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EDITORIAL COMMENT

Electrogram Morphology Recurrence

A Step Forward or Just a Recurrent Story?*

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In the last 2 decades, the introduction of various substrate-based ablation approaches for persistent types of atrial fibrillation (AF) has resulted in only limited improvement in outcomes.[1] At the root of these seemingly never-ending suboptimal results resides a lack of clear understanding of mechanisms underlying AF and absence of clear criteria for electrogram processing technologies to identify target sites for ablation therapy.[1] For this reason, state-of-the-art electrogram recording software and processing techniques, such as 3-dimensional electroanatomic mapping system, are booming business. Currently, our arsenal of approaches to identify the AF-related arrhythmogenic substrate, containing complex fractionated atrial electrograms, low-voltage areas, dominant frequency, Shannon's entropy, or focal impulse and rotor mapping, is broad. However, the detection of arrhythmogenic regions during persistent AF remains challenging. It is generally assumed that persistent AF is characterized by a complex interplay of multiple wave fronts, endocardial and epicardial breakthroughs, or rotational activity. Each of these mechanisms has a significant effect on electrogram morphology.

In this issue of *JACC: Basic to Translational Science*, Yoo et al[2] introduced a novel electrogram processing technique and systematically examined the relationship with traditional AF electrogram measurements and the underlying atrial structure. They performed a high-density biatrial epicardial mapping study in a canine model of persistent AF. By comparing bipolar atrial electrograms in 6 atrial subregions, they showed that the electrogram morphology recurrence (EMR) measurements—recurrence percentage (Rec%) and cycle length of the most recurrent electrogram morphology (CL_R)—were regionally dependent, with Rec% predominantly being greatest in the appendages and CL_R being lowest in the posterior left atrium. Importantly, Rec% and CL_R correlated moderately to poorly with traditional measurements, such as fractionation interval, Shannon's entropy, and dominant frequency. Although Rec% reflected the stability of rotational activities, comparisons with the other traditional measurements were not reported. None of the electrogram measurements correlated with atrial fibrosis and myofibril orientation. Remarkably, Rec% and CL_R changed significantly to parasympathetic blockade, hampering accurate reproducibility if the autonomic state of a patient varies throughout the procedure.

The authors should be congratulated on a well-designed study. By a thorough assessment of both established traditional electrogram measurements and the novel recurrence processing technique, the authors provide strong preclinical evidence to support their hypothesis that EMR measurements—Rec% and CL_R—may be more accurate indicators of the arrhythmogenic substrate for AF than any of the previously investigated electrogram measurements.

The rationale for this study was based on a prior clinical AF study, in which none of the patients with shortest cycle length of the most frequent electrogram morphology (CL_R) in the right atrium had a successful outcome of left atrial ablation.[3] As Rec% provides a measure of the consistency of electrogram morphology, areas with the highest recurrence rate and shortest cycle length are close to AF drivers because of their consistent and high rate activation.

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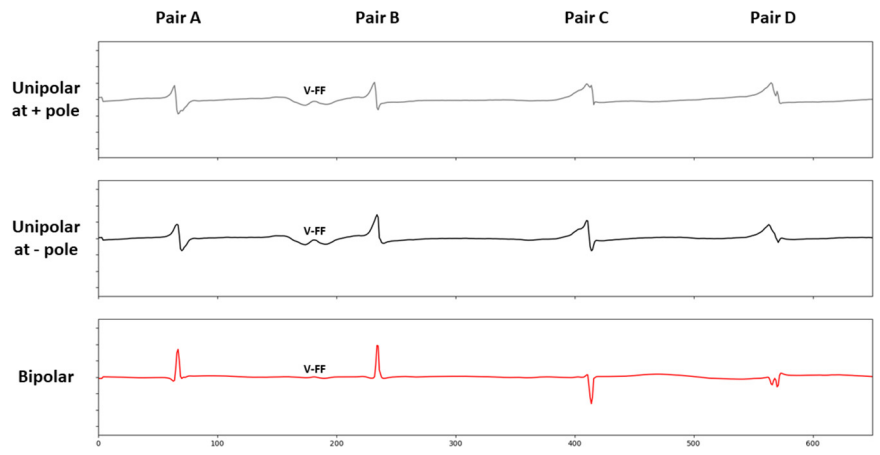
FIGURE 1 Conversion of Unipolar to Bipolar Electrograms



Example of epicardial unipolar electrograms and corresponding bipolar electrograms, recorded at the left atrial appendage in an atrial fibrillation patient. V-FF= ventricular far-field.

This rationale requires 2 conditions. First, persistent AF should be driven by a consistent source of activation. Second, other areas further away from the driver should not have recurrent morphologies with short cycle length. However, several observations from other studies are contradictive with the findings by Yoo et al.[2] We observed by simultaneous endocardial and epicardial mapping that the substrate of progressive types of persistent AF consists of endo-epicardial asynchrony with many epicardial and endocardial breakthroughs, which form a large reservoir of widespread, nonrepetitive AF sources. Parameswaran et al[4] also showed—by simultaneous endocardial and epicardial mapping of 2 minutes of continuous recordings of persistent AF—the temporal heterogeneity of endo-epicardial asynchrony combined with transient rotations and nonsustained focal waves. However, fibrillatory wave fronts have a tendency to follow a path of previous excitation because of the distribution of refractoriness left by the receding tail of the previous wave front and functional block of competing pathways by the wave front edge.[5] This so-called linking of atrial excitation will also result in recurrent morphologies. Another important determinant of linking of fibrillation waves is the presence of anatomical boundaries in the atria. In particular, the circumscribed anatomical entrance of the appendages, which favor uniformity of direction of fibrillatory waves, will result in electrograms containing potentials with similar morphology and short intervals. This has been observed in clinical studies and experimental settings. It therefore remains questionable whether targeting areas in the left atrial appendage with high Rec% and relatively short CL_R will improve ablation outcomes.

There are numerous factors that influence atrial potential morphology, including, underlying electrophysiological properties, tissue structure, and recording technology. The latter may especially have severe consequences for the proposed methodology.

Because a bipolar electrogram is the product of 2 unipolar electrograms, several technical and mathematical factors influence its morphology. First, bipolar potentials are affected by the direction of the wave front in relation to the recording electrodes. When comparing a parallel orientation of bipoles to the direction of the wave front to a transversal orientation, 30% of sites with fractionated electrograms were missed in the other pole orientation.[6] Second, in case of inhomogeneous activation patterns, larger interelectrode distance increases electrogram fractionation of bipolar potentials. Therefore, the diverse morphology of bipolar potentials because of interelectrode spacing and catheter orientation complicates the use of bipolar electrogram morphology during complex activation patterns.

Converting fractionated unipolar electrograms to bipolar electrograms is prone to serious errors, as demonstrated in **Figure 1**. Bipolar single potentials can change significantly because of small timing differences between the poles (pairs C and D). Conversely, changes in morphology of single potentials may still result in a similar bipolar potential

(pairs A and B). In the case of complex fractionated potentials, small timing difference between the peaks of unipolar fractionated potentials itself can drastically alter corresponding morphology of bipolar potentials. Hence, unipolar EMR measurements may be preferred over bipolar EMR measurements.

Although their conclusion needs further clinical confirmation, the current study convincingly demonstrated the mechanistic basis of this novel processing technique for potential future therapeutic options. The findings presented here by Yoo et al[2] should provoke new research questions to decide whether EMR measurements will be a step forward or whether it is just a recurrent story resulting in similar outcomes as other measurements for persistent AF ablation. Is the EMR measurement also accurate in patients with years or decennia of persistent AF, as the model for persistent AF was induced by 6-8 weeks of rapid atrial pacing? Will its susceptibility to autonomic modulation (such as anesthesia) result in heterogeneous results? Is this technique feasible on longer or separate repetitive recordings, or will its results be equivocal, as changes in temporal heterogeneity in electrogram morphology were not reported?

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