

# Simulation of Acquired LQT Syndrome Using Human Virtual Ventricular Cardiomyocyte Model

Shumo Zhao<sup>1</sup>, Cunjin Luo<sup>1,2</sup>, Ying He<sup>3</sup>, Linghua Li<sup>4</sup>

<sup>1</sup>School of Computer Science and Electronic Engineering, University of Essex, Colchester, UK

<sup>2</sup>Key Laboratory of Medical Electrophysiology of Ministry of Education and Medical Electrophysiological Key Laboratory of Sichuan Province, Collaborative Innovation Center for Prevention and Treatment of Cardiovascular Disease, Institute of Cardiovascular Research, Southwest Medical University, Luzhou, China

<sup>3</sup>School of Computer Science, University of Nottingham, Nottingham, UK

<sup>4</sup>School of Integrative Medicine, Southwest Medical University, Luzhou, China

## Abstract

*Acquired long QT syndrome is a cardiac channelopathy, usually manifested by prolonged QT intervals in the electrocardiogram, which can lead to arrhythmias and an increased risk of sudden death. However, there is a diversity of drugs that target LQT syndrome. In this study, we simulated acquired LQT syndrome on a model of human ventricular cardiomyocytes and tested the therapeutic effects of potassium supplements and the L-type calcium blocker nifedipine on this basis. The results showed that the L-type calcium blocker and potassium ion supplementation could effectively shorten the action potential and QT interval of the ECG in cardiomyocytes and shorten the effective non-response period. Taken together, this study provides data to support the use of calcium channel blockers and potassium supplementation as a new treatment for LQTS.*

## 1. Introduction

Long QT syndrome is a common cardiac disorder caused by mutations or damage to ion channels in the ventricular myocardial cells [1]. Impairment of ion channels leads to delayed repolarization of the heart, which prolongs the QT interval and leads to arrhythmias. Long QT syndrome is associated with many complications such as polymorphic ventricular tachycardia, arrhythmias, and sudden cardiac death, so multiple paradigms need to be emphasized in drug selection to screen for appropriate drugs. Because LQT syndrome leads to a longer QT interval and because the longer the QTc, the greater the risk of Tdp generation, L-type calcium blockers, which are

effective in eliminating Tdp generation, were chosen for this study.

## 2. Method

In this article a computer model of the human ventricle was used, in the ten Tusscher et al [2]. cardiomyocyte model. In this study, a pacing cycle length of 1000 ms was chosen. one-dimensional cell membranes were modeled in the form of capacitors, which include various ion channels whose currents go to generate the action potential of the heart. In this study, E-4031 was chosen as a blocker of the IKr ion channel, which is blocked by modulating the conductance Gkr of IKr [3-7]. In order to simulate the calcium channel blocker, the L-type calcium current was macroscopically regulated using the proportionality factor (SgICaL) to achieve the effect of blocking this ion channel. And the potassium ion supplementation was simulated by adjusting the extracellular membrane potassium ion concentration (Ko=10) [8]. Stimulation was applied to 20 fixed PCLs using S1S2 protocol [9-12] based on TNNP model, and ERP was calculated at minimum time interval so as to obtain its dependence on APD, and the period of PCL=600,550ms was selected for recording.

Table 1. Effect of blocking this ion channel.

E-4031	Gkr	nifedipine	SgICaL
0.1µm	0.03366	1µm	0.2
1µm	0.004437		

## 2.1. Results and Data analyses

Figure 1 shows the comparison of epicardial cells in the LQT pathological state and the state after the administration of calcium blockers. I chose to administer 0.2 $\mu$ m [13] nifedipine to the two pathological states of acquired long QT syndrome separately, and it can be clearly observed that there is a significant trend of shortening of action potential of cardiac myocytes (from 390 $\pm$ 10ms to 296 $\pm$ 10ms) after the administration. Also, since the plateau phase is formed by calcium inward flow and potassium outward flow, the inactivation of calcium channels is accelerated after blockade, leading to an earlier potential difference formation thus reaching the end of rapid repolarization quickly.

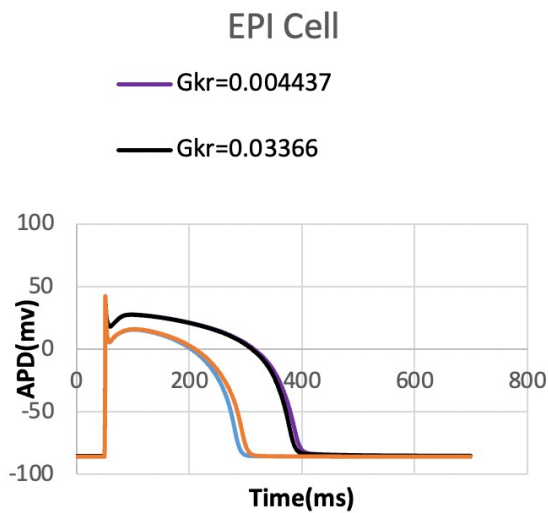
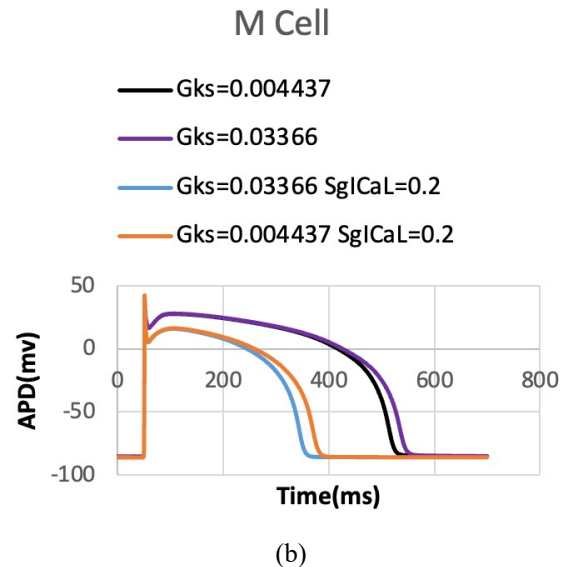
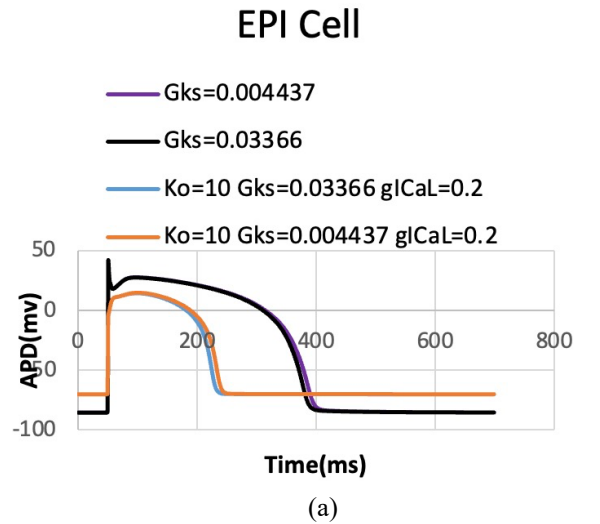


Figure 1. The epicardial cells in the LQT pathological state and after the concomitant use of calcium blockers and potassium supplements

It is evident that the action potential of cardiac myocytes is further shortened (from 390 $\pm$ 10 ms to 240 $\pm$ 10 ms) with potassium supplementation compared to calcium blocker only, and the resting potential of the cells is changed from -86.7 to -70.9 v due to the increase in the threshold potential caused by the increase in the extracellular potassium ion concentration and the blockage of ICaL. which is unable to counteract the outflow of potassium ions, making the plateau period shorter.



Figures 2(a) and 2(b) show the action potential images of M cells, where a more pronounced change in action potential can be observed (from 521 $\pm$ 10ms to 379 $\pm$ 10ms in Figure 2(a)) (from 521 $\pm$ 10ms to 282 $\pm$ 10ms in Figure 2(b)).

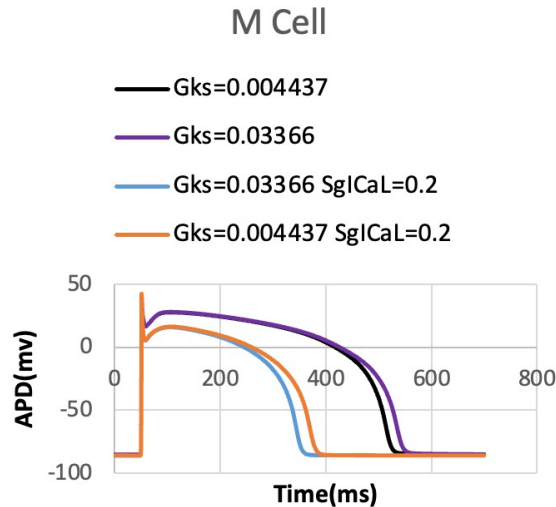


Figure 3 The action potential map of IKr current, and it can be observed that the blocking rate of IKr increases with the increase of E-4031 administration concentration.

Figure 4 shows the pseudo-ECG, this image can visually reflect the changes in the QT interval, which is also the most clinically relevant to visualize the therapeutic effect of the drug. It can be observed that in the pathological state the QT interval length is (516+10ms) and after the concomitant administration of calcium blockers and potassium supplements to the heart, a significant shortening of the QT interval length is produced (QTc=410+10ms) and there is a slight decrease in the peak of the T wave. This suggests that both drugs have a significant therapeutic effect on LQT and can reduce the risk of arrhythmia generation.

Figure 5 shows the length of the QT interval for different external potassium concentrations and the size of the ERP at PCL = 600 ms and PCL = 550 ms. It can be clearly found that ERP decreased significantly (from 463 to 400) after the administration of the drug (from 451 to 400), representing a decrease in the effective non-return period and proving that the arrhythmia can be effectively relieved after the administration of the drug.

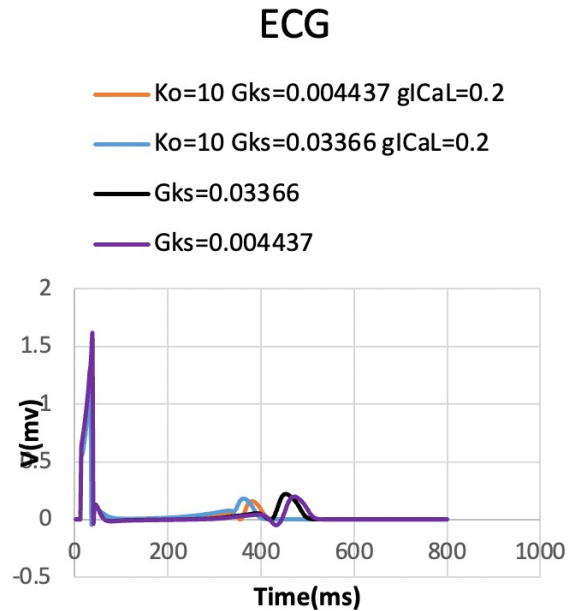


Figure 4 The pseudo-ECG

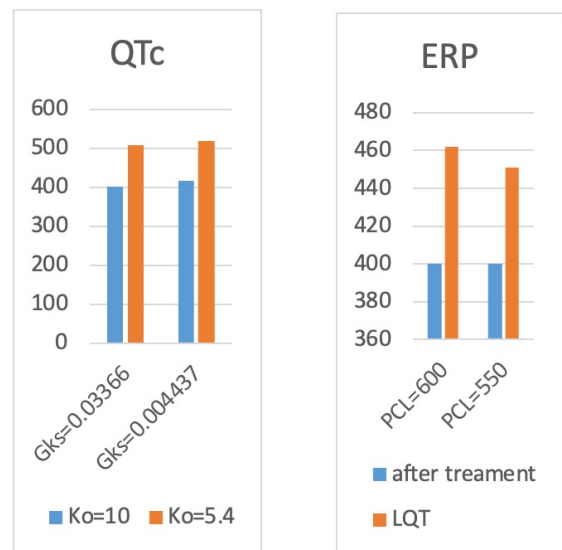


Figure 5 The length of the QT interval

#### 4. Conclusion

This study provides valid data to support the use of calcium blockers in the treatment of LQT syndrome. By analyzing one-dimensional data including pseudo-ECG, it was determined that this type of drug can be effective in shortening action potential and QT intervals, while the adjunctive therapeutic effect of potassium supplementation was investigated.

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Cunjin Luo, PhD  
School of Computer Science and Electronic Engineering  
University of Essex,  
Colchester, CO4 3SQ  
UK  
[cunjin.luo@essex.ac.uk](mailto:cunjin.luo@essex.ac.uk)