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The chicken or the egg? Voltage and calcium dynamics in the heart

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T-WAVE ALTERNANS, corresponding to repolarization alternans in the ventricles, has been shown to predict the risk of cardiac arrhythmias and sudden cardiac death (13, 25). Theoretical studies have shown that arrhythmogenic repolarization alternans can originate from either the dynamics of membrane voltage (12, 14, 33) or intracellular calcium (Ca_i) cycling (21, 28, 34). In reality, however, both of these factors always coexist, since voltage and Ca_i are bidirectionally coupled through calcium-dependent ionic currents (1). This makes it a challenging problem to identify experimentally the sources of instabilities. For example, alternans in Ca_i cycling also causes alternans in action potential duration and vice versa, raising a classic “chicken or egg” conundrum (30).

Experiments in isolated myocytes using action potential-clamp (4, 32) or voltage-clamp (8, 10) techniques, in which Ca_i alternans was observed to occur without alternans of the voltage waveform, represented the first step toward an experimental solution. At best, however, these experiments demonstrate only that Ca_i cycling is capable of generating dynamic instabilities. Moreover, a shortcoming of action potential or voltage-clamp studies is that the system under these conditions has been modified, which may alter its dynamics. In addition, clamping Ca_i (the theoretical counterpart of the voltage clamp) to determine whether voltage alone is capable of generating electrical instabilities is not experimentally feasible (4, 8, 10, 32). Thus, even though recent experimental evidence (19, 31) favors the idea that repolarization alternans in tissue originates predominantly from an instability in Ca_i cycling, the degree of Ca_i instability is always being modulated by the level of the voltage instability, and vice versa. Although initial efforts (27) have been made to develop theoretical criteria to distinguish whether the discordant alternans observed in tissue arises predominantly from voltage or Ca_i cycling, their quantitative contributions remain challenging to define.

In this issue of *American Journal of Physiology-Heart and Circulatory Physiology*, Jordan and Christini (11) analyze the interaction between voltage and calcium dynamics by carrying out simulation studies with four different action potential models. They employed combinations of action potential voltage clamping, Ca_i -transient clamping (which is possible in simulations), and dynamical stability analysis to determine the roles that voltage and Ca_i coupling play in regulating action potential stability and the development of alternans. Based on their modeling results, they propose novel single-cell experiments that incorporate action potential voltage clamping, Ca_i imaging, and real-time measurement of action potential stability to provide a possible experimental strategy for assessing the relative contributions of voltage and Ca_i coupling to the regulation of action potential stability in real cardiac myocytes.

This effort by Jordan and Christini (11) represents an important step. A practical issue is whether their protocols are experimentally feasible, since, as the authors acknowledge, their approach may fail under noisy conditions. Ca_i -cycling instabilities arise from multiple factors: the gain of sarcoplasmic reticulum calcium release, calcium uptake by sarcoplasmic reticulum, and interactions of calcium with myofilaments or mitochondria, which add additional complexity to this already complicated problem. At the tissue level, the problem becomes even more challenging, since none of the techniques mentioned above is directly applicable to intact tissue or intact hearts. Besides voltage and calcium coupling, spatial coupling and tissue size are additional factors regulating dynamical instabilities at the tissue level (5, 7, 24, 26). For example, alternans that becomes discordant in space, as measured by cycle length (2), voltage (17), or Ca_i transient (20) patterns, is a dynamic consequence of the couplings between voltage, calcium, and tissue properties (9, 26). In general, the “chicken or egg” problem becomes much more complicated and difficult in intact tissue than in isolated cells.

Nevertheless, it is of paramount importance to generate experimental strategies to identify the sources of instabilities so that effective therapeutic targets can be developed. In addition to causing repolarization alternans in isolated cells and intact tissue, dynamical instabilities have been shown to be important for other aspects of cardiac arrhythmogenesis (22). In isolated cells, dynamical instabilities arising from voltage and calcium coupling can lead to automaticity and afterdepolarizations (3, 18, 29), triggers initiating reentrant arrhythmias. In cardiac tissue, these instabilities cause spiral wave breakup leading to fibrillation and its maintenance (4, 6, 15, 16, 23). Because of the high level of complexity and nonlinearity, intuitive interpretation of experimental data is unlikely to provide complete insights into these phenomena. Ideally, the best strategy will be to identify “signatures” that can be used to determine the dynamic origins of instabilities without grossly altering the system properties of the system. Mathematical modeling and nonlinear dynamics provide a systematic approach for identifying such “signatures” of the origins of dynamical instabilities, as in the study by Sato et al. (27) and in the novel protocols proposed in this study by Jordan and Christini (11). These theoretical strategies can then be combined with experimental techniques at the system level to test their validity. This type of integrative approach will be key to solving not only the “chicken or egg” conundrum of repolarization alternans but also many other problems in the field of biology.

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