Use of Ion Channel Dynamics To Control Dangerous Cardiac Arrhythmias—A Computational Study

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The complexity of the relationship between the dynamics at the ion channel level and the macroscopic properties of action potential propagation in the heart has long hindered investigation of the roles played by ion channels in life-threatening cardiac rhythm disorders. As a result, much of the research into this important multiscale relationship has been conducted by substituting the simpler but less comprehensive dynamics associated with morphological features of action potentials, such as their duration and intervening resting intervals, for the full dynamics of the ion channels. In our ongoing studies, we demonstrate the ability of computational methods, in combination with advanced mathematical techniques, to provide new insight into the relationship between ion channel functioning and cardiac action potential dynamics. We show that mathematical eigenmode methods can be applied to the patterns of action potential formation in isolated cardiac cells stimulated at regular intervals to diagnose fully and completely the cause-and-effect relationship between ion channels and so-called alternans, the alternation of action potential morphology from one beat to the next, a pattern linked to the onset of ventricular fibrillation (VF) in a number of studies. Similarly, we have used computer-aided eigenmode methods to uncover the ion channel basis underlying the breakup of rotating action potential waves in ventricular muscle, another pattern associated with VF. In both cases, the computer analysis has led to surprising new ideas that can be used in the control of these dangerous action potential patterns. For example, the analysis shows that alternans in single cells is most effectively controlled by applying electrical stimuli in the early plateau phase of the action potential, not in the repolarization phase as one might expect. Experiments performed on small cardiac preparations support this idea. The analysis also provides an example of how a single stimulus can stabilize a rotating wave over a region many space constants in extent, contrary to common intuition. These new ideas may lead to more effective electrical intervention therapies for controlling and eliminating deadly action potential propagation patterns in the heart.

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