

Sarcoplasmic Reticulum Luminal $[Ca^{2+}]$ Regulates the Spontaneous Ca^{2+} Release Events and Consequently Arrhythmia

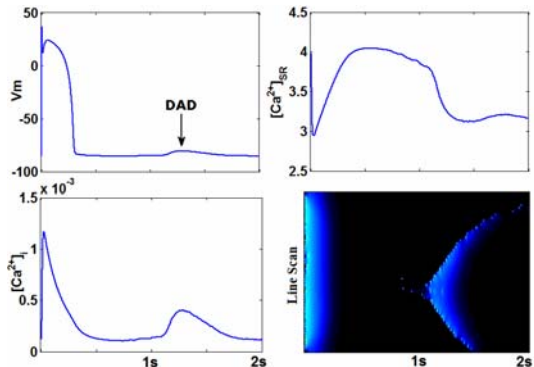
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The intracellular Ca^{2+} release from sarcoplasmic reticulum (SR) provides the major Ca^{2+} source required in cardiac excitation-contraction coupling. The important role that SR luminal Ca^{2+} concentration plays in regulating ryanodine receptors (RyRs) has been demonstrated by many experimental observations. However, the precise relationships between the Ca^{2+} loading status of SR and intracellular Ca^{2+} dynamics as well as electrophysiological characteristic are not completely clear.

In this paper, we developed a multi-scale mathematical model by coupling a two-dimensional spatially Ca^{2+} reaction-diffusion model with an action potential model of the ventricular myocyte. The proposed multi-scale model was applied to study the effects of changes in SR Ca^{2+} content on subcellular spatiotemporal Ca^{2+} cycling, and on the possible membrane potential changes caused by aberrant Ca^{2+} release events. The simulation results showed that 1) the spontaneous sparks increased when SR Ca^{2+} content was elevated in a diastolic myocyte, and vice versa, which suggested a positive regulating effect of SR luminal $[Ca^{2+}]$ on Ca^{2+} release; 2) under the conditions that SR Ca^{2+} was overloaded, spontaneous Ca^{2+} sparks and waves might also occur without any external stimulus, and 3) once formed, the propagation of Ca^{2+} waves was accelerated as the SR Ca^{2+} content increased. Moreover, those spontaneously occurred Ca^{2+} release events elevated cytoplasmic $[Ca^{2+}]_i$ and then activated Na^+-Ca^{2+} exchange current that depolarized the sarcolemma transiently, which might cause a delayed after-depolarization (DAD).

These findings suggest that regulation of RyRs by SR luminal $[Ca^{2+}]$ plays an important role in formation and propagation of Ca^{2+} waves and consequently heart arrhythmia with overloaded SR Ca^{2+} content.



Typical results show a paced action potential, followed by a spontaneously Ca wave which causes a DAD when SR Ca^{2+} was overloaded.