A SMALL NUMBER OF CELLS IS SUFFICIENT TO TRIGGER A CARDIAC ARRHYTHMIA: STOCHASTIC COMPUTATIONAL STUDIES

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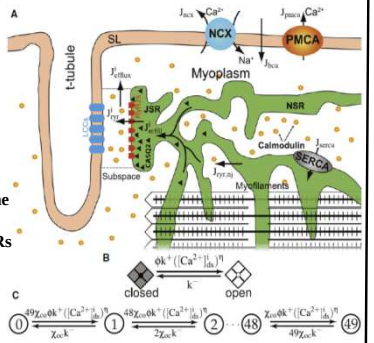
ABSTRACT

Cardiovascular disease is the leading cause of death world-wide due in large part to arrhythmias. Here we examine the cellular and subcellular basis of Ca^{2+} dependent arrhythmias. In order to understand how calcium dynamics, plays a role in arrhythmogenesis, we have investigated normal and dysfunctional Ca^{2+} signaling in heart cells at high temporal and spatial resolution. Spontaneous calcium release occurs normally as Ca^{2+} sparks. Under pathological conditions, Ca^{2+} sparks can combine to form Ca^{2+} waves. These propagating elevations of $[Ca^{2+}]_i$ can activate inward Na^+-Ca^{2+} exchanger current (INCX) that contribute to early after-depolarization (EADs) and delayed after-depolarizations (DADs). However, how cellular currents lead to full depolarization of the myocardium and how they initiate extra systoles is still not fully understood. Some earlier studies that have investigated this question suggest that as many as about ~700,000 cells must undergo such behavior to initiate a propagating action potential or an arrhythmia [3]. Here we present the results of our study which explores how many cells must be entrained to initiate arrhythmogenic depolarizations in "realistic" computational models. The model presented here suggests that only a small number cells must activate in order to trigger an arrhythmogenic propagating action potential. These conditions were examined in 1D, 2D, and 3D taking into account heart geometry. The finding that only a small number of cells is required to trigger an arrhythmia provides a plausible mechanism by which cardiac arrhythmias might occur.

INTRODUCTION

Cardiovascular disease is the leading cause of death world-wide and this is due in large part to arrhythmias. Here we examine the cellular and subcellular basis of Ca^{2+} dependent arrhythmias. In order to understand how calcium dynamics, plays a role in arrhythmogenesis, we have investigated normal and dysfunctional Ca^{2+} signaling in heart cells at high temporal and spatial resolution. Here we present our findings on the processes that lead to the initiation of an arrhythmia.

WHOLE-CELL CICR MODEL



Schematic of SR Ca^{2+} leak model and release site schematic.
(A) Model compartments and Ca^{2+} fluxes (solid arrows).
(B) Transition state-diagram for the two-state Markov chain describing a single RyR.
(C) Transition-state diagram for the Markov chain representing the RyR cluster where each state indicates the number of open RyRs (No) in the CRU (e.g., 0, 1, 2, 48, 49) [1].

- Rat ventricular myocyte:
- 20,000 CRUs/cell

Each CRU:

- 7 L-type Ca^{2+} channels (LCCs) + 49 RyR2
- Novel LCC model using Markov chain with both V_m- dependent activation/inactivation and Ca^{2+}-dependent inactivation.
- Model RyR2 as 2-state with both cytosolic Ca^{2+} sensitivity and luminal Ca^{2+} regulation.
- RyR gating incorporate energetic coupling formulation [2].
- A small population of non-junctional LCCs (10%), RyR (5%).

RESULTS

Action Potential (AP) Propagation

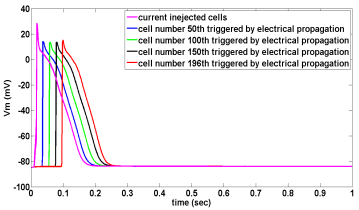
- There are two ways to trigger propagating Action Potential.
  - Current injection.
  - Spontaneous Ca^{2+} release during HF.

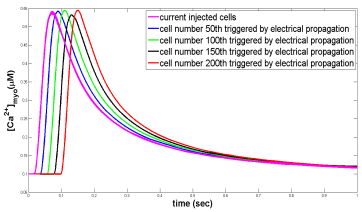
HEART FAILUE (HF) CONDITIONS

Heart failure (HF) is accompanied by a number of changes including the following

- A reduction of potassium channel expression (-30%)
- A decrease in SERCA expression (-20%).
- An increase in sodium-calcium exchanger expression (+100%).
- Phosphorylation of RyRs (+50%) .
- A reduction in t-tubular membrane due to rearrangement (-25%) so that the RyRs are no longer apposed with the t-tubular membrane which we call orphaning, i.e. subspace volume increases 30x.

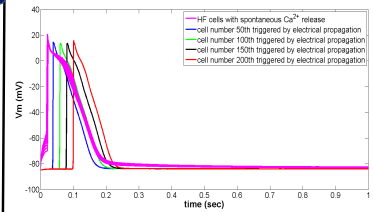
ARRHYTHMIA INITIATION IN 1D TISSUE

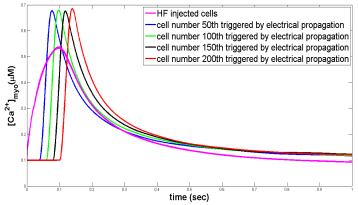




Current injection into 4 cells (magenta) results in a propagating action potential in a 1D cable of cells.

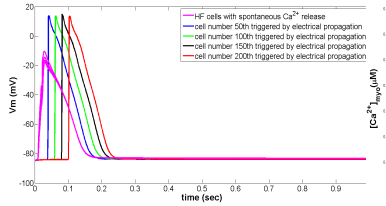
The current-injection induced action potential triggers calcium release in the 1D cable of cells.

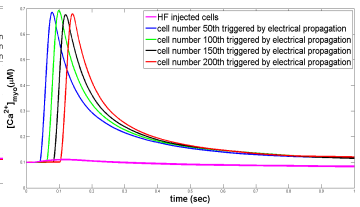




Under HF conditions, opening 10 RyR channels in 50% of the release units results in a propagating action potential.

The calcium rises slowly in the triggered cells resulting in depolarization. The action potential spreads rapidly to other cells activating calcium release.





AP with normal and HF parameters. Cells with corresponding amplitude when Na and Ca current are blocked in 1-d.

Ca^{2+} wave with normal and HF parameters. Cells with corresponding amplitude when Na and Ca^{2+} current are blocked in 1-d.

ARRHYTHMIA INITIATION IN 2D TISSUE

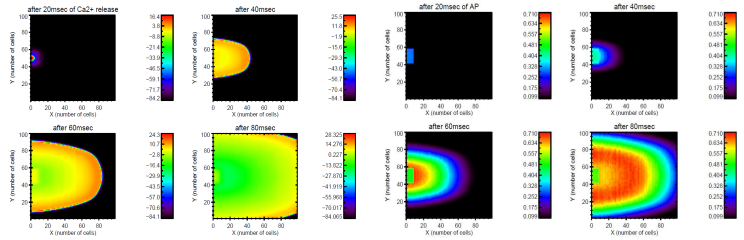
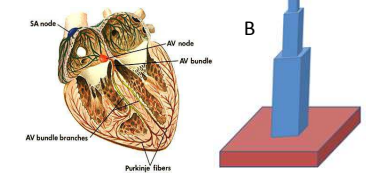


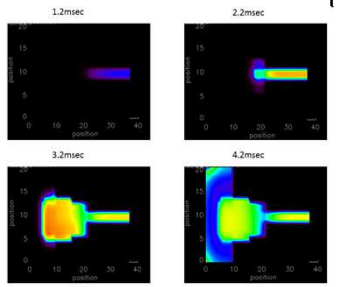
Table (at right)
Number of Cells Needed to Trigger Propagating Action Potential.

Protocol	1D	2D	3D
Current injection	4	18	40
Calcium release During HF	10	140	850
DAD	4	120	200

ARRHYTHMIA INITIATION SITE

Even several hundred cells seems a large number to generate an arrhythmia. The heart has many fine structures such as Purkinje fibers and trabeculae (lining the chambers of the heart) that are in effect 1D structure (A) [4]. We use simulated trabeculae that interface with the heart wall (B) and we were able to reduce the number of cells to 12 for triggering arrhythmic by current injection and for the HF conditions the number of cells reduced to only 64.





CONCLUSIONS

- The model presented here supports the idea that spontaneous calcium release during conditions such as heart failure or in an EAD can result in an action potential through activation of Na^+-Ca^{2+} exchange.
- Simulations suggests that only relatively small number of cells are needed to trigger a propagating action potential with the number increasing as dimensionality increases from 1D to 2D to 3D.
- Fine structures in the such as Purkinje Fibers and Trabecula provide a virtual 1D media in which an arrhythmia can be initiated. This greatly reduces the number or cells needed to initiate an arrhythmia in the 3D heart.

ACKNOWLEDGMENTS

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