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Computational modeling of "leaky" ryanodine receptors and triggered arrhythmias in heart cells

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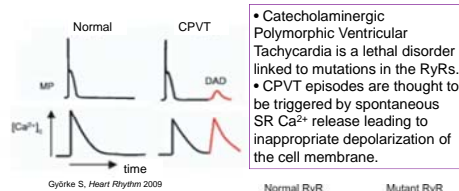


Abstract

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 arrhythmic risk under different conditions.

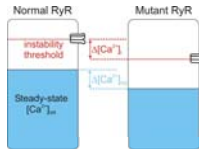
Our simulations produced several novel, counterintuitive, and testable predictions. First, RyR leakiness may either increase or decrease the risk of arrhythmia, depending on the experimental conditions. Second, altering the Ca^{2+} entry into the myocyte with each beat qualitatively changes the relationship between leakiness and arrhythmic 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.

Background

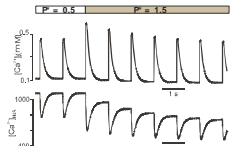


- Catecholaminergic Polymorphic Ventricular Tachycardia is a lethal disorder linked to mutations in the RyRs.
- CPVT episodes are thought to be triggered by spontaneous SR Ca^{2+} release leading to inappropriate depolarization of the cell membrane.

Cardiac myocytes can be characterized by a steady-state value of $[Ca^{2+}]_{SR}$ and an instability threshold – the level of $[Ca^{2+}]_{SR}$ at which Ca^{2+} waves occur. Leaky RyRs reduce both.



After an instantaneous increase in P^* , Ca^{2+} transient amplitude increases for the first few beats, but returns to its original level as $[Ca^{2+}]_{SR}$ decreases.



Objective

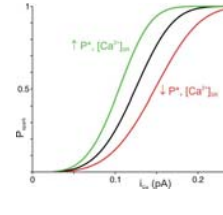
To use an integrative computational model to determine quantitatively how changes to ryanodine receptor "leakiness" may increase or decrease the risk of arrhythmia.

Specifically, we sought to determine the effects of:

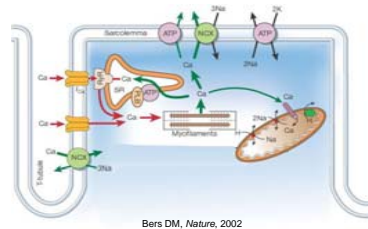
- increased or decreased Ca^{2+} entry
- enhanced or suppressed Ca^{2+} spark triggering
- changing the concentration of extracellular Ca^{2+}

Terminology

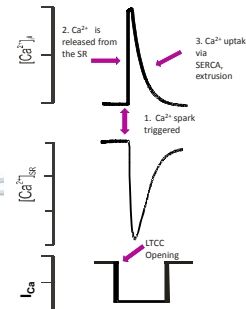
- P^* wave:
 - the variable that specifies arrhythmia risk
 - calculated according to identical rules governing the normal triggering of calcium transients
- P^* :
 - $P^*_{mutant}/P^*_{wildtype}$
 - defines changes in RyR gating
- Coupling Fidelity (CF): the probability that an individual L-Type Ca^{2+} channel opening will trigger a Ca^{2+} spark



Approach



The Model:



The model simulates Ca^{2+} movements in the ventricular myocyte.

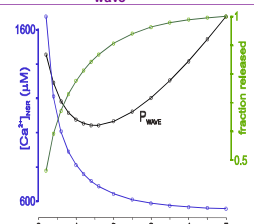
Each cycle simulates:

- triggering of a percentage of Ca^{2+} sparks (rules according to Sobie & Ramay, J. Physiology, 2009)
- release of JSR Ca^{2+} into cytosol
- Ca^{2+} movements:
 - Influx
 - Extrusion
 - Buffering
 - Transfer between compartments
- Computation of P^* wave:
 - proportional to the probability that a spark triggers a neighbor
 - governed by the same rules as spark triggering

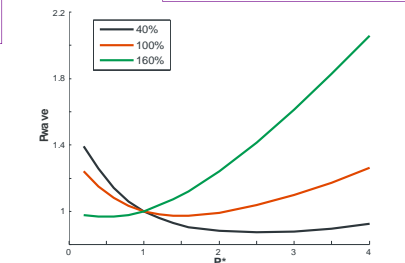
Results

Ca^{2+} Entry Without Changing Spark Triggering:

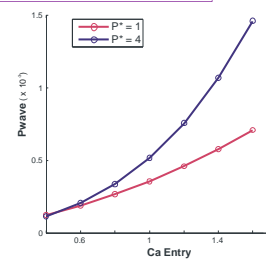
Non-monotonic dependence of P^* wave on P^*



Either an increase or a decrease in P^* can increase steady-state arrhythmic risk, depending on the resulting $[Ca^{2+}]_{SR}$.



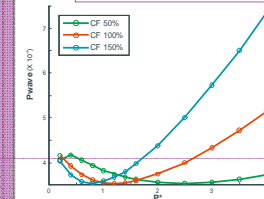
At lower $[Ca^{2+}]_i$, arrhythmia risk increases as RyR leakiness decreases.
At higher $[Ca^{2+}]_i$, arrhythmia risk increases as RyR leakiness increases.



As RyR leakiness increases, the risk of arrhythmia increases in a non-linear fashion.

Results

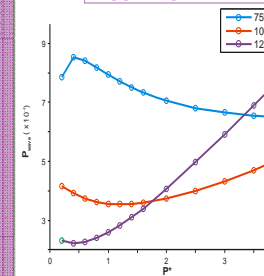
Changes in Ca^{2+} spark triggering without changing Ca^{2+} entry:



The simulations suggest that in the physiological range triggering more sparks is protective at low P^* .

Results

Coupling of Ca^{2+} entry to Ca^{2+} spark triggering:



In these simulations, changes in extracellular $[Ca^{2+}]_i$ altered both Ca^{2+} entry and triggering of Ca^{2+} sparks. Unexpectedly, the simulations show that reducing extracellular Ca^{2+} increases the risk of arrhythmias.

There is a reduced risk of arrhythmia at higher $[Ca^{2+}]_i$ due to the spark triggering effect – increased triggering of Ca^{2+} sparks is more protective than the deleterious effect of increased Ca^{2+} influx.

Conclusions

- RyR leakiness may either increase or decrease the risk of arrhythmia, depending on experimental conditions.
- Altering the amount of Ca^{2+} entry into the cell with each beat qualitatively changes the relationship between leakiness and arrhythmia risk.
- Decreasing extracellular $[Ca^{2+}]_i$ can increase, rather than decrease, the risk of arrhythmia due to altered triggering of physiological Ca^{2+} release.

Acknowledgments

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