Studying the effects of antiarrhythmic drugs on restitution properties of action potential duration of canine ventricular cells

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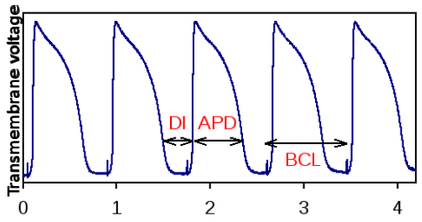
Background

- Sudden cardiac death caused by arrhythmias is a major cause of death in the world.
- Restitution plays a vital role in heart function. The electrical restitution describes the functional relationship betweens the action potential duration (APD) and the preceding diastolic interval (DI).
- Restitution hypothesis suggests that the slope of the restitution curve (RC) governs the transition to alternans.
- We use mathematical models to examine the effect of antiarrhythmic drugs on restitution properties of APD.

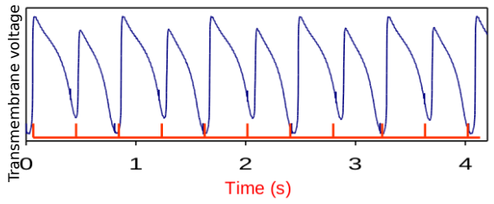
Cardiac electrophysiology



- Electrical pulses above a threshold value cause cardiac cells to produce an action potential (AP).
- We characterize the action potential by measuring the
  - action potential duration (APD), the time during which voltage is above a certain threshold,
  - diastolic interval (DI), the time between the end of one AP and the beginning of the next,
  - basic cycle length (BCL), the time between successive stimuli.

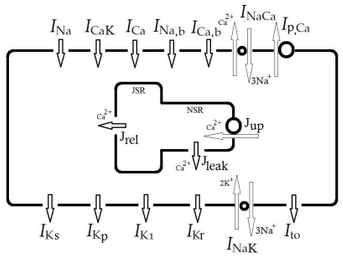
Cardiac alternans

Alternans is a long-short alternation in APD and is a precursor of ventricular fibrillation.



The Fox model

The Fox model is a mathematical model of the ionic currents flowing into and out of a canine ventricular cell.



We simulate the transmembrane voltage, V:

$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} = -I_{ion} + I_{stim}$$

I_{ion}: net membrane current, I_{stim}: external stimulus current and C_m: cell capacitance per unit surface area.

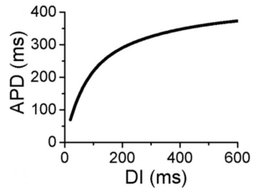
Implementing drug effect

- We study the effect of three different classes of antiarrhythmics:
  - Class I: Na^+ channel blockers.
  - Class III: K^+ channel blockers
  - Class IV: Ca^{2+} channel blockers.

  by multiplying the current of interest by $(1-\varepsilon)$ in our model.
- ε is the efficacy of the drug; ε ranges from 0 to 1.

Restitution

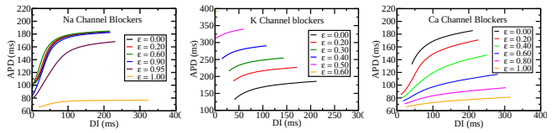
- It has been proposed theoretically that the maximum slope of the restitution curve (RC), describing APD as a function of DI, equal to one predicts the onset of alternans in cardiac cells.



- We use two different restitution protocols, dynamic protocol and S1-S2 protocol to construct the RCs for the model under study.

Dynamic Restitution

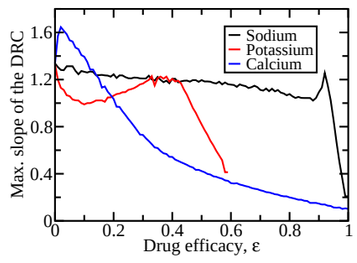
In the dynamic restitution protocol, the cell is paced at a given BCL until the steady state is reached, and the APD and preceding DI are recorded. Then the process is repeated for a range of BCLs.



- For Na^+ channel blockers, the shape of the RC remains the same for a wide range of drug efficacies.
- For K^+ channel blockers, the RC get steeper with increase in efficacy of the drug.
- For Ca^{2+} channel blockers, the RC flattens with increase in efficacy of the drug.

Drug induced change in the slope of dynamic RC

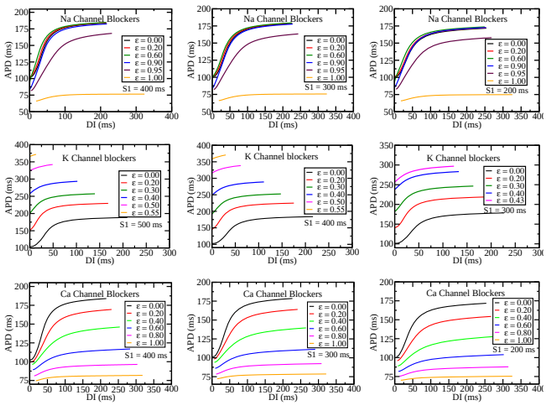
- The drug-induced change in the maximum slope of the RCs is shown for Na^+, K^+ and Ca^{2+} channel blockers as a function of drug efficacy.



- For no drug effect, the slope of the RC is 1.35.
- For Na^+ channel blockers, the slope of the RC increases at a drug efficacy of 0.95 and thereafter decreases as the APD vanishes at high efficacies.
- For K^+ channel blockers, the slope of the RC slightly decreases until the efficacy of 0.1 and thereafter increases with increase in the efficacy of the drug. The slope again decreases as the drug efficacy exceeds 0.45.
- For Ca^{2+} channel blockers, the slope of the RC decreases with increase in the efficacy of the drug.
- Ca^{2+} channel blockers are most efficient in lowering the slope of the RC.

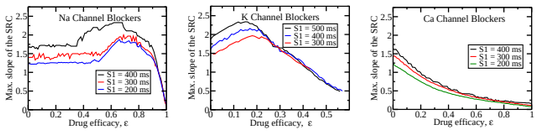
S1-S2 Restitution

In S1-S2 restitution protocol, the cell is paced at a fixed BCL (S1) until steady state is reached and is then perturbed by a stimulus (S2). Then the APD produced by the S2 stimulus is plotted against DI measured between S2 and the last S1.



The S1-S2 restitution shown are for 3 different values of S1 with Na^+, K^+ and Ca^{2+} channel blockers.

Drug induced change in the slope of S1-S2 RCs



- For Na^+ channel blockers, the slope remains the same for a certain range of efficacy and then increases with increase in efficacy. The slope then decreases again with increasing efficacy.
- For K^+ channel blockers, the slope first increases with increase in efficacy and then decreases with increase in efficacy.
- For Ca^{2+} channel blockers, the slope decreases with increase in efficacy of the drug.

Conclusions

- We see three distinct behaviors for restitution in the three classes of antiarrhythmics.
- The variation in slope of the RCs with efficacy for both protocols is different for the three classes of drugs.
- Dynamic RC is unique for a given cell whereas the S1-S2 RC depends on the choice of S1.