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Mapping Ventricular Fibrillation: A Simplified Experimental Model Leads to a Complicated Result

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Minimally invasive recording techniques such as Holter monitoring and surface lead ECGs provide the opportunity to observe the incidence of arrhythmic events without significantly changing the heart. Despite significant effort and decades of work in this area, noninvasive mapping from the body surface does not provide sufficient resolution or accuracy to interpret the complex activation patterns and wavefronts that maintain ventricular fibrillation (VF).¹ Therefore, cardiac mapping of VF has been performed with various cardiac models that facilitate the direct recording of cardiac activation patterns. Mapping of cardiac arrhythmias with a few epicardial electrodes decades ago has progressed to advanced panoramic optical mapping techniques with thousands of simultaneous recordings.² The epicardial surface of the heart has been mapped extensively, with more limited data obtained from endocardial mapping methods. Transmural mapping is significantly more difficult to perform without altering the heart to such an extent that it is no longer representative of an intact heart model. Transmural activation has been recorded with scattered or closely spaced plunge needles, or optrodes^{3, 4}; however, these techniques are technically challenging and cause local ischemia and significant changes in the electrophysiological substrate of the heart. Perfused wedge preparations provide a window to glimpse transmural activation patterns optically, but this technique also significantly alters VF patterns.⁵ All of the available cardiac mapping techniques provide a view of a portion of the heart with some modification to it that may alter VF activation patterns. Interpretation of mapping studies in which activity of only part of the heart is recorded is difficult. Investigators performing ventricular tachycardia (VT) or VF mapping find that increased temporal and spatial resolution as well as recordings from inaccessible areas of the heart would be useful in understanding complex activation patterns and wavefronts that occur during cardiac arrhythmias.

Computer simulations provide an opportunity to understand certain mechanisms of cardiac arrhythmias. Computer simulations allow for simultaneous observation of all simulated tissue without causing observer error. Unfortunately, physiologically accurate models are difficult to construct, in part because we are still learning about the elements required to build the models. On a cellular level, we are still gaining an understanding of ion channels, gap junctions, connexons, charge pumps, metabolism, excitation-contraction coupling, signaling, gene expression, and other phenomenon. Current cardiomyocyte models involve dozens of equations that describe ion channel behavior, charge pumps, leak currents, and other factors that affect cellular electrophysiology.⁶ Creating 3-dimensional models with thousands or

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millions of these simulated cells becomes a challenging task that requires immense computing power. Fiber orientation, anatomical obstacles, tissue heterogeneities, pharmacological interventions, and external events such as pacing, defibrillation, and stretch activation are difficult to simulate accurately in computer models. Creating a physiologically accurate model of normal cardiac tissue is daunting; simulating pathological conditions requires significantly altered models for which the required physiological data is not currently available. For these reasons, computer simulations have not been able to replace experimental models in many areas of arrhythmia research.

Decades of cardiac mapping and simulations have revealed that VF is a complex phenomenon maintained by many mechanisms such as spiral wave (SW) reentry, intramural and endocardial foci, intramural wandering wavelets, and anatomically anchored mother rotors.^{2, 7} In this issue of *Heart Rhythm*, a study performed by Ishiguro et al. takes advantage of traditional optical mapping techniques that allow for observation of only the most epicardial layer of the heart.⁸ In order to eliminate contributions from tissue that cannot be mapped, the endocardium and the bulk of the myocardium was cryoablated, leaving only a thin layer of epicardium (~1 mm). One important mechanism of VT and VF maintenance was preserved in this model used by Ishiguro et al: SW reentry.⁹ By performing the study on this reduced experimental model, they have eliminated other mechanisms such as intramural and endocardial foci, intramural wandering wavelets, and anatomically anchored mother rotors.

Ishiguro et al. reported that sodium current (I_{Na}) blockade with pilsicainide caused a prolongation of functional block lines and an increase in reentrant path length, which may have led to a decrease in wavefront-tail interactions. The result was stabilization of SW reentrant circuits at longer cycle lengths than in control hearts. They reported that L-type calcium current ($I_{Ca,L}$) blockade with verapamil shortened action potential duration and VT cycle length and likewise increased the stability of reentrant circuits. Surprisingly, $I_{Ca,L}$ and I_{Na} blockers combined destabilized SW reentry by causing large spatial drift of the circuit and decremental conduction that led to termination of VT. Even in this simplified model of VT that exhibits only SW reentry, two distinct channel blockers that independently increase SW reentry stability lead to breakdown of SW reentry when given together. In a more intact model of VF or VT, the influence of $I_{Ca,L}$ and I_{Na} blockers on SW reentry would be difficult to distinguish from the effect of these channel blockers on the other mechanisms of VF maintenance.

While this model has the advantage of isolating a single mechanism of VF maintenance, there are numerous reasons that VF and VT patterns in this model may not be representative of VF and VT in human subjects. A partial list of these limitations includes: 1) isolation and perfusion of the heart changes VF patterns¹⁰, 2) cryoablation technique eliminates transmural reentry¹¹, 3) anatomical anchors and structures thought to be important in reentry and VF maintenance are altered and eliminated^{12, 13}, 4) electrically induced VF in healthy hearts may not be the same as VF in ischemic hearts^{14, 15}, 5) the Purkinje and specialized conduction system of the heart were eliminated^{16, 17}, 6) collagenous septae between muscle bundles may be more sparse in the epicardial layer than in the bulk of the myocardium¹⁸, 7) only one surface of the heart was mapped which limits the incidence of reentry to circuits entirely contained in the mapped region¹⁹, 8) the electromechanical uncoupling agent may have changed electrophysiological properties of the surviving layer^{10, 20, 21}, 9) staining for optical mapping may change electrophysiological activation patterns^{10, 22}, 10) rabbit and human VF patterns differ significantly²³, 11) elimination of sympathetic and parasympathetic inputs²⁴, 12) transmural variations in gap junction distribution, ionic currents, and action potential characteristics were eliminated²⁵, and 13) verapamil and pilsicainide may not cleanly affect only L-type Ca^{2+} ($I_{Ca,L}$) and Na^{+} (I_{Na}), respectively^{26, 27}.

The model used by Ishiguro et al. substantially modifies the heart and renders it incapable of maintaining VF. Ishiguro et al. have been careful not to overstate the findings of the study due to the limitations of the experimental model. They have, however, provided valuable insight into the role of $I_{Ca,L}$ and I_{Na} separately and jointly on SW reentry in an experimental model of 2-dimensional cardiac tissue. The effect of verapamil and pilsicainide in more intact hearts and on other mechanisms of VF and VT maintenance are not discussed by the authors. Further testing in more intact models will be required to determine what the net effect of $I_{Ca,L}$ and I_{Na} on VF and VT maintenance with the added complexity of larger and more intact heart models.

While simplified experimental models have the potential to modify the arrhythmia that is being studied, they may provide opportunities reduce complexity and to separate competing mechanisms that may otherwise be indistinguishable. VF is perpetuated by multiple mechanisms that are difficult to study and understand when they exist together. As demonstrated by the study of Ishiguro et al., even models that reduce complexity by limiting VT maintenance to a single mechanism may have unexpected results. Experimental models that modify VF activation patterns may still provide important insights into the mechanisms that drive and maintain VF. Reduced experimental models have an important role in understanding specific mechanisms and phenomenon in cardiac arrhythmia research, but care must be taken when relating the findings from studies using these models to human subjects and to clinical application.

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