**Role of Transient Outward Current (Ito) in Action Potential Duration (APD)**

Introduction:

Carmeliet (1999) discussed about the transient lengthening of the APD after onset of ischemia. According to him “the transient lengthening of the action potential during the first initial seconds of ischemia can be partly due to a drop in local temperature (>1°C) . Other explanations include a reduction in electrogenic pump current, a fall in IK1 as a consequence of intracellular acidosis, and an acute inhibition of transient outward current (Ito )”.

Verkerk et al.(1996) observed the transient increase in APD and attribute it to the transient outward current, Ito. In particular, they claim that their data "clearly show that 4-AP, a blocker of Ito, abolishes the action potential prolongation induced by metabolic inhibition."

Ito is not present in the Luo-Rudy guinea pig model, which may explain why our models do not reproduce the transient increase in APD. Luo and Rudy say in their discussion "it should be mentioned that several ionic currents were not included in the present model. These include the transient outward current (Ito), which will be incorporated in future models once sufficient experimental data become available. Although Ito is not observed in guinea pig ventricular cells (of the type modeled here), it is a very important current for repolarization in ventricular cells of other species (e.g., dog, rabbit, and rat) and should be included in models of the ventricular action potential in these species."

Hence, our goal is to include transient outward current (Ito) in our model and to see the role of it in action potential duration (APD). I am using the equation for Ito from Gaur and Rudy (2007) paper.

Results:

We compare the action potential with and without Ito. The shape of the action potential is completely different when Ito is incorporated in LRd model. Figure 1 (right) shows a prominent phase 1 repolarization and a 'spike-and-dome' action potential morphology. We did not find the significant change in APD with and without Ito.

Figure 1: Transmembrane potential as function of time without (left) and with (right) transient outward current.

Comparison of APD:

We decreased the amount of transient outward current (Ito) (by 75% and 100%) when ischemia is introduced in our model. Ischemia is introduced after half a minute in our simulations. Slight uptake in APD is noticed when challenge (ischemia) is imposed in our simulation.

Figure 2: APD versus time with no Ito (left) and with 25% of Ito (right).

Comparison of train of action potential

Figure 3: Comparison of train of transmembrane potential as function of time before and after the ischemia is incorporated in our model with different amount of Ito.

Discussion:

Our result is qualitatively similar to the experimental finding of Verkerk et al. (1996) and Shotwell et at. (2013) but quantitatively different. The upswing we found is very small compared to Verkerk et al. (2000) and Shotwell et al. (2013).

Future work:

We are thinking of:

1. changing some parameter values used in the model,
2. changing the pacing rate
3. varying the delayed rectifier potassium currents.