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Atrial fibrillation: Can electrograms be interpreted without repolarization information?

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Major unmet needs in managing patients with atrial fibrillation (AF) are to track AF propensity, monitor therapeutic response, and ultimately predict AF episodes. We are disappointingly far from these goals because our basic tools in AF—atrial electrograms and their classic interpretation—provide limited actionable data on substrates, their progression, AF initiation, or critical sites that maintain AF.¹

A major limitation of clinical AF studies is that classic interpretation² is challenging, focusing on unipolar and bipolar electrogram activation timing and qS-type deflections but largely ignoring repolarization.³ However, AF operates at the limits of dynamic activation and recovery. Thus, defining beat-to-beat repolarization is critical to identify whether AF electrograms are local or far-field (ie, within refractoriness of prior cycles) (Figure 1),⁴ when activity encroaches on recovery to cause block, reentry, and AF,^{4,5} and to compute phase⁶ to reveal sources that drive human AF in recent clinical⁷ or human atrial optical mapping⁸ studies.

Human atrial activation and recovery in AF have traditionally been measured by monophasic action potentials (MAPs)⁴ that record local activity.³ Unipolar² and bipolar electrograms in AF, on the other hand, summate far-field events that are often asynchronous wavelets. This challenges conclusive interpretation of “qS” or “rR” shapes in AF,⁹ unlike organized rhythms such as flutter in which local and far-field signals indicate the same wavefront. Moreover, atrial refractoriness is seen in MAPs³ yet has been obscure in bipolar and unipolar signals (Figure 1). The unipolar activation-recovery interval may approximate refractoriness in the ventricles¹⁰ but is undemonstrated in the atria.

Identifying atrial repolarization from standard electrodes

Into this field comes the timely work of Verrier et al,¹¹ who set out to detect atrial repolarization from standard electrograms in order to determine AF susceptibility. Using

standard clinical catheters, the authors recorded atrial repolarization (T_a) waves in anesthetized pigs and studied the impact of vagus nerve stimulation and of atrial ischemia or acetylcholine plus epinephrine on AF inducibility. T_a waves correlated with MAP recordings, and PT_a intervals (the “atrial QT”) shortened during right or left vagus nerve stimulation. Ischemia or autonomic stimulation caused alternans (TWA_a) and spatiotemporal heterogeneity (TWH_a) of T_a , which preceded AF onset from a trigger. The authors concluded that standard catheters can measure T_a waves and indices of vulnerability (TWA_a and TWH_a) that precede AF.

AF prediction

This study advances the science of AF prediction. There is clear interest in magnetic resonance imaging as a tool to identify AF substrates, yet structural indices may not fully identify dynamic risk for AF. The authors’ findings are in agreement with clinical studies in which indices of atrial MAPs^{12,13} predict AF, potentially via conduction slowing⁵ that interacts with MAP alternans⁴ to cause block/reentry and initiate AF. The findings of Verrier et al¹¹ may enable such prediction from standard electrodes, such as pacemaker leads.

Novel detection of atrial repolarization

The means by which Verrier et al¹¹ revealed atrial repolarization from standard catheters is of interest and previously had been challenging. First, catheters were placed in the lateral right atrium, which minimizes the ventricular QRS that often overshadows atrial repolarization because the PR interval is inconveniently similar to the human atrial action potential duration (~200–300 ms in sinus rhythm, 100–160 ms at fast rates).^{4,12} Whether this method applies throughout both atria must be determined. Second, atrial action potentials often are triangular (Figure 1, first complex), with the flat slope from “plateau” to final repolarization causing a more gradual gradient (dV/dt) and flat T_a (much like mouse and rat ventricles that lack clear T waves). In their Figures, Verrier et al¹¹ show well-developed T_a waves, even in bipolar recordings, which may reflect specific atrial regions or may be dynamic. Again, this should be tested widely in the atria. Third, the authors’ analysis residue may have facilitated detection of TWA_a and TWH_a despite the limitations of unipolar and bipolar signals for detecting repolarization.

Limitations and future directions

All models of AF have limitations. Verrier et al¹¹ did not test their measures of atrial repolarization clinically, which is required to ensure that this approach is not specific to their porcine model. In terms of prediction, AF induction is a poor predictor of clinical AF, so alternative endpoints are needed. Clinically, AF often follows sympathetic rather than vagal stimulation and is uncommonly associated with ischemia,¹⁴ so these data must be tested in clinical AF scenarios.

If repolarization metrics can be obtained routinely during clinical AF, then the impact would be substantial. Accurate repolarization data may clarify the debate on complex fractionated atrial electrograms by identifying which signal components are far-field vs “pivot points.”¹

Repolarization data also may help resolve the dichotomy that optical mapping—the gold standard—mostly shows that rotors sustain AF (including in human atria⁸), yet most classic electrogram analyses of AF do not¹⁵. Finally, repolarization data may enable tracking of response to therapy.

Concluding statements

Verrier et al¹¹ should be congratulated for demonstrating that dynamic atrial repolarization may be detected from routine clinical catheters. Although their results require further validation, they hold promise both as predictive tools and as aids in improving AF mapping and resolving the mechanistic debate. We look forward to exciting future developments in this area.

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Figure 1.

Repolarization information simplifies interpretation of atrial electrophysiology.

Simultaneous monophasic action potentials (**top**) and bipolar electrograms (**bottom**) in human left atrium during atrial fibrillation (AF). **Top:** Beat-to-beat tracking of repolarization time, indicated by time to $\approx 70\%$ repolarization (APD_{70}) in the monophasic action potential,³ shows that clinical electrograms in human AF may poorly indicate true local activation. Several deflections (nonfractionated and fractionated) fall well within APD_{70} and likely are far-field (see text and Narayan et al⁹).