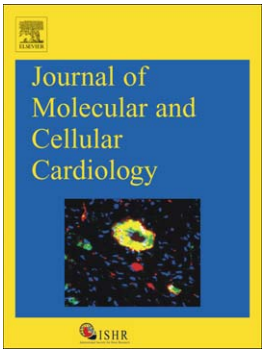

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Ryanodine Receptor Sensitivity Governs the Stability and Synchrony of Local Calcium Release during Cardiac Excitation-Contraction Coupling

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Abstract

Calcium-induced calcium release is the principal mechanism that triggers the cell-wide $[Ca^{2+}]_i$ transient that activates muscle contraction during cardiac excitation-contraction coupling (ECC). Here, we characterize this process in mouse cardiac myocytes with a novel mathematical action potential (AP) model that incorporates realistic stochastic gating of voltage-dependent L-type calcium (Ca^{2+}) channels (LCCs) and sarcoplasmic reticulum (SR) Ca^{2+} release channels (the ryanodine receptors, RyR2s). Depolarization of the sarcolemma during an AP stochastically activates the LCCs elevating subspace $[Ca^{2+}]$ within each of the cell's 20,000 independent calcium release units (CRUs) to trigger local RyR2 opening and initiate Ca^{2+} sparks, the fundamental unit of triggered Ca^{2+} release. Synchronization of Ca^{2+} sparks during systole depends on the nearly uniform cellular activation of LCCs and the likelihood of local LCC openings triggering local Ca^{2+} sparks (ECC fidelity). The detailed design and true SR Ca^{2+} pump/leak balance displayed by our model permits investigation of ECC fidelity and Ca^{2+} spark fidelity, the balance between visible (Ca^{2+} spark) and invisible (Ca^{2+} quark/sub-spark) SR Ca^{2+} release events. Excess SR Ca^{2+} leak is examined as a disease mechanism in the context of "catecholaminergic polymorphic ventricular tachycardia (CPVT)", a Ca^{2+}-dependent arrhythmia. We find that that RyR2s (and therefore Ca^{2+} sparks) are relatively insensitive to LCC openings across a wide range of membrane potentials; and that key differences exist between Ca^{2+} sparks evoked during quiescence, diastole, and systole. The enhanced RyR2 $[Ca^{2+}]_i$ sensitivity during CPVT leads to increased Ca^{2+} spark fidelity resulting in asynchronous systolic Ca^{2+} spark activity. It also produces increased diastolic SR Ca^{2+} leak with some prolonged Ca^{2+} sparks that at times become “metastable” and fail to efficiently terminate. There is a huge margin of safety for stable Ca^{2+} handling within the cell and this novel mechanistic model provides insight into the molecular signaling characteristics that help maintain overall Ca^{2+} stability even under the conditions of high SR Ca^{2+} leak during CPVT. Finally, this model should provide tools for investigators to examine normal and pathological Ca^{2+} signaling characteristics in the heart.