

# Calcium Leakage from SR Ryanodine Receptors

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In ventricular myocytes, ryanodine receptors (RyR2s) are the intracellular ion channels responsible for release of  $\text{Ca}^{2+}$  from the sarcoplasmic reticulum (SR). During each cardiac cycle, many RyR2s are triggered by  $\text{Ca}^{2+}$  influx through L-type  $\text{Ca}^{2+}$  channels, resulting in a large increase in intracellular  $[\text{Ca}^{2+}]$ , which then leads to myocyte contraction. In resting cells, RyR2s can open spontaneously, resulting in "leak" of  $\text{Ca}^{2+}$  from the SR into the myoplasm. Because inappropriate leak of  $\text{Ca}^{2+}$  is thought to be linked to arrhythmias in disease states, it is important to obtain a quantitative understanding of SR  $\text{Ca}^{2+}$  leak.

A RyR2 opening spontaneously can open and release  $\text{Ca}^{2+}$  from the sarcoplasmic reticulum (SR). The  $\text{Ca}^{2+}$  released from the SR can trigger adjacent RyR2 to open through a positive feedback process known as  $\text{Ca}^{2+}$ -induced-  $\text{Ca}^{2+}$ -release. When many of the RyR2 within a cluster are opened, the release can be visualized experimentally as a  $\text{Ca}^{2+}$  spark. However, when only one or a few RyR2s open, the  $\text{Ca}^{2+}$  leakage that results cannot be observed directly. We used computational modeling to generate quantitative predictions of how different factors influence visible and invisible SR  $\text{Ca}^{2+}$  leak.

A modified Monte Carlo computational model of a RyR2 cluster, based on Sobie et al (2002) discoveries, was used to simulate the opening of the receptors and  $\text{Ca}^{2+}$  release from the SR. Understanding that the gating of RyR2 depends on the  $[\text{Ca}^{2+}]$  in both the SR and the myoplasm, we varied the  $[\text{Ca}^{2+}]$  in both these regions to observe the effects on each would have on RyR2 behavior. Using the data generated from the RyR2 model simulations, the  $\text{Ca}^{2+}$  leak was calculated. The volume of the region between the RyR2 clusters and the cell membrane was also varied because experiments suggest that the close spatial coupling between the SR and cell membranes may be disrupted in heart failure.

Our simulation results reveal that: 1) the probability of a spontaneous RyR2 opening will trigger a spark is dependent on the  $[\text{Ca}^{2+}]$  in the SR, as  $[\text{Ca}^{2+}]$  increased the probability increased. The  $[\text{Ca}^{2+}]$  in the resting myoplasm made negligible differences. 2) The  $[\text{Ca}^{2+}]$  in the myoplasm, however, have a greater effect on the rate of RyR2 opening than the SR  $[\text{Ca}^{2+}]$ . Increase in myoplasmic  $[\text{Ca}^{2+}]$  increased the opening rate. 3) As a result, leak depends on the  $[\text{Ca}^{2+}]$  in both region, but more in the myoplasm. 4) The leak was also dependent on the subspace volume. Increasing the volume leads to a greater invisible leak.