APD versus Time in Challenge-Response Experiment

Introduction:

Shotwell et al. (2013) used mechanistic modeling and nonlinear longitudinal regression to study challenge to response experiment. They performed a series of experiments in isolated rabbit hearts. The cardiac tissue was challenged with intermittent anoxia and the cardiac action potential duration (APD) was measured as a function of time. They found a sharp irregular response for the change in APD over time. Within each anoxic period, their time course of APD was characterized by small initial upswing followed by a sharp decline, and the recovery period was characterized by a sharp initial upswing followed by a period of stability. We are interested to see the nature of the APD over time during intermittent challenges via computer simulation.

Methods:

We used the Luo-Rudy dynamic (LRd) model (1994) to simulate the electrical behavior of a ventricular myocyte. The LRd model does not calculate the variation of extracellular ion concentration. To calculate these concentrations dynamically, ionic fluxes were considered to flow between three compartments: the intracellular space, the interstitial extracellular clefts, and a bulk extracellular medium. In the bulk extracellular medium ion concentrations were constant, and in the interstitial extracellular cleft ion concentrations were changed with the equation taken from Rodriguez et al. (2002)

$$\frac{d[S]_o}{dt} = -\frac{A_m}{V_{cleft}F} I_{S,tot} - \frac{[S]_o - [S]_{bulk}}{\tau_{diff}} ,$$

where

$[S]_o$ = Extracellular concentration of ion S

A_m = the area of the myocyte = 1.534×10^{-4} cm^2

V_{Cleft} = Volume of the interstitial cleft = 5.182×10^{-6} μL

F = Faraday constant = 96485 C/mol

$I_{S,tot}$ = total ionic current associated to ion S

$[S]_{bulk}$ = extracellular ion concentration in the bulk = 5.4 mM for $[K]_{e,bulk}$ and 140 mM for $[Na]_{e,bulk}$

τ_{diff} = time constant for diffusion of ions from the interstitial clefts to the bulk extracellular medium = 1000 ms for the normoxic value and can be changed.

Results:

We ran the program for 500 sec with no stimulus to get the resting state values for transmembrane potential, the different intracellular and interstitial extracellular cleft ion concentrations, and the ion channel gates. Then we calculated the action potential duration (APD) as a function of time (Figure 1).

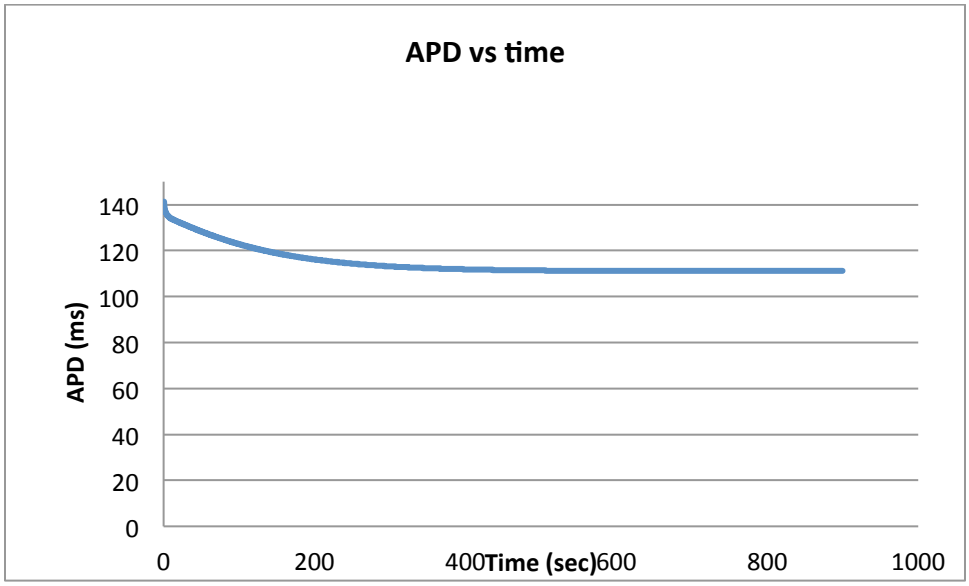

Figure 1: Action potential duration over time.

Elevated $[K]_e$ is one of the major component conditions of acute ischemia. It has a major effect on cell excitability by depolarizing the resting membrane potential. We imposed the intermittent challenges by increasing the extracellular potassium ion concentration $[K]_e$ to 12 mM. In Figure 2, at 15 sec, one intermittent challenge was imposed and in Figure 3, two intermittent challenges were imposed at 15 and 36 sec by rising $[K]_e$ to 12 mM. Each challenge was lasted for 6 seconds. During each ischemic period the time course of APD decreased gradually, followed by a sharp upswing upon return to normal $[K]_e$. We didn't get the small initial upswing as soon as the challenge is imposed as noticed by Shotwell et al. (2013). However, we can change the τ_{diff} to change the shape of the APD over time during ischemia.

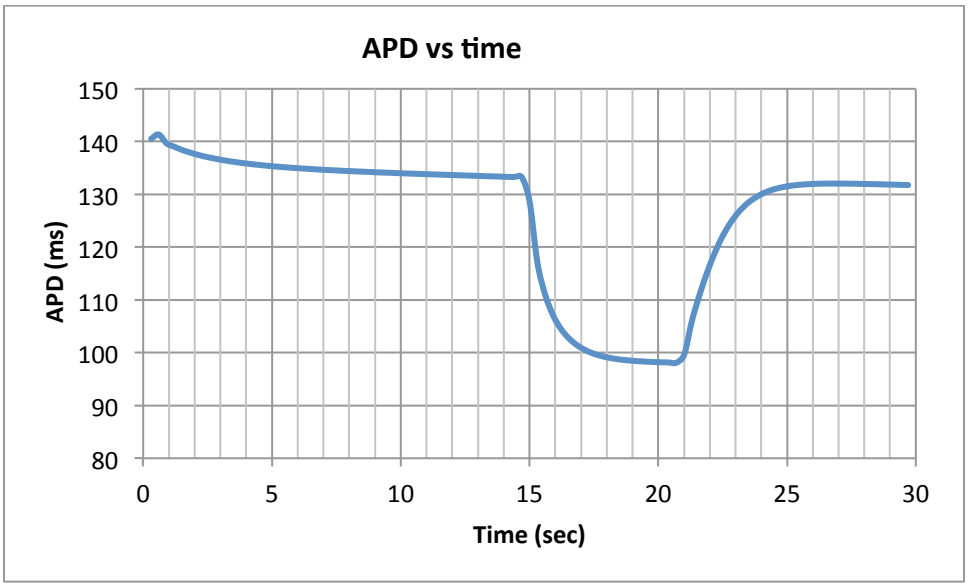

Figure 2: Action potential duration as a function of time. At 15 sec, heart was challenged with ischemia by increasing the $[K]_e$ to 12 mM. The challenge lasted for 6 seconds.

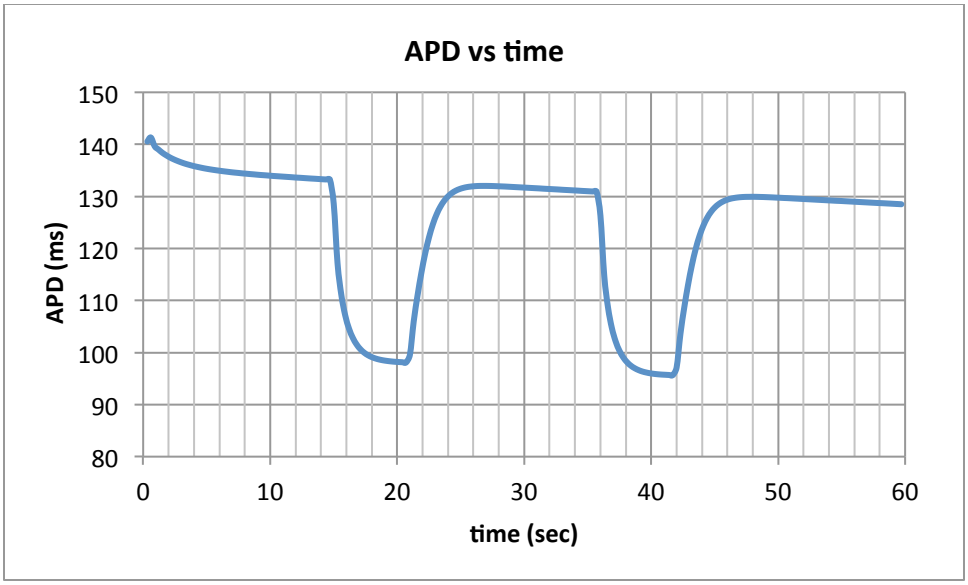

Figure 3: Action potential duration over time. In two subsequent time periods, heart was challenged with ischemia. The two challenges lasted for 6 seconds each, and were separated by 15 seconds.

References:

Luo CH, Rudy Y, 1994, A dynamic model of the cardiac ventricular action potential. I. Simulations of ionic currents and concentration changes. Circ Res, 74:1071-1096.

Rodriguez B, Ferrero JM Jr, Trenor B, 2002, Mechanistic investigation of extracellular K+ accululation during acute myocardial ischemia: a simulation study. Am J Physiol, 283:H490-H500.

Shotwell MS, Drake KJ, Sidorov VY, Wikswo JP, 2013, Mechanistic analysis of challenge-response experiments. Biometrics, 69:741-474.