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Preventing recurrence through analysing recurrence

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Determining optimal ablation therapy approaches for persistent patients with atrial fibrillation (AF) is challenging primarily because it is difficult to classify the mechanisms underlying AF in an individual patient. Ablation strategies typically include pulmonary vein isolation (PVI), together with either additional ablation lines to separate regions of atrial tissue or focussed ablation lesions to target specific electrical or structural features. For example, common specific ablation targets include areas of high electrogram fractionation, as well as areas thought to correspond to either atrial fibrosis (identified as low signal amplitude or using imaging) or to electrical drivers (identified by local activation time or phase mapping). Nademanee et al. pioneered the targeted ablation of complex fractionated atrial electrogram (CFAE) signals with the motivation that these areas represent slowed conduction and pivot points of re-entrant wavelets, demonstrating excellent success rates of 95% AF termination following CFAE ablation. However, unfortunately other centers failed to replicate this success. In addition, the recent STAR AF II clinical trial found no improvement in persistent AF ablation outcome with the addition of either linear ablation or CFAE ablation to PVI ablation. Targeted ablation of electrical drivers is a promising approach; however, reliably identifying drivers is challenging even when assessing activation patterns from globally acquired electrical data. Gaining a deeper biophysical understanding of how the electrophysiological features of the tissue that drive AF are translated into the specific electrogram signal content may facilitate the more robust identification of electrical drivers of AF from readily available sequential mapping data, and ultimately guiding treatment strategies.

Complex fractionated atrial electrograms are challenging to interpret because electrogram fractionation arises from multiple different mechanisms. Narayan et al. demonstrated this clinically by using monophasic action potential (MAP) catheters to measure the local refractoriness of atrial tissue to classify the type of fractionation on bipolar electrograms. Their findings showed that far field signals account for 67% of fractionation, with other types including rapid localized AF sites (8%), spatial disorganization (17%), and fractionation following AF acceleration accompanied by MAP alternans (8%). Jadidi et al. showed that CFAE distribution varies depending on both wavefront direction and the rate of activation, measuring different CFAE maps for sinus rhythm, paced rhythms, and AF. Theoretical studies by Spach et al. and later Jacquemet et al. showed that microscale obstacles including collagenous septa in fibrotic remodeling, which could provide a pivot point for anchoring re-entrant activity, affect the electrogram morphology. Hence, CFAE reflect both functional and structural properties of the atrial substrate.

The study by Baher et al. in this issue of *Journal of Cardiovascular Electrophysiology*, aims to automatically distinguish CFAEs originating from active versus passive tissue sites by means of directly quantifying how recurrent a particular electrogram confirmation is. They do so through the use of recurrence quantification analysis (RQA), a standard signal processing technique used to evaluate recurring patterns within complex signals. The authors argue that such a technique has the advantage here that it directly uses the raw time-series traces and does not rely on pre-processing of the signals to obtain metrics such as activation times or specific morphological metrics, which can indeed introduce errors and bias. A comprehensive evaluation is performed of the ability of their algorithm to detect active sites from electrograms obtained from both biophysically-detailed computational simulations (in which active versus passive sites can be readily distinguished) along with clinical patient ablation data (in which, by definition of the problem to be solved, such a definition is more challenging). The authors conclusively demonstrate that active AF drivers exhibit electrograms with higher recurrence, which can be quantified and thus distinguished from active sites by means of RQA analysis. Due to the potentially straight-forward integration of their methodology into clinical electro-anatomical mapping software, these findings could have significant clinical impact and provide a robust means of identifying AF drivers and improving ablation outcomes.

Consistent use of definitions and terminologies are critical to the interpretation of this study and implementation of the proposed
microfibrotic structure acts to "pattern repeated across multiple beats. This is more likely if which is not considered in this study. For example, a region of fibrosis rotors or focal areas of repetitive ectopy, while passive mechanisms study findings. In silico, active mechanisms were modeled as stable active and passive mechanisms is also paramount to interpreting the study findings. In silico, active mechanisms were modeled as stable rotors or focal areas of repetitive ectopy, while passive mechanisms were wavebreak, slow conduction and double potentials. Importantly, these passive mechanisms could arise with a degree of repeatability, which is not considered in this study. For example, a region of fibrosis could lead to slow conduction or wavebreak with the same activation pattern repeated across multiple beats. This is more likely if microfibrotic structure acts to "channel" activation only along the direction of the surviving myocyte bundle giving almost identical electrogram signatures on consecutive beats. Clinically multiple criteria were considered for active driver CFAE classification including (a) a mean CL <120 ms, (b) demonstration of a progressive frequency gradient from the CFAE site to the rest of the atrium, (c) immediate termination of AF during ablation at the site, and (d) inability to sustain AF after the ablation. Since the only ablation applied was PVI, this presumably means that active driver sites were only located around the left atrial/pulmonary vein (LA/PV) junction. Most importantly, measuring the success of their algorithm in the clinical environment is challenging because it requires the definition of active and passive CFAE to do so; however, if CFAE could indeed be reliably and simply classified clinically as active and passive, there would be less need for the developed methodology. Future further testing and validation of the approach on ex vivo optical mapping experiments, in combination with electrogram mapping, may provide a more robust means of active/passive classification.

The in silico testing of this algorithm required the generation of atrial substrates exhibiting electrogram fractionation, which was implemented through regional heterogeneity in acetylcholine concentration to create dispersion of refractoriness. Stable re-entry and focal ectopy were exhibited in regions of higher acetylcholine concentration, and wavebreak in areas of lower acetylcholine concentration. CFAEs arose due to functional properties, including rotor meander, wavebreak, slow conduction, and double potentials. This choice of modeling methodology will affect the range of electrogram morphologies observed across the simulations. For example, recent studies have shown that different methodologies for modeling atrial fibrosis will affect electrogram morphology differently. Additional investigation into RQA analysis of electrograms arising from different structural substrates is warranted to further understand active versus passive mechanisms.

Bipolar electrograms are often used clinically as their construction typically eliminates the ventricular signal artefacts present in unipolar signals; however, their amplitude depends on wavefront direction. In addition, fractionation of bipolar electrograms has multiple etiologies and depends on electrode spacing. Recent studies have utilized "omnipolar" electrogram mapping, derived from a regularly-spaced grid of electrodes, to determine orientation independent wavefront trajectories with a reliable measure of voltage amplitude and speed. The orientation independence of omnipolar mapping may overcome many of the challenges associated with interpreting bipolar electrogram fractionation and may be used in conjunction with the algorithm of Baher et al to increase the clinical robustness of this methodology.

Baher et al should be congratulated on the careful combination of detailed in silico testing of their algorithm, along with later direct clinical testing and validation in the same study. Their findings highlight the importance of increased mechanistic understanding of electrogram morphology for improving ablation therapy, and the potential of applying such automated signal processing algorithms in the clinical environment.

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REFERENCES


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