Nonlinear Dynamics involving Action Potential Duration in Relation to Cardiac Arrhythmias

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Introduction

Sudden Cardiac Death is one of the leading causes of deaths in the United States and is known to be caused by abnormalities of heart rhythm, or cardiac arrhythmias. The leading cause of sudden cardiac death is due to ventricular fibrillation (VF). VF is associated with a spatiotemporally disorganized electrical activity that prevents the ventricles from pumping blood to the body. Understanding the mechanisms of VF and its precursors is critical for developing effective therapies. Using mathematical modeling of a rabbit ventricular cell and tissue, we investigated how the change in properties of ion channels such as conductance, affects instabilities of action potential waves at the tissue level.

Methods: S1S2 & Action Potential Duration (APD) Restitution Curve

APD restitution is the relationship between APD at beat *n+1* and the diastolic interval (DI) at beat *n* (**Fig 1**). To find the APD restitution curve, we used the S1S2 protocol shown in **Fig 2**. The myocyte is paced with many beats (S1) and then with a premature stimulus (S2) to see the response of APD to DI. In other words, to find APD, we altered the coupling interval (S2) between two consecutive beats to change DI.

Figure 1

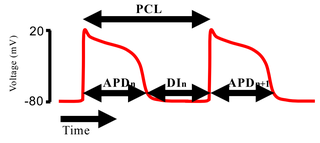
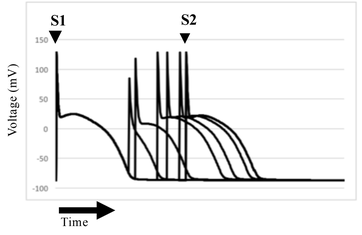
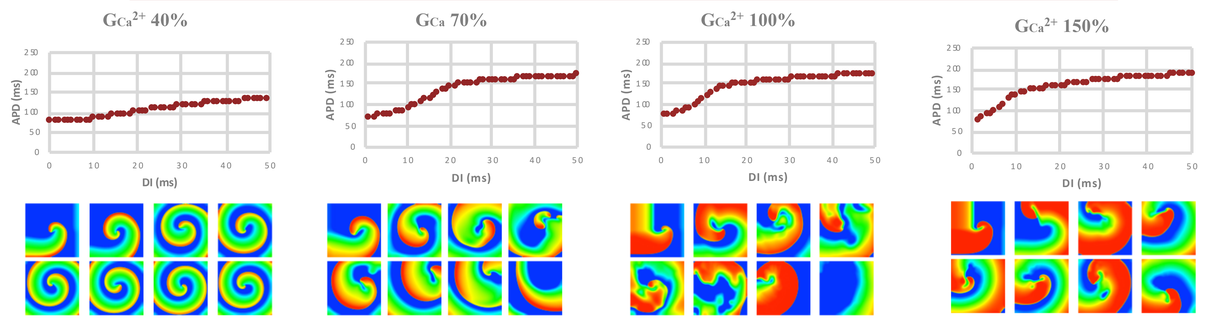


Figure 2



Results: Effects of Ca^{2+} Channel Conductance



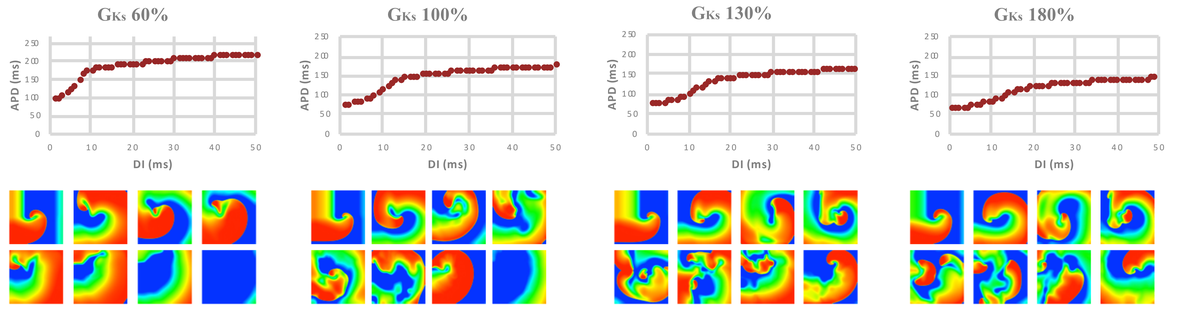
Decreasing the conductance to **40%,** we find the slope of the APD restitution curve is **much shallower** compared to when the conductance is not altered. The 2D images show that there is a consistent spiral wave, displaying signs of **ventricular tachycardia.**

Decreasing the conductance to **70%,** we find the slope of the APD restitution curve is **shallower** than when the conductance is not altered. The 2D images show the break up of the initial spiral wave and its termination.

When the conductance is **not altered**, hence **100%**, we find the complete breakup of the spiral wave that was initiated. Eventually, the spiral wave disappeared. We will treat this as the **control.**

Increasing the conductance to **150%**, we find the slope of the APD restitution is **steeper** than the non-altered conductance. The 2D images show the consistent reentry of the initial spiral wave, displaying signs of **ventricular fibrillation.**

Results: Effects of K^+ Channel Conductance



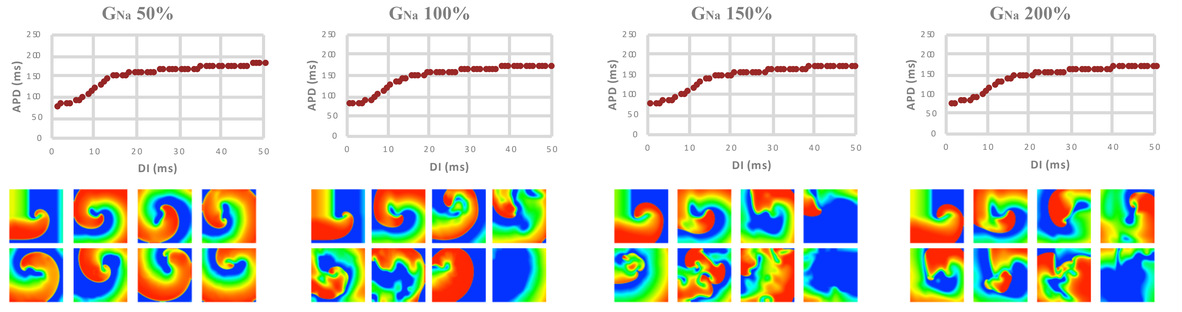
Decreasing the conductance to **60%,** the slope of the APD restitution curve is **steeper** than when the conductance is not altered. The 2D images show that the initial spiral wave breaks up completely.

When the conductance is **not altered**, hence **100%**, we find the complete breakup of the spiral wave that was initiated. We will treat this as the **control.**

Increasing the conductance to **130%,** the slope of the APD restitution curve is **shallower** than when the conductance is not altered. The 2D images show a consistent reentry of a spiral wave, which is a sign of **ventricular fibrillation**

Increasing the conductance to **180%,** the slope of the APD restitution curve is **shallower** than when the conductance is not altered. The 2D images show a consistent reentry of the spiral waves, which is a sign of **ventricular fibrillation.**

Results: Effects in Na^+ Channel Conductance



Decreasing the conductance to **50%,** the slope of the APD restitution curve is **slightly steeper** than when the conductance is not altered. The 2D images show the consistent reentry of initiated the spiral wave.

When the conductance is **not altered**, hence **100%**, we find the complete breakup of the spiral wave that was initiated. We will treat this as the **control.**

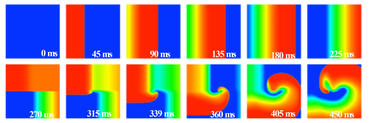
Increasing the conductance to **150%,** the slope of the APD restitution curve is **slightly steeper** than when the conductance is not altered. The 2D images show the complete break up of the spiral wave that was initiated, this occurred at a faster rate.

Increasing the conductance to **200%,** the slope of the APD restitution curve is **slightly steeper** than when the conductance is not altered. The 2D images show the complete break up of the spiral wave that was initiated, this occurred at a much faster rate.

Generation of Spiral Waves

We initiated a spiral wave by using a cross-field stimulation onto the 2D tissue (**Fig 3**). We used a 1000 by 1000 (~15 cm × 15 cm) array to model the ventricular wall tissue, where one element within this array represents a single cell.

Figure 3 : Cross-field stimulation



Conclusions

We showed that the steepness of the APD restitution curve correlates to the appearance of spiral wave break-ups. We demonstrate that by using nonlinear dynamics, we can theoretically predict susceptibility to arrhythmias in patients from the single cell property (i.e. steepness of APD restitution curve).

Future Directions

We list the following Anti-arrhythmic drugs that are considered in these cases:

Class I: Na^+ channel blockers.
Example: *Quinidine, Procainamide.*

Class III: K+ channel blockers.
Example: *Sotalol*

Class IV: Ca^{2+} channel blockers.
Example: *Verpamil*

In this study we simply varied the conductance of different ion channels. In our future study, we will model and simulate interactions between these ion channels and drugs.

References

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