Relationship between the Potassium Currents Block and the Occurrence of Early after Depolarizations in the Setting of Sodium Current Blockade

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Abstract

HYPOTHESIS: We sought to model different degrees blockade of the IKr and IKs in the setting of mild to moderate INa blockade and to study its relationship to the induction of EADs METHODS: We used the cese 1.4.5 platform to run Luo-Rudy Model II of mammalian ventricular action potential. We applied a range of blockade levels to the INa (scaling factor of 50-100%). Then we paced the cell for 5 minutes at a cycle length of 2000 ms to reach steady state before each adjustment of the scaling factors for the IKr or IKs.We adjusted the blockade scale of each current by steps of 1-10% and looked for occurrence of EADs. RESULTS: At each level of blockade of IKs there was a "critical level" of blockade of IKr after which the EADs started occurring and vice versa. At mild to moderate levels of INa blockade there is a linear relationship between the minimum levels of IKs and IKr blockade at which EADs occur. When INa is blocked, EADs needed lesser degree of potassium currents blockade to occur.

1. Introduction

The blockade of the inward sodium current (INa), rapidly activating potassium current (IKr) and the slowly activating potassium current (IKs) is commonly seen in the clinical setting.

Many antiarrhythmic medications act by blocking one or more of those channels. However, numerous other medications affect those channels as well. This is typically considered as side effect if those medications were used for non-antiarrhythmic indication.

Early afterdepolarizations (EADs) are a type of triggered activity found in heart muscle.

The combined blockade may result in EADs and clinical ventricular arrhythmias [1-2].

We sought to model different degrees blockade of the IKr and IKs in the setting of mild to moderate INa blockade and to study its relationship to the induction of EADs

2. Methods

We used a Pentium core duo IBM-Lenovo Thinkpad X60 laptop and the cese 1.4.5 platform (from http://cese.sourceforge.net/ [3]) to run Luo-Rudy Model II of mammalian ventricular action potential.

We matched temperature, serum sodium, and serum potassium to those commonly seen in the clinical settings. We applied a range of blockade levels to the INa (scaling factor of 50-100%, corresponding to 50% blockade to no-blockade).

Then we paced the cell for 5 minutes at a cycle length of 2000 ms to reach steady state before each adjustment of the scaling factors for the IKr or IKs.

We adjusted the blockade scale of each current by steps of 1-10% and looked for occurrence of EADs.

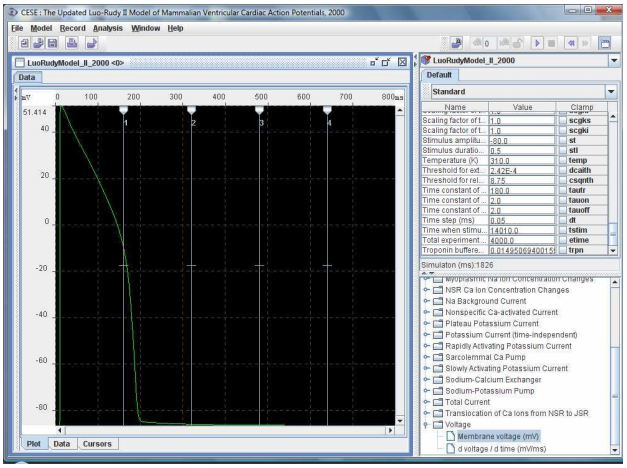

Figure 1: Screenshot of the cese platform running Luo-Rudy Model II to simulate a single heart beat under normal conditions.

3. Results

At each level of blockade of IKs there was a "critical level" of blockade of IKr after which the EADs started occurring and vice versa.

At a scaling factor of 50% for the INa and 7% for IKs, EADs occurred regardless of the IKr blockade.

However, with the same INa blockade and at a scaling factor of 55% for IKs, a complete blockade of IKr (i.e. scaling factor of 0%) was needed to induce EADs.

When there was no blockade to the INa, EADs occurred at IKs scale of 7.5% regardless of IKr and a complete IKr blockade was needed to induce EADs when IKs was 35%.

We noted that the INa blockade effect on facilitating EAD induction is more prominent at higher levels of block for IKr allowing for EADs to occur with less IKS blockade.

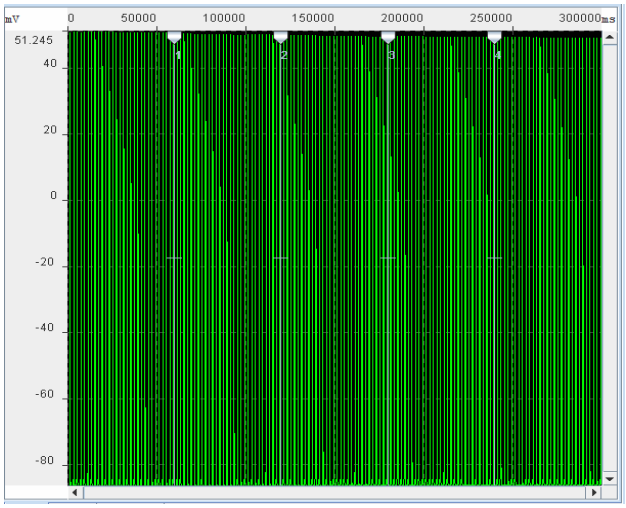

Figure 2: Ventricular action potentials acquired by pacing the model at a BCL of 2000 ms for 5 minutes to reach a steady state.

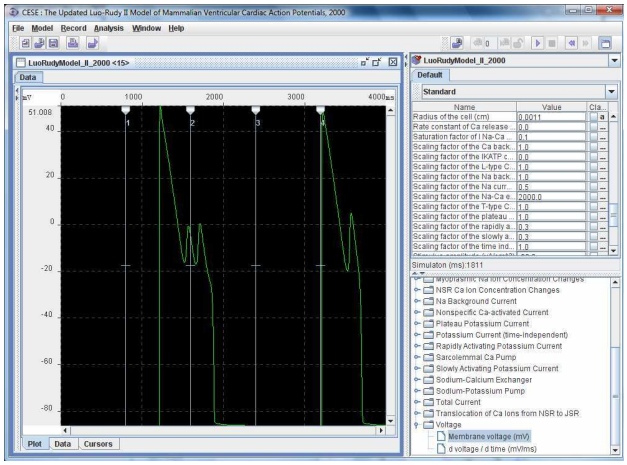

Figure 3: Examples of EADs that were induced with blockade of IKs, IKr and INa.

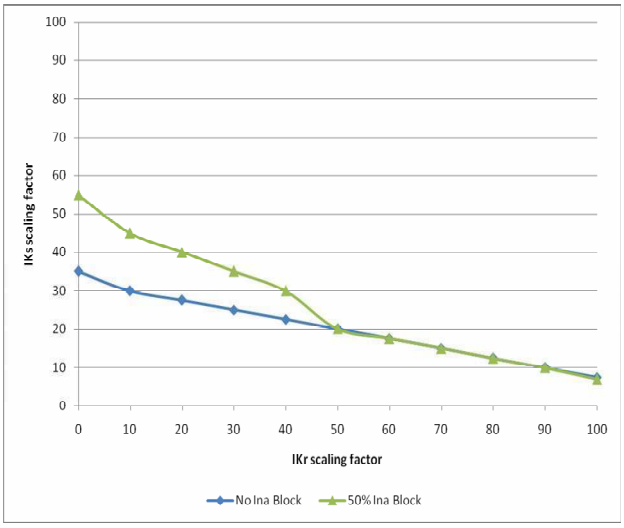

Figure 4: Relationship between the minimum IKr and IKs blocks required to induce EADs with and without INa block

4. Discussion and conclusions

At mild to moderate levels of INa blockade there is a linear relationship between the minimum levels of IKs and IKr blockade at which EADs occur.

When INa is blocked, EADs needed lesser degree of potassium currents blockade to occur.

Further investigation is warranted to see if these results are reproducible using different models or at different BCLs.

References

[1] CESE (Cell Electrophysiology Simulation Environment) website. [cited 2007 April 1]; Available from http://cese.sourceforge.net

[2] Studenik, CR, Zhou, Z, January, CT. Differences in action potentional and early and after depolarization properties in LQT2 and LQT3 models of long QT syndrome. Br J Pharmacol. 2001 Jan; 132(1):85-92.

[3] Viswanathan PC, Rudy Y. Cellular arrhythmogenic effects of congenital and acquired long-QT syndrome in the heterogeneous myocardium. Circulation. 2000 Mar 14; 101(10):1192-8.

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