

# Computational modeling of “leaky” ryanodine receptors and triggered arrhythmias in heart cells

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Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a rare inherited disorder caused primarily by mutations in the gene encoding for the ryanodine receptor (RyR), the key intracellular calcium release channel in the heart. Patients with CPVT have structurally normal hearts; however, lethal arrhythmias may transpire during exercise or emotional stress linked to increased levels of circulating catecholamines. Arrhythmias in CPVT are thought to be triggered by spontaneous sarcoplasmic reticulum (SR) calcium release leading to inappropriate depolarization of the cell membrane.

The current accepted understanding is that “leaky” RYRs are responsible for the arrhythmias in CPVT. However, increasing the RyR open probability decreases the  $[Ca^{2+}]_{SR}$ , and this change makes spontaneous  $Ca^{2+}$  release and arrhythmias less likely. Instantaneously increasing the RyR “leakiness” causes the  $Ca^{2+}$  transient amplitude to increase for the first few beats, but this quickly returns to the original levels as the  $[Ca^{2+}]_{SR}$  decreases. Hence, there is no reason to assume that “leaky” RyRs will increase the risk of the arrhythmia. We implemented an integrative computer model that simulates  $Ca^{2+}$  movements between the extracellular space, cytosol, and SR. The model considers both the normal, physiological triggering of SR  $Ca^{2+}$  release and the risk of spontaneous, pathological  $Ca^{2+}$  release. With this model we evaluated how changes in RyR “leakiness” and  $Ca^{2+}$  movements across the cell membrane may increase or decrease arrhythmia risk under different conditions.

Our simulations produced several novel, counterintuitive, and testable predictions. First, RyR leakiness may either increase or decrease the risk of arrhythmia, depending on the experimental conditions. Second, altering the  $Ca^{2+}$  entry into the myocyte with each beat qualitatively changes the relationship between leakiness and arrhythmia risk. Third, and perhaps most surprisingly, decreasing extracellular  $Ca^{2+}$  can increase rather than decrease the risk of arrhythmia due to altered triggering of physiological  $Ca^{2+}$  release. These results demonstrate the value of computational modeling for the analysis of the multiple interacting components of complex biological systems and may be of use in determining the best course of treatment for patients with CPVT.