D_{\text{max}} = \max\{d_l; i = 1, \ldots, N_l\} \tag{14}
\]

where \( d_l \) represents the length of each diagonal line.

\[
\text{ENT} = -\sum_{l=\text{line}}^{N} P(l) \ln P(l) \tag{15}
\]

Embedding dimension, \( m \), was selected using the false nearest neighbor algorithm [25] and was set \( m = 5 \) for calculating recurrence of actual wavefront direction, and \( m = 5, 10, \) and \( 15 \) respectively for RQA of Egm-C when \( zc = 1, 2, \) and \( 3 \) respectively. Since using discrete time series, delay was set, \( r = 1 \). Radius was set at \( 40 \) for actual wavefront direction, and \( 3, 9, \) and \( 15 \) for Egm-C calculations for \( zc = 1, 2, \) and \( 3 \) respectively. The line parameter, which defines the minimal line length of diagonal lines to be considered deterministic, was set as \( 2 \) for WD and Egm-C with \( zc = 1, 2, \) and \( 5 \) for Egm-C with \( zc = 2 \) and \( zc = 3 \) respectively. Absolute values were used without normalizing distances beforehand.

2.5. Statistical analysis

All values are expressed as a mean value \( \pm \) SD. Associations between RQA parameters via Egm-C and WD were made using Pearson’s correlation coefficient. Fisher r-to-z transformation was used to compare different correlations. Continuous variables from normal distributions were compared using Student’s t-test, while data from non-normal distributions were compared using the nonparametric Mann Whitney test. A p-value less than 0.05 was considered statistically significant.

3. Results

3.1. Relationship of Egm-C to actual wavefront direction

Based on the simulation of flat wavefronts with uniform conduction velocity from different directions during sinus rhythm (every 5° from −90° to 90°), the relationship between the first, second, and third zero crosses is shown in Fig. 3. Although not linearly related, it is clear that the timing between zero crosses is a function of the approaching wavefront direction, with wavefronts oriented more perpendicular to the axis of the bipole giving wider electrograms, and those oriented parallel being narrower. In addition, wavefronts approaching from left have opposite direction than those approaching from the right.

3.2. RQA of actual wavefront direction

Recurrence plots obtained from different sites in the model are displayed in Fig. 4. As expected, at points within the stable rotor but outside the meandering core, wavefront direction was generally quite similar throughout the 15 s window resulting in very high recurrence rates with stable periodic behavior (Fig. 4A). Note that while highly recurrent, the wavefront direction at the beginning of the signal does not recur with the direction at the end of the signal (left upper/right lower corner of recurrence plot shown in Fig. 4A) due to drift in the meandering rotor core. This drift changes the angle of the approaching wavefront by 10–15° relative to the bipole over the 15 s recording. At points within areas of multiple wavelet reentry, lower recurrence rates were observed (Fig. 4B). At points where transient rotational activity was seen for several rotations before extinguishing, this behavior was clearly depicted by unstable periodic orbits within a more chaotic background in the recurrence plot (Fig. 4C). A recurrence map of the model, showing recurrence rates for the series of actual wavefront direction at each point in the model is shown in Fig. 5A.

3.3. RQA of Egm-C

Egm-C was calculated with the number of zero-crosses within each activation set at \( zc = 1, 2, \) and \( 3 \). RQA variables calculated from Egm-C were correlated with those derived from the series of actual wavefront directions and are shown in Table 1 for each setting. High correlation was seen between the two methods and was improved when \( zc = 2 \) compared with \( zc = 1 \) (\( p < 0.02 \) for all variables). No additional benefit was gained by increasing \( zc \) from 2 to 3.

Similar to the results obtained for actual wavefront direction, RQA of Egm-C demonstrated markedly stable periodic behavior around the core
of the rotor and chaotic behavior in areas of multiple reentry (Fig. 4D, E, and F). Comparisons of bipolar electrograms from the area of the stable rotor \((n = 169)\) to those elsewhere in the model \((n = 1313)\) yielded significant differences. Recurrence rates \((0.33 \pm 0.16 vs 0.01 \pm 0.02,\)
often be approximately half of that for wavefront direction. Similarly, REC for Egm-C will be roughly twice as long for Egm-C series using patterns of actual wavefront directions. Note that the length of an Egm-C of longest diagonal line (196 ± 10 vs 29 ± 66, p < 0.001), and entropy (3.88 ± 0.86 vs 1.07 ± 1.09, p < 0.001) were all significantly higher in the area of the stable rotor. In areas of transient rotational activity, RQA of Egm-C also reliably displayed unstable periodic orbits, mirroring the patterns of actual wavefront directions. Note that the length of an Egm-C series using zc = 2 with N activations will be 2N. Thus diagonal lines in the recurrence plot will often be roughly twice as long for Egm-C compared to actual wavefront direction. Similarly, REC for Egm-C will often be approximately half of that for wavefront direction.

Overall, recurrence rates were similar when calculated from Egm-C (zc = 2) and actual wavefront direction (0.094 ± 0.213 vs 0.086 ± 0.225), and good correlation was seen between the two methods (r = 0.96). At locations where the predominant wavefront direction was nearly parallel (within 10°) to the bipole, recurrence rates of Egm-C underestimated that of actual wavefront direction (0.010 ± 0.024 vs 0.037 ± 0.141, p = 0.001), and correlation between Egm-C and wavefront direction was still significant but reduced (r = 0.81, p < 0.001). This occurred for example just directly above and below the core of the rotor for horizontal bipoles.

4. Discussion

The presence and extent of recurring wavefront directionality patterns within a signal can provide important information about the underlying dynamics of the system from which it was obtained. Bipolar electrograms contain important information about wavefront direction. A wavefront approaching a horizontal bipole from left to right yields an electrogram opposite in sign than a wavefront from right to left (Fig. 3). Similarly, wavefronts oriented relatively parallel to the axis of the bipole will yield narrower electrograms than those oriented perpendicular. In this paper we describe a novel method, Egm-C, to transform a continuous bipolar voltage signal during AF into a discrete time series representative of wavefront directions. Egm-C is a measure of the direction and width of initial electrogram components, and thus reduces a complex electrogram morphology into a simpler metric while retaining the important information about wavefront directionality. This allowed us to perform RQA on this discrete measure of wavefront direction and examine local dynamics during AF. RQA of Egm-C yielded markedly similar results to that of actual wavefront direction calculated from intracellular signals. We demonstrated that areas within stable rotors produce uniform activation wavefronts and thus exhibit repetitive RQA patterns of Egm-C, while areas of multiple wavelet reentry are affected by constantly changing wavefronts and such recurrent patterns are less evident.

Conventional methods to localize stable sources of AF have included identification of areas of highest dominant frequency or shortest mean cycle length. Both these methods, however, have significant limitations and have not reliably correlated with each other [26]. Dominant frequency is not only a reflection of activation rate but can also be significantly influenced by electrogram characteristics such as signal complexity and variation in amplitude and regularity [27], as well as far-field electrical activity and signal-to-noise ratio [28]. Importantly, neither time domain measurements nor spectral analysis over relatively short windows accurately portray the spatiotemporal variation present in AF [29]. Additional measures have been utilized to quantify the degree of AF organization and complexity. Morphological wave-similarity analysis quantifies organization as the degree of atrial electrogram repetitiveness [5,6]. Complexity of signals has been evaluated both qualitatively (by visual inspection) and quantitatively, using measures in the time domain (short mean intervals between deflections) [30] or using nonlinear metrics such as correlation dimension and Shannon entropy [31,32]. While complex electrograms may occur at important sources of AF, they are often nonspecific and may represent passive phenomena such as double potentials, slow conduction, or wavebreak [33]. Approaches that combine frequency and complexity [34] or rate and regularity [35] metrics have also been implemented. More recently, the use of phase mapping in areas with high similarity index was associated with the presence of repetitive rotational activity [36], however, not all rotational electrical activity is important in the maintenance of AF. Both modeling and clinical mapping data suggest that passive rotors may form transiently in bystander areas. Indeed in this study, intermittent rotational activity is seen to occur transiently in areas of wavebreak. None of the aforementioned techniques are specifically designed to assess the dynamics of the AF signal over time. RQA is a nonlinear tool designed to assess the degree of periodicity, chaos, or randomness of dynamical systems and provides direct measures of determinism, stationarity, and stability of AF signals. This information about AF dynamics may provide important mechanistic insights not available by these other means.

Previous approaches utilizing RQA during AF have either used the
continuous voltage series directly [8,9] or evaluated recurrence of cross-correlations of electrogram morphology in a single dimension [37]. The advantage of discretization of the electrogram into the time series, Egm-C, is that it allows an analysis of the repeating patterns of wavefront direction without being confounded by similarities in quiescent baselines or in similar electrogram components contained within activations from disparate directions.

Electrograms during AF often contain a series of sharp deflections representing local electrical activity interrupted by a relatively quiescent baseline between activations. At other times or locations, signals can be more complex and relatively devoid of flat baselines, with apparent continuous electrical activity present. When calculating RQA on continuous AF signals, recurrences often occur within relatively isoelectric baselines. Thus RQA performed in this fashion can serve as a measure of the complexity (or lack of isoelectric baseline) of the signal [8]. However, it provides little information about the patterns of the direction of approaching wavefronts which may have important mechanistic implications.

Another approach has identified electrograms between isoelectric baselines and cross-correlated the voltage signal directly [37]. Recurrent correlations with similar electrogram morphology essentially yields recurrence plots with single dimension and thus does not take advantage of the dynamical information provided by multi-dimensional embedding. By shortening each electrogram into a simple representative vector correlated with directionality, we are able to perform higher dimension reconstruction of our series and potentially gain more information about non-linear dynamics.

In this model RQA of Egm-C clearly identifies very different dynamics between a meandering rotor and areas of multiple wavelet reentry. In addition to this analysis neatly identifies unstable periodic behavior such as occurs with transient rotors. This type of approach may provide important insight in underlying AF mechanisms as well as identifying potentially attractive targets for ablation.

4.1. Limitations of study

The techniques described in this manuscript were only applied to a single model with simulated signals free of background noise. Determination of Egm-C is dependent on identification of electrogram onset and thus its performance in highly fractionated signals or those with low signal-to-noise ratio remains to be determined.

5. Conclusion

It is feasible to transform continuous voltage signals during AF into a discrete time series, Egm-C, which is determined by and correlates well with local wavefront direction. RQA of the Egm-C time series demonstrates clearly different dynamics between a meandering rotor and an area of chaotic wavebreak. Further studies will be needed to evaluate the performance of this technique in noisy, complex signals and assess the utility of this approach in clinical AF.

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