The transient outward potassium current plays a key role in spiral wave breakup in ventricular tissue

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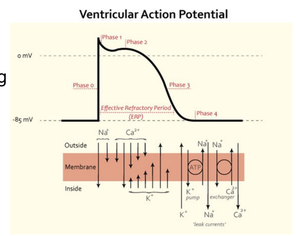
Abstract

Spiral wave reentry as a mechanism of lethal ventricular arrhythmias has been widely demonstrated in animal experiments and recordings from human hearts. It has been shown that in structurally normal hearts spiral waves are unstable, breaking up into multiple wavelets via dynamical instabilities. However, many of the second-generation action potential models give rise only to stable spiral waves, raising issues regarding the underlying the mechanisms of spiral wave breakup. In this study, we carried out computer simulations of two-dimensional homogeneous tissues using five ventricular action potential models. We show that the transient outward potassium current (I_{to}), although it is not required, plays a key role in promoting spiral wave breakup in all five models. As the maximum conductance of Ito increases, it first promotes spiral wave breakup and then stabilizes the spiral waves. Increasing Ito promotes single-cell dynamical instabilities, including action potential duration alternans and chaos, and increasing Ito further suppresses these action potential dynamics. These cellular properties agree with the observation that increasing Ito first promotes spiral wave breakup and then stabilizes spiral waves in tissue. Implications of our observations to spiral wave dynamics in the real hearts and action potential model improvements are discussed.

Methods

Cardiac ventricular electrophysiology has been modeled through various mathematical formulations that describe ionic currents passing through the cellular membrane under various conditions. An example action potential with the underlying ionic current physiology is shown to the right.



We carry out single-cell and two-dimensional (2D) tissue simulations with different ventricular myocyte action potential (AP) models. The differential equation for voltage for single-cell simulations is as follows:

$$\frac{dV}{dt} = -\frac{I_{ion} + I_{sti}}{C_m}$$

where C_m = 1 uF/cm^2 is the membrane capacitance, Iion the ionic current density, and Isti the external stimulus current density. The differential equation for voltage of 2D tissue is as follows:

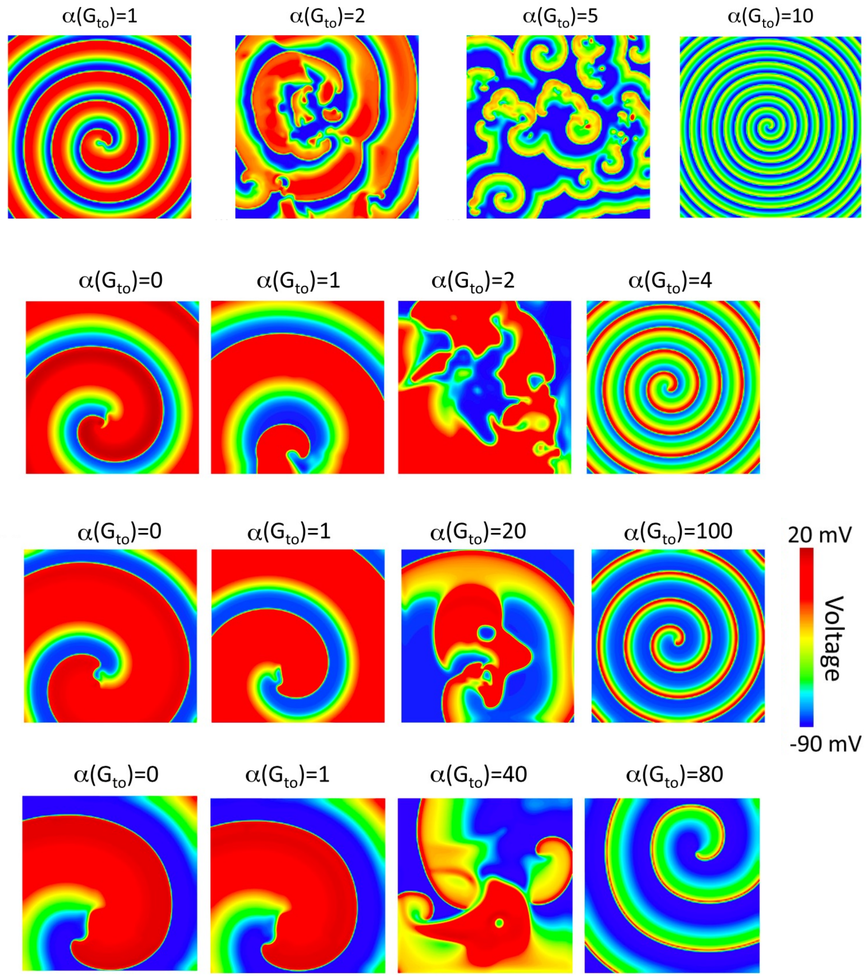
$$\frac{\partial V}{\partial t} = -\frac{I_{ion}}{C_m} + D\left(\frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V}{\partial y^2}\right)$$

where D is the diffusion constant. We used the following models: (1) the 1991 Luo and Rudy (LR1) guinea pig ventricular AP model; (2) the 1994 Luo and Rudy (LRd) guinea pig ventricular AP model with later modifications; (3) the Mahajan et al. rabbit ventricular AP model; (4) the O'Hara et al. (ORd) human ventricular AP model; (5) the 2004 ten Tusscher et al. (TP04) human ventricular AP model.

Results

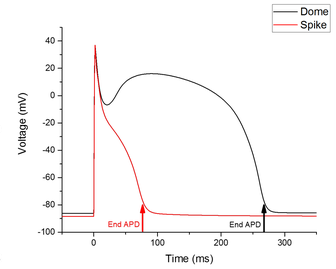
In each model, we generate a spiral wave in 2D tissue to be representative of monomorphic ventricular tachycardia (VT). Additionally, for each model, we vary the maximum conductance of the transient outward potassium current (I_{to}), and simulate the spiral waves in time. A spiral wave will do one of two things: remain a *stable* spiral wave (monomorphic VT) or become *unstable* and cause spiral wave breakup (ventricular fibrillation, VF).

In all the models, zero or low conductances of I_{to} (g_{to}) lead to only stable spiral waves. However, increased levels of g_{to} results in spiral wave breakup. Further increases in g_{to} stabilizes the spiral waves. In summary, in each model there is a certain range of g_{to} which promotes spiral wave breakup. The following are snapshots of the 2D simulations from 4 of the models; from top to bottom, LRd, Mahajan, TP04, and ORd.



Conclusion

A well-known effect of I_{to} is to promote a so-called spike-and-dome action potential Morphology (see right). As the maximum conductance of Ito increases, AP duration (APD) initially increases but then suddenly decreases once the maximum conductance reaches a certain value. This same effect can exhibit a large effect on APD restitution properties as shown in computer simulations and experiments.



We are not aware of any direct experiments demonstrating the role of I_{to} in spiral wave stability. In one experimental study, 4-AP, a selective blocker of I_{to}, converted VF to VT. This may agree with our simulation results suggesting that increasing I_{to} conductance promotes spiral wave breakup (e.g., VT to VF) and blocking I_{to} stabilizes spiral waves (VF to VT). In optical mapping experiments of arrhythmias in Brugada syndrome by Aiba et al., they observed VT and VF in different animals, and VT occurred in the ones with shortened APD and flattened APD restitution curves. This can be explained by the fact that a stronger I_{to} shortens APD and stabilizes spiral wave reentry as seen in our simulations.

In summary, the maximum I_{to} conductance is another key parameter that can promote spiral wave breakup in cardiac tissue. It may contribute to the unstable spiral wave dynamics observed in experiments of normal hearts and may play important roles in promoting the transition from VT to VF in Brugada syndrome.

Funding

This work was supported by National Institutes of Health, under Grants No. R01 HL133294 and No. T32-GM008185

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