In silico Cardiomyocyte Action Potential Modeling Using GLP Manual Patch Clamp Inhibition Profiles from CiPA Ion Channels

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INTRODUCTION

The Comprehensive *in vitro* Proarrhythmia Assay (CiPA) requires the use of multi-ion channel inhibition profiling using high throughput screening (HTS) and *in silico* modeling of cardiomyocyte action potential. This study aimed to apply *in silico* modeling to ion channel inhibition generated with manual patch clamp under conditions associated with conduct of GLP studies.

METHODOLOGY

IC50 values for the standard CiPA related cardiac ion channels (i.e., Nav1.5, Kv4.3, Cav1.2, hERG, KvLQT1 and Kir2.1) were tested with cisapride (1 μM), terfenadine (1 μM), amiodarone (1 μM) and verapamil (10 μM). HEK 293 cells with stable ion channel expression were used in manual whole-cell patch clamp configuration. The O'Hara-Rudy and ten Tusscher models were applied to manual patch clamp inhibition profiles and the duration of the cardiac action potentials at 90% repolarization (APD90) were calculated during stable pacing of single cells at 60 bpm (Figs 2 to 5).

Figure 1. Scheme of *in silico* components

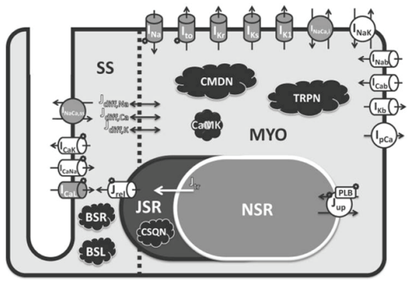


Figure 2. Drug effects using the O'Hara-Rudy model (IKr, INa, ICaL, Ito, IK1, IKs)

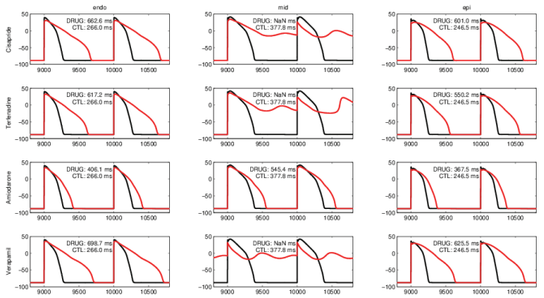


Figure 3. Drug effects using the ten Tusscher model (IKr, INa, ICaL, Ito, IK1, IKs)

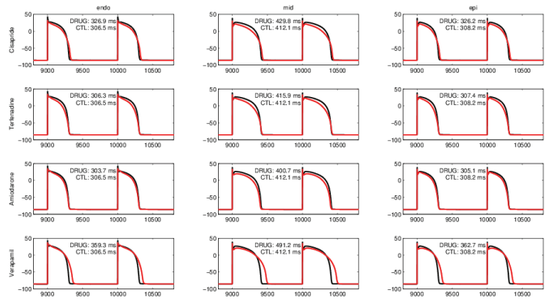


Figure 4. Drug effects using the ten Tusscher model (IKr only)

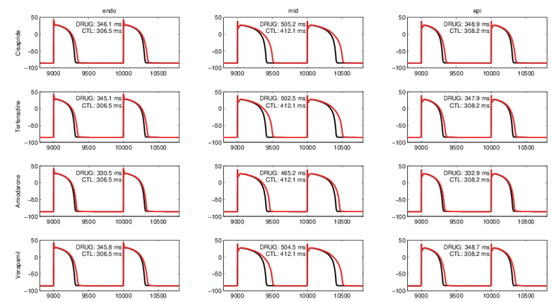


Figure 5. Drug effects using the ten Tusscher model (IKr , INa, ICaL only)

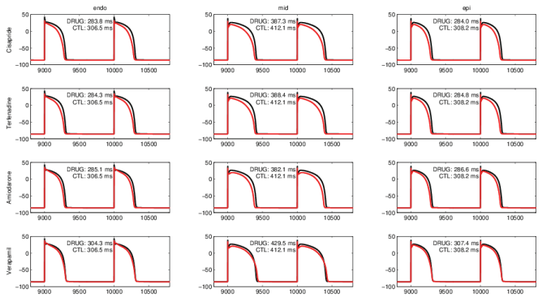


Figure 6. Drug effects using the O'Hara-Rudy model (IKr only)

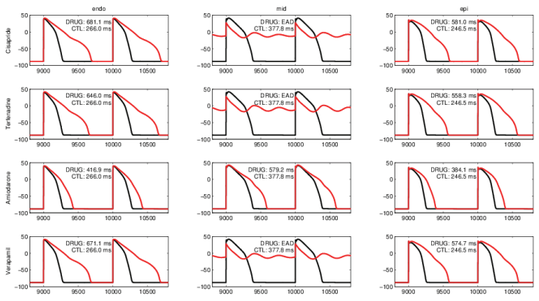
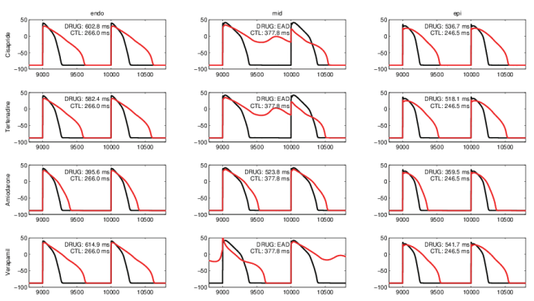


Figure 7. Drug effects using the O'Hara-Rudy model (IKr, INa, ICaL only)



DISCUSSION AND CONCLUSION

Discussion: A HTS method was used for CiPA related *in silico* modeling. Our results suggest that manual patch clamp inhibition profiles obtained using GLP study conditions can be applied to *in silico* modeling and quantitatively predicts cardiomyocyte APD changes and consequently QT prolongation. The O'Hara-Rudy model, using the 6 cardiac ion currents proposed for CiPA, predicted changes to the cardiac APD with the ultimate goal to estimate ECG effects. The use of a truncated panel (i.e., IKr only or IKr, INa, or ICaL only) illustrates the high contribution of IKr in APD estimation with this model. When using the ten Tusscher model, APD was predicted to decrease with a truncated panel using IKr, INa, or ICaL only illustrating the nuance of the ion channel balance in this model. Overall, the ten Tusscher model under-performed the O'Hara-Rudy model for pharmacological estimations of drug effects on APD with a truncated panel.

Conclusion: Manual patch clamp data obtained per GLP conditions can be used for *in silico* modeling. Application of the O'Hara-Rudy *in silico* model using the full panel of 6 cardiac ion currents (i.e. IKr, INa, ICaL, Ito, IK1, IKs) yielded the expected results relative to expected drug effects.