Spatial Relationship Between Atrial Fibrillation Drivers and the Presence of Repetitive Conduction Patterns Using Recurrence Analysis on In-Silico Models

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Abstract

Catheter ablation treatment for atrial fibrillation (AF) is still suboptimal, possibly due to the difficulty to identify AF drivers. Recurrence analysis can be used to detect and eventually locate repetitive patterns that tend to be generated by AF drivers. In this study, we aimed to understand the spatial relationship between repetitiveness in recurrence analysis and rotor positions in an in-silico AF model. AF was simulated in a detailed three-dimensional model of the atria considering different degrees of endomysial fibrosis (0% and 70%). Rotors driving AF were tracked based on phase singularities obtained from transmembrane potentials. Activation-phase signals calculated from electrograms (4x4 electrode grid, 3 mm spacing) were used for recurrence analysis. Intervals with and without long-lasting sources inside the electrode coverage area were determined; the recurrence in both groups of intervals was quantified and compared with each other by calculating the recurrence rate (RR) per AF cycle length. RRs were lower during intervals with sources for both 0% and 70% fibrosis groups (0.56 [0.36;0.85] vs. 0.90 [0.80;0.97], $p < 0.001$ *and 0.73 [0.41;0.84] vs. 0.87 [0.76;0.92],* $p < 0.001$*, respectively). These results indicate that recurrences are found in the area adjacent to the sources but not on the sources themselves, thus suggesting that recurrence analysis could contribute to guide ablation therapy.*

1. Introduction

Ablation therapy of atrial fibrillation (AF) has limited success rates, in particular for persistent AF patients [1]. While pulmonary vein (PV) isolation is the standard approach, targeting driving mechanisms outside the PVs has been proposed as an alternative or complementary ablation strategy [1].

Many techniques have been used to define substrate suitable for ablation, including mapping of dominant frequencies, phase and complex fractionated electrograms, targeting AF driving mechanisms such as functional reentries and ectopic foci [1]. However, rates of success of ablation of those targets are still unsatisfactory.

One common characteristic of possible ablation targets is that repetitive conduction patterns are expected to be observed close to these drivers [2]. In this respect, a suitable tool for investigating the presence of recurrent behavior in a dynamical system (or of repetitive patterns in the signals coming from it) is recurrence analysis [3]. Recurrence analysis has previously been used in the context of AF to visualize dynamic patterns [2], quantify complexity and stability of conduction patterns [2, 4, 5], identify regions of complex fractionated electrograms [6], and differentiate stationary rotors from regions of wavelet breakup [7]. In order to be able to use recurrence analysis as a tool to guide ablation strategies, it is relevant to understand the relationship between the location of AF sources and the repetitive patterns related to them in realistic scenarios.

In this study, we applied recurrence analysis on simulated AF unipolar electrograms (EGM) obtained from a highly detailed, three-dimensional in-silico model of the atria. We focused the analysis on long-lasting meandering rotors contained within limited regions of the atria, aiming to understand the outcomes of recurrence analysis from signals obtained directly on the drivers and their vicinity.

2. Methods

AF was simulated in a highly detailed three-dimensional model of the human atria (uniform finite difference grid with 0.2 mm resolution), including atrial wall thickness, intra and inter-atrial structures and realistic electrophysiology corresponding to AF patients [8]. AF was initiated

in the simulations by incremental pacing (280 to 124 ms intervals during the first 2.5 s of simulation) from 20 different sites in the atria. When initiated, AF was simulated for 15 seconds. Two sets of simulations were generated, with no fibrosis and severe fibrosis, to simulate AF progression. For severe fibrosis, 70% of the atrial cells, distributed in random patches along both atria, were assigned conduction properties of fibrotic tissue [8].

Phase singularities (PS) were detected using the transmembrane potentials [9] and clustered over space (within a 4 mm radius) and time (within a 10 ms window) to form PS trajectories. Isolated PS trajectories with duration below 100 ms were excluded from the analyses; the remaining PSs were projected onto the endocardial surface to spatially correlate the PS positions with the intracardiac data.

Unipolar EGMs were calculated via the forward solution to the endocardial surface with 1 mm resolution and 1 kHz sampling frequency. Virtual electrodes arranged in a 4 by 4 grid (3 mm spacing) were placed in 16 regions of the atria (Fig. 1) and used to measure the EGMs. Activation times were detected on the EGMs by maximum negative deflection [7] and used to build an activation-phase signal, where the phase is linearly interpolated between the transitions from $+\pi$ to $-\pi$, which are localized at the activation times.

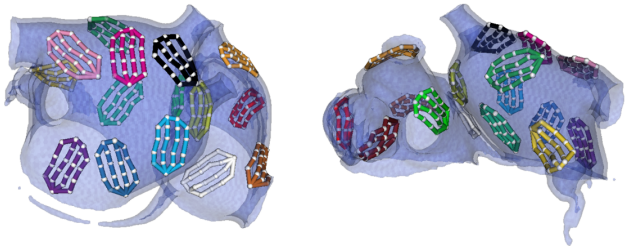

Figure 1. Distribution of electrode arrays on the endocardial surface of the model

Geodesic distances between each PS and the center of the electrode arrays were calculated and used to determine time intervals in which the sources were harbored under the areas covered by the electrodes (source under - SU). To account for meandering of sources in and out of the measured area, these intervals were merged if occurring within a window of one AF cycle length (AFCL), as estimated from the median interval between activation times. Similarly, intervals in which sources in the vicinity of the measured regions (sources near - SN) were annotated as those outside the marked intervals for harbored sources. A threshold of 5 AFCLs was used to exclude short intervals in both SU and SN intervals, thus focusing the analyses on long lasting repetitive patterns.

Recurrence plots (RP) were generated for the selected intervals as described previously [2]. Briefly, distance matrices were built by comparing phase snapshots (i.e. the phase of all electrodes simultaneously at a given time) at a reduced sampling frequency of 200 Hz to improve computational times, using the average cosine of the phase difference in all electrodes as a distance measure (Eq. 1). Distance matrices were transformed into binary RPs by applying a distance threshold of 0.15, which is equivalent to an average difference of phase corresponding to 12.7% of the AFCL (i.e. 0.8 rad). Points with lower distances than the threshold were marked as recurrences. To remove false positive recurrences, which might occur due to the similarity of consecutive activation-phase snapshots, the recurrent plots were eroded, replacing horizontal or vertical lines by a single recurrence at the time point with minimal distance.

$$D = 1 - \left(1 + \frac{\sum \cos(x - y)}{\text{length}(x)}\right) \cdot \frac{1}{2} \qquad (1)$$

The degree of repetitiveness of a recurrence plot can be expressed by the recurrence rate (RR), defined as the percentage of recurrent points in the plot (excluding the main diagonal, which is always recurrent). The RR was calculated for every SU and SN interval and normalized by the corresponding AFCL, so that a RR of 1 indicated a single recurrence occurring each AF cycle on average. RRs of these intervals were compared within each simulation, fibrosis group and between fibrosis groups applying a Mann-Whitney U test. Paired comparisons of average RR values of SU and SN intervals obtained within the same electrode array were performed with the Wilcoxon signed-rank test. Significance level was set at 0.05 and values are given either as mean$\pm$ standard deviation of median [interquartile range] depending on the normality of the data.

3. Results

AF was initiated in 7 simulations of the 0% fibrosis group and in 11 simulations of the severe fibrosis group. An average number of 3.4 ± 1.3 and 4.7 ± 1.7 simultaneous PS trajectories were identified for each group, respectively. For the group without fibrosis, 24 ± 13 SU intervals lasting 2.1 ± 2.7 s were detected, whereas 28 ± 9 SN intervals lasting 3.5 ± 3.6 s were observed in all 16 electrode arrays. For the severe fibrosis group, 38 ± 9 SU intervals (2.3 ± 2.4 s) and 25 ± 10 SN intervals (2.2 ± 2.7 s) were detected.

Fig. 2 shows the calculated RRs for the SU and SN intervals, for simulations with no fibrosis (Fig. 2A) and severe fibrosis (Fig. 2B). It is possible to observe that RR was lower in the recordings on the location harboring the driver as compared to the region adjacent to the source, for both fibrosis groups (no fibrosis: 0.78 [0.54;0.85] vs. 0.91 [0.80;0.97], $p < 0.001$; severe fibrosis: 0.73 [0.48;0.85] vs. 0.89 [0.79;0.94], $p < 0.001$).

The same behavior is observed when comparing SU and SN intervals within the recurrence plots of each electrode

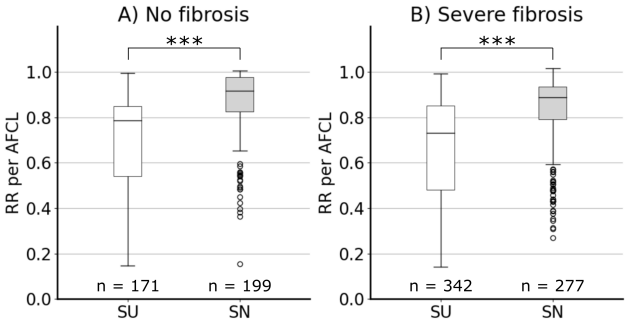

Figure 2. RR for intervals with sources within (SU) and near (SN) the measured area for the no fibrosis (A) and severe fibrosis (B) groups. $***-p<0.001$

array ($p<0.05$ for electrodes in both fibrosis groups), and when considering all electrode arrays in single simulations ($p<0.05$ in all simulations). No significant differences were observed between SU (0.78 [0.54;0.85] vs. 0.73 [0.48;0.85], $p=0.43$) or SN intervals (0.91 [0.80;0.97] vs. 0.89 [0.79;0.94], $p=0.43$) obtained with the different degrees of fibrosis, indicating that observed effect might be independent of increasing levels of atrial remodeling.

Fig. 3 illustrates the spatial distribution of RRs in the vicinity of stable sources, as well as the corresponding recurrence plots obtained in the selected intervals. It is possible to observe very regular repetitive patterns in recurrent plots that were obtained by electrodes positioned on the path of conduction promoted by the source, but not directly on the core of the rotational activity. In these plots, long diagonal lines as present, spaced by the AFCL and thus indicating that a repetitive pattern occurs at this interval, yielding a high RR per AFCL. In contrast, the recurrence plot obtained directly on top of the sources shows shorter lines and areas without any recurrence, which translates into a lower RR per AFCL. This feature can be used to locate regions harboring stable sources, by moving mapping catheters from regions with higher RR to regions with lower RR along the direction of conduction.

4. Discussion and Conclusion

In this study, we explored the spatial relationship between the degree of recurrences, measured by the RR, and the existence of long-lasting (more than 5 AFCLs) rotational sources inside the mapped areas. We used a three-dimensional model of the human atria in order to have the complete information over the position of rotational AF sources and high coverage of the atria using similar electrode density as in the clinical practice, thus enabling the direct correlation between the observed recurrent patterns and driver location in a realistic setting.

Previous studies applying recurrence analysis to endo- or epicardial EGMs have made meaningful steps towards the use of this technique to guide ablation therapy. Van Rosmalen et al.[4] have identified repetitive patterns in high density epicardial mappings of human AF, but a minority of those comprised of rotational activity. The present results suggest that this might be due to the lower RRs observed when the sources are within the mapped area, which would not necessarily be observed as intervals with high repetitiveness in recurrence plots. Such intervals are more likely, as observed in the aforementioned study, to correspond to peripheral waves, possibly originating from nearby AF drivers.

The meandering of rotors plays an important role in the behavior observed in the present study. Most of the PSs in our model meander in regions larger than the area covered by the electrode arrays, thus resulting in varying patterns over the AFCLs, which are reflected by the lower RRs. These results are in agreement with a two-dimensional modeling study [7], where analyses focused on the directionality of propagating waves found higher repetitive patterns close to meandering rotors than on their core. Further research is necessary to evaluate whether this effect is observed in realistic clinical EGMs, since the data used in both studies comprise of noise-free modeled EGMs.

Finally, since rotational waves are not the only possible maintaining mechanism of AF, further investigation is needed to evaluate the behavior of other sources such as transmural breakthroughs. Applying a technique focused on repetitive patterns rather than specific mechanisms might help increase the current suboptimal rates of success in extra-PV ablation strategies, especially when combined with other techniques tailored to detect such mechanisms.

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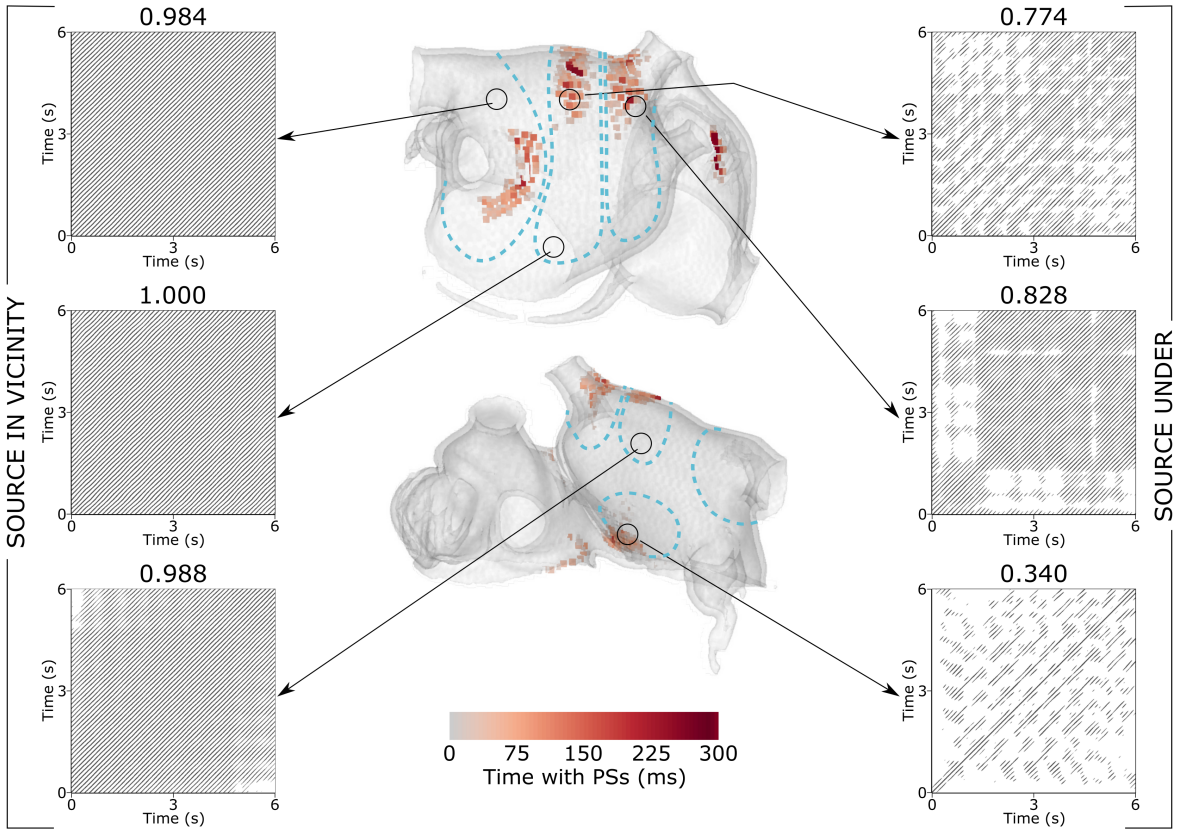

Figure 3. Source density map for a 6 s period and examples of recurrence plots for electrode arrays on stable sources (right) and neighboring regions (left), with corresponding RRs. Black circles point to the center of electrode arrays, and blue dashed lines mark the qualitatively determined regions of influence based on the propagation of transmembrane potentials, for each analyzed source. Plots obtained from electrodes on the sources show shorter diagonal lines and regions without recurrence, while plots in their vicinity show uniformly spaced diagonal lines at AFCL intervals.

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