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The Quest for Rotors in Atrial fibrillation: Different Nets Catch Different Fishes

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Despite remarkable progress in catheter ablation of atrial fibrillation (AF), primarily based on elimination of pulmonary vein (PV) arrhythmogenicity, identification of drivers beyond the thoracic veins specifically in patients with persistent AF remains problematic.[1] The hypothesis that AF could be maintained by drivers in the form of reentrant circuits was first proposed about 100 years ago.[2,3] However during the second half of the 20th century the prevailing hypothesis was that AF maintenance depended on multiple wavelets that randomly propagate across the atria and perpetually annihilate and re-generate.[4] With the development of high-resolution optical mapping techniques, the original thought of a single or a small number of reentrant drivers of AF has re-emerged.[5] Both simulation and experimental studies in animal models have demonstrated that despite the spatiotemporal complexity of wave propagation during AF, measurable deterministic properties of high frequency sources, rotors and hierarchical distribution of dominant frequency (DF) play a critical role in the perpetuation of AF.[6–10] However, these important mechanistic studies involved toxic voltage sensitive dyes and high density mapping ex-vivo with detailed off-line analysis of electrograms, primarily in the frequency domain. Therefore, clinical utility of these seminal findings have been limited.

In an attempt to localize extra-pulmonary venous drivers of AF, targeting of “complex fractionated atrial electrograms” (CFAEs) has been proposed. CFAEs have been described based on time-domain characteristics that included a short cycle length, electrogram fractionation or continuous activation and have been thought to indicate sites of conduction slowing, block, rotors or autonomic innervation, all of which are possible mechanisms of AF. Few clinical studies suggested better clinical outcomes with ablation of CFAEs, either as a standalone ablation strategy or in conjunction with PV isolation and/or linear ablation, than with other more conventional techniques whereas other studies failed to demonstrate an incremental role. Ablation of CFAEs often involved extensive atrial ablation, including linear and multiple repeat procedures. Therefore, a potential confounding role of atrial debulking could not have been unequivocally excluded. Subsequently a variety of automated algorithms utilizing time- or frequency-domain parameters have been employed in rather

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small-scale clinical studies. However, an incremental role of these algorithms has not been convincingly demonstrated to date.

Thus with the much need to further improve the understanding and outcomes of catheter ablation of AF, particularly persistent AF, the report by Narayan et al published in this issue of Heart Rhythm[11] is a timely contribution. In this report, the authors used a 64-electrode atrial, mapping system in a patient with persistent AF who has failed prior catheter and surgical ablation attempts. The system showed for the first time a stable rotor as a driver of AF and guided ablation, which resulted in termination of AF after a relatively short application. The report therefore implicitly suggests that a mapping approach utilizing an algorithm primarily based on phase analysis of simultaneously recorded electrograms through a multichannel panoramic approach (basket catheter) is effective in identifying rotors driving AF.

Although presence of rotors in human AF was predicted, clinical demonstration of their presence has remained elusive. Because the mapping algorithm, specifically the phase analysis, was not disclosed in detail in this report, it may be appropriate to briefly review here the technique and its potential inherent limitations. The phase analysis of activation during fibrillation was pioneered by Gray et al[12] who used a lag-return method of voltage sensitive fluorescence time-series to determine the stage of the high resolution optical action potentials in their cycle and to show a never before seen self-organized rotors in the midst of fibrillation during ventricular fibrillation in rabbits. Chen et al employed the method for the first time in the sheep atria during AF to demonstrate non-random distribution of wavebreaks and how they relate to functional reentry (rotors).[13] Subsequently, Warren et al[14,15] established a more mathematically rigorous approach of utilizing the Hilbert transform to calculate the optical action potential phases accounting for their multiple frequency components and the link between discrete rotor activity as a driver and the highest dominant frequency (DF)..[16,17]

An important question is whether the results of phase analysis can be influenced by the mapping modality and technique employed: 1) Optical mapping of action potentials during AF is more suitable for phase analysis than the extracellular electrogram recordings which are subject to artifacts in signal morphology; 2) Far-field potentials, particularly due to ventricular activation, are essentially absent in optical mapping but often contaminates electrical recordings; 3) Simultaneous electrode-tissue contact with a basket catheter is often less than satisfactory at some, if not most, of the electrodes, limiting the fidelity of the data; 4) There is a marked difference between the typical resolution of optical mapping and panoramic electrocardiographic mapping using a basket catheter. During optical mapping the size of each pixel is usually <1 mm. Using the panoramic electrogram mapping with a basket catheter placed in a left atrium of 5 cm in diameter in the present case, rotational activity was reported at areas with ≥20 mm average inter-spline distance after spatial interpolation of phase data. However, during interpolation of phases there is an inherent bias toward detection of possibly non-existent rotors as the interpolation algorithm is devised to demonstrate mainly rotational activity. For example, if a focal discharge is located between 4 electrodes and the activation wave reaches each electrode at a different time sequentially, the interpolated Hilbert-based phase map is likely to display a rotational activity in the area

between the electrodes. The interpolation problem can further be exacerbated by motion: Atrial tissue can move non-uniformly relative to the fixed electrodes of a basket catheter during cardiac and respiratory cycles. Since the phase representation of the voltage-time series highlights differences in activation time disregarding variation in voltage, any periodic motion of the tissue can translate into a wavebreak and a misleading notion of reentrant activity.

In conclusion, although it is not absolutely clear whether the AF driver in this patient was a focal discharge or a rotor, the report by Narayan et al has important implications: 1) It demonstrates the importance of full panoramic simultaneous mapping of electrical activation; 2) It suggests that a residual driver of AF following prior ablation attempts can be effectively identified; and 3) AF can be successfully eliminated by targeted ablation of a single driver capable of maintaining AF. Since ablation at the core of a rotor would not be expected to have any termination effect on rotational activity, it is likely that ablation in this report includes a large area that interfered with the path of rotational activation. The authors should be commended for a major step forward in applying phase analysis based on Hilbert transformation in near real-time mapping of drivers of AF in the human heart. However, the utility, efficacy and wide adoption of this method will largely depend on detailed analysis and validation of the mapping approach.

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