Computational Analysis of the Effects of KCNJ2-linked E299V Mutation Short QT Syndrome and Its Potential Therapeutic Targets

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Abstract

Short QT syndrome (SQTS) is a cardiac disorder characterized by arrhythmia and even sudden cardiac death (SCD). SQTS variant 3 (SQT3) has been linked to the KCNJ2 gene mutations, which directly increasing the inward rectifier K^+ current (I_{K1}). There have been many studies on the effects of the mutation KCNJ2 D172N that cause the SQT3, but the potential effect of the mutation KCNJ2 E299V is little known. Therefore, we aim to predict and compare the potential effects of ion channels blocking under the E299V mutation. In this study, a biophysically detailed computer model of the heart which was developed by was coupled with the KCNJ2 E299V mutant I_{K1} patch clamp data. Effects of a combined action of blocking of I_{K1} and I_{CaL} was also simulated under the E299V mutant condition. Our simulation data showed that a combined action of blocking of I_{K1} and I_{CaL} prolonged the cardiac cell action potential duration (APD) and QT interval under SQT3 E299V condition, and demonstrated that blocking of I_{K1} and I_{CaL} produced a therapeutic effect under SQT3 E299V. This study provides new evidence that blocking of I_{K1} and I_{CaL} may be a potential treatment for SQTS patients.

1. Introduction

The inward rectifier potassium current (I_{K1}) plays an important role in the cardiac functions. If I_{K1} is abnormal, it can cause serious heart diseases such as short QT syndrome (SQTS) [1-3]. SQTS was first found and describe in 2000 [4]. SQTS is a disorder that the QT interval in the QRS complex of the ECG is reduced. The short QT interval on the ECG is due to an accelerated cardiac repolarization serving as substrate for atrial and ventricular arrhythmias leading to syncope and even sudden cardiac death (SCD) [5]. Until now, 8 subtypes of SQTS have been described. Increased I_{K1} induces rapid repolarization of the action potential (AP), causing SQTS variant 3 (SQT3) [5]. SQT3 is a cardiac disorder caused by KCNJ2 gene mutations (such as D172N and E299V) that cause functional changes in the heart, leading to arrhythmia and SCD [6-8].

There have been many studies on the understanding of the mechanism and genetic bases of SQTS in the heart. Dominic et al. identified the mechanism of atrial arrhythmia caused by KCNJ2 D172N and E299V mutations in SQT3 using virtual computational atrial models [9]. Jeong et al. investigated the electrophysiological changes and concomitant mechanical responses according to the expression levels of the KCNJ2 E299V mutation during cardiac arrhythmia [10]. In spite of rapid development in understanding the mechanisms of SQTS, mush less is known about the treatment for SQTS patients. There has been very limited research to test drug effects in SQTS patients. A few anti-arrhythmic drugs such as disopyramide, quinidine, sotalol, ibutilide have been tested in SQT1 patients [11-13], but little known about the treatment for SQT3 patients. Accordingly, in this study, we aim to use computational modelling method to predict the potential effects of a combined action of blocking of I_{K1} and I_{CaL} was SQT3 associated with the E299V mutation.

2. Methods

To study the potential effects of a combined action of blocking of I_{K1} and I_{CaL} on SQT3, we modified and used the mathematical model of the human ventricular cell by ten Tusscher et al. to simulate the cardiac AP (see the following equation) [14].

$$\frac{dV}{dt} = \frac{I_{ion} + I_{stim}}{C_m}$$

Here, V is the membrane potential of myocardial cells and t represents time. I_{ion} is the sum of all ion currents, I_{stim} is the current produced by an external stimulus, and C_m is the capacitance of the cell membrane.

To simulate the change in I_{K1} currents in the wild-tyoe condition (WT), the heterogeneously expressed E299V mutation condition (WT-E299V), and the homogeneously expressed E299V mutation condition (E299V), respectively, [10]

WT:

$$I_{K1} = \frac{0.24731(V - E_k)}{0.86426+e^{0.0904(V-E_k)}} - 0.06519$$

WT-E299V:

$$I_{K1} = \frac{0.11905(V - Ek + 2.4)}{0.04092+e^{0.01732(V-E_k)}} - 0.36212$$

E299V:

$$I_{K1} = 0.06634(V - E_k + 6.5) - 2.44009$$
$$*10^{-4}(V - E_k)2 - 0.5183$$

Initiation and conduction of action potentials in tissue models was modelled with the mono-domain equation,

$$C_m \frac{\partial V}{\partial t} = -(I_{ion} + I_{stim}) + \nabla \cdot (D\nabla V)$$

Where D is the conductivity tensor (diffusion coefficient) describing the tissue conductivity.

For 1D tissue computations, the stand used was a single fibre, 15 mm long with 100 nodes that were spaced 0.15 mm apart. The pseudo-ECG was computed by the method proposed by Gima and Rudy [15].

We analyzed the effects of a combined action of blocking of I_{K1} and I_{CaL} by using a simple pore block theory [16-18].

3. Results

3.1 Single cell simulations

Figure 1-3 show the action potentials under the WT, WT-E299V, and E299V condition with the combined action of blocking of I_{K1} and I_{CaL}, respectively. The cell was stimulated at a pacing rate of 1.25 Hz frequency. The simulation results indicated that blocking of I_{K1} and I_{CaL} prolonged action potential both under SQT3 WT-E299V and E299V mutant conditions. The resting potential values were not markedly changed under the E299V mutant conditions.

3.2. Tissue simulations

Using a strand model of ventricular tissue, we computed a pseudo-ECG (Figure 4-6). Consistently with action potential simulations, a prolongation of QT interval on the ECG by blocking I_{K1} and I_{CaL} can be observed both under SQT3 E299V mutation conditions.

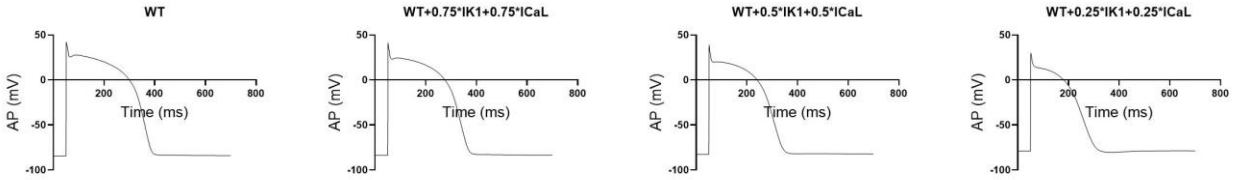

Figure 1. Action potentials under the WT condition with the combined action of blocking of I_{K1} and I_{CaL}.

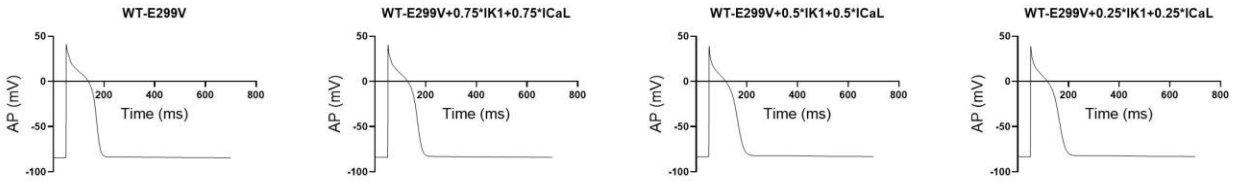

Figure 2. Action potentials under the WT-E299V condition with the combined action of blocking of I_{K1} and I_{CaL}.

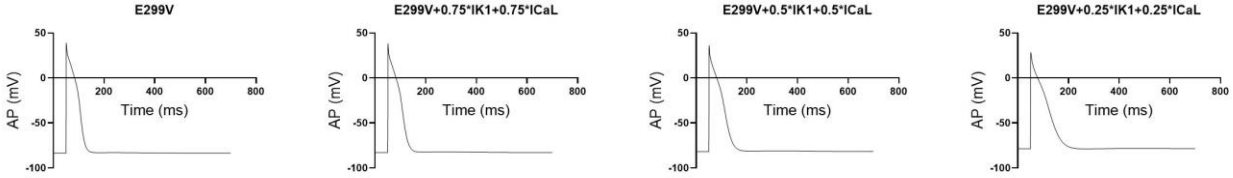

Figure 3. Action potentials under the E299V condition with the combined action of blocking of I_{K1} and I_{CaL}.

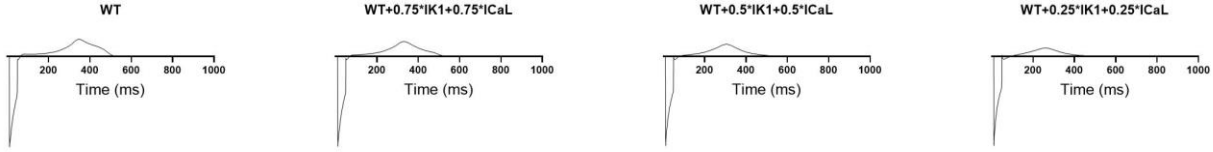

Figure 4. ECGs under the WT condition with the combined action of blocking of I_{K1} and I_{CaL}.

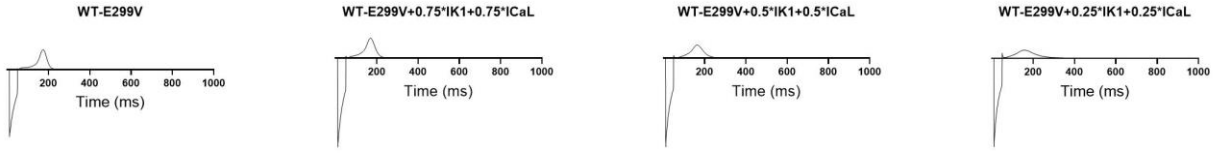

Figure 5. ECGs under the WT-E299V condition with the combined action of blocking of I_{K1} and I_{CaL}.

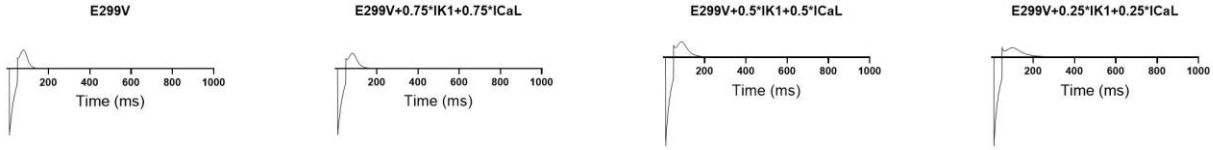

Figure 6. ECGs under the E299V condition with the combined action of blocking of I_{K1} and I_{CaL}.

4. Conclusion

In this study, we used a computer modelling and simulation approach to gain potential effects of blocking I_{K1} and I_{CaL} on SQT3 E299V mutation. Our findings are summarized as follows: (1) the modified I_{K1} formulations reproduce the dynamic properties of I_{K1} under SQT3 E299V condition; (2) blocking I_{K1} and I_{CaL} prolongs the action potentials; (3) blocking I_{K1} and I_{CaL} prolongs the QT intervals. Collectively, these findings showed that the anti-arrhythmic effects of blocking I_{K1} and I_{CaL} on SQT3 E299V mutation.

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