Basis for the Induction of Phase-Two Reentry in the Brugada Syndrome: Insights from Computer Simulations

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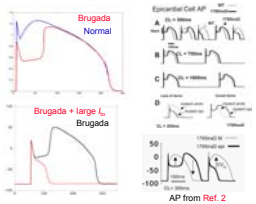
Abstract

Introduction. The Brugada syndrome is characterized by a dysfunction of sodium channels that can result in delayed formation of the action potential dome or even complete loss of the dome during phase two in the right epicardial ventricular layers where Ito is large. The repolarization pattern in these cases is believed to give rise to phase two reentry; however, little is known about the specific conditions that allow or suppress its initiation. **Methods.** Ionic cell models for normal epicardial, endocardial and M cells were developed in addition to two epicardial Brugada models that reproduced the action potential shape of experimentally measured human Brugada MAPs and the Luo-Rudy dynamic model with Brugada. These models were used in 1D cables, 2D slabs, and a 3D canine ventricular model to show ST-segment elevation on ECG leads V1-V3 and to study induction of reentry by phase two. **Results.** In 1D, phase two reentry can be induced when a region with loss of dome is adjacent to a region with a delayed dome, independent of stimulation site. In 2D, phase two reentry can be initiated when three regions (lost dome, delayed dome, and normal) are present, and sustained reentry initiates following an activation from any stimulus site outside the normal tissue. In 3D, sustained phase two reentry requires taking into account the different resistivity between the epicardial and M cell layers. **Conclusions.** The inducibility of phase 2 reentry depends on a number of factors, including Ito and resistivity distribution, rate and direction of stimulation, and most importantly, the shape of the late plateau, the action potential duration with loss of dome, and the rate of sodium inactivation.

Models

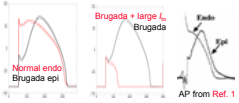
Model 1

Constructed to reproduce the action potential similar to the ones obtained by the Luo-Rudy dynamic model modified to incorporate a Na^+ channel mutation that causes both Brugada and long-QT syndrome.[2]

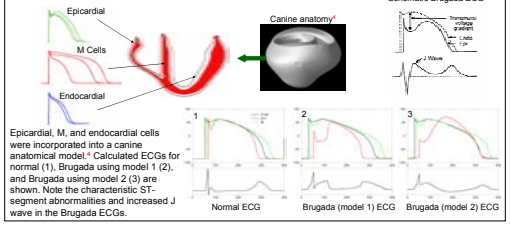


Model 2

Constructed to reproduce a monophasic action potential measured in human.[3]

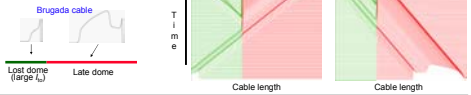


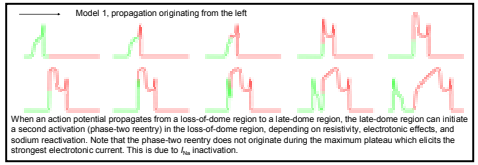
ECG Characteristics

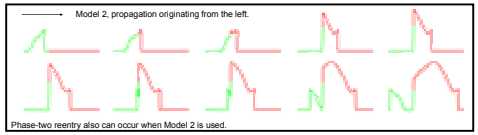


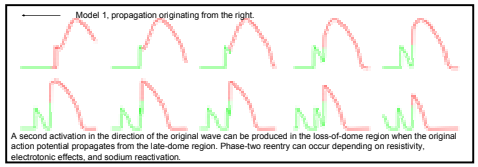
Dynamics in One Dimension

Phase two reentry in 1D can be produced using the Brugada cell models when some region has large I_{to} and the action potential loses its dome.

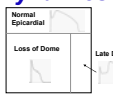




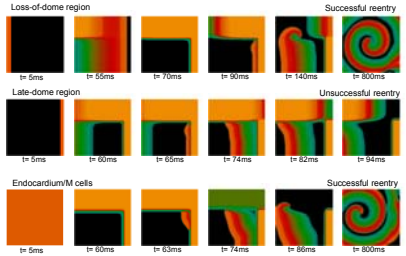




Dynamics in Two Dimensions

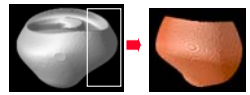


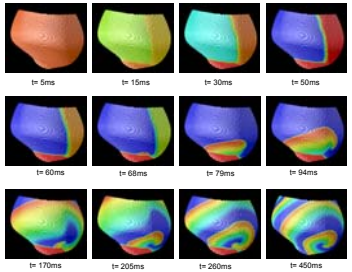
In 2D, phase-two reentry can initiate sustained reentrant activity, depending on the stimulus site with respect to the normal epicardial, late-dome and loss-of-dome regions.



Dynamics in Three Dimensions

Phase-two reentry, under proper conditions, also can initiate sustained reentrant activity in a 3D RV free wall preparation leading to a fast torsades de pointes.





The low coupling between M and epicardial cells is important for the development of phase-two reentry in 3D.

Discussion

Achieving phase-two reentry requires a delicate balance of electrotonic currents, tissue resistivities, sodium reactivation rate, threshold for excitation, and relative duration of APs.

Conditions necessary for phase 2 reentry:

- Slow pacing. Allows larger electrotonic currents as Brugada APDs have larger plateaus.
- Recovery of sodium channels in loss-of-dome region. Even when electrotonic currents are large, no excitation can be produced unless I_{Na} reactivation has occurred.
- Resistivity. Cell coupling is an important determinant of the voltage profile, which indicates whether it is possible to bring a cell's voltage above threshold by electrotonic currents.
- Relative duration of action potential between loss-of-dome and late-dome regions. The shorter the APD in the lost dome region, the sooner cells can recover for a phase-two re-excitation.

Important points:

- Phase 2 reentry requires that a region of high potential injects sufficient current to produce a voltage profile that elevates the membrane potential of the cells in some regions above threshold to produce a propagating wave.
- Recovery from I_{Na} inactivation has a critical role in the successful induction of triggered activity.

References

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This research was facilitated through an allocation of advanced computing resources by the National Computational Science Alliance, through the support of the National Science Foundation, and the computations were performed in part on the National Science Foundation Terascale Computing System at the Pittsburgh Supercomputing Center.