Simulation of KCNJ2-linked Short QT Syndrome in Human Ventricular Tissue

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Abstract

In the present study we developed a computer models of human ventricular cell and tissue to simulate SQT3 syndrome that is associated with gain-in-function of I_{K1} channel arising from KCNJ2 gene mutation. We explored the functional effects of Kir2.1 D172N mutation-induced changes in I_{K1} on the electrical action potentials (APs) of cardiac cells and electrical wave conduction in ventricular tissues. Two scenarios were considered: one considered wild type (WT), heterozygous (WT-D172N) and homozygous (D172N), the other considered EPI, MIDDLE, ENDO cell types in heterogeneous ventricular wall. In cellular simulations, we computed action potential duration (APD), current traces of I_{k1} during APs. In 2D tissue simulations, the functional effects of the SQT3 on the characteristics of ECG were computed. It was shown that under the SQT3 condition, the action potential duration was abbreviated, magnitude of I_{k1} current during APs was increased and QT interval in pseudo- ECG was abbreviated dramatically. Such changes under the D172N condition were more remarkable than those under the WT-D172N condition. In conclusion, increased I_{k1} associated with SQT3 condition accelerates ventricular repolarization, which may increase arrhythmogeneity of ventricular fibrillation leading to sudden cardiac death.

1. Introduction

The Kir2.1 D172N is a gene mutation in KCNJ2 that is responsible for the I_{k1} ionic channel. A previous study [1] has demonstrated that the type-3 Short QT Syndrome (SQT3) is related to the Kir2.1 D172N mutation, which resulted in an amino acid change from aspartic acid to asparagine at position 172 in the Kir2.1 potassium channel. SQT is associated with increased risks of cardiac arrhythmias, such as ventricular fibrillation, that lead to sudden cardiac death. However, the functional effects of the Kir2.1 D172N mutation on ventricular electrical activities at cellular and tissue levels have not been fully understood yet.

Clinical data have shown that ECGs of patients with the Kir2.1 D172N mutation exhibit the characteristics of abnormal abbreviation of QT interval, manifesting the major characteristics of SQT. Further study by El Harchi et al. [2] have shown that the Kir2.1 D172N mutation resulted in preferential augmentation of the outward component current based on data from whole-cell patch-clamp recordings of Kir2.1 current at ambient and physiological temperatures. In theory, with the increasing I_{k1} through mutant Kir.2.1 channels, the QT interval of ECG is expected to abbreviate, but the casual link between the two has not been fully established. Therefore, the aim of this study was to investigate possible actions of the Kir2.1 D172N mutation on electrophysiological activities of cardiac cells and ECG waveform.

At present, there is no accurate experimental model of SQT3. Therefore, based on the work of Adeniran et al. [3], we further investigated the mechanisms by which the Kir2.1 D172N mutation induces SQT by using cellular models of ventricular cells and 2D idealised computer model of ventricular tissue that took into account of the electrical heterogeneity of transmural ventricle wall. Using these cell and tissue models, we simulated the effects of the Kir2.1 D172N mutation on the waveform of ECG, and cellular depolarization and repolarization processes in WT, WT-D172N, D172N conditions. The obtained results provided insights towards understanding the mechanisms by which the Kir2.1 D172N mutation abbreviated ventricular action potential duration leading to short QT intervals.

2. Methods

In the single cell model and 2D idealised model of human ventricular tissue, to represent the ventricular electrophysiological properties, we used the Tusscher et al. model [4], which is described as follows:

$$\frac{dV}{dt} = -\frac{I_{ion} + I_{stim}}{C_m} \quad (1)$$

$$\frac{\partial V}{\partial t} = -\frac{I_{ion} + I_{stim}}{C_m} + \nabla \cdot (D \nabla V) \quad (2)$$

$$I_{ion} = I_{Ks} + I_{Kr} + I_{Na} + I_{K1} + I_{to} + I_{bNa} + I_{CaL} + I_{bCa} + I_{NaK} + I_{NaCa} + I_{pK} + I_{pCa} + I_{NaL} \quad (3)$$

where V (mV) is the transmembrane potential, C_m (pF) is the membrane capacitance, I_{ion} (pA) is the sum of ionic currents, I_{stim} (pA) is the externally applied stimulus current, and t (ms) is time, D (mm^2ms^{-1}) is the diffusion tensor, ∇ is the gradient operator. For definitions of each components of I_{ion}, please see ten Tusscher et al. [4].

In order to simulate the functional effects of SQT3, we took into account of three main situations: wild type (WT), heterozygous (WT-D172N) and homozygous (D172N) [2]. According to Ref. [3], I_{k1} formulations were modified based on the experimentally determined properties of Kir2.1 D172N channels, which are described as follows:

$$I_{k1} = G_{k1}\sqrt{\frac{K_0}{5.4}}x_{k1\infty}(V - E_k) \quad (4)$$

$$x_{k1\infty} = \frac{\alpha_{k1}}{\beta_{k1} + \alpha_{k1}} \quad (5)$$

WT:

$$\alpha_{k1} = \frac{0.07}{1 + e^{0.017(V - E_k - 200.2)}} \quad (6)$$

$$\beta_{k1} = \frac{3e^{0.0003(V - E_k + 100.2)} + e^{0.08(V - E_k - 8.7)}}{1 + e^{-0.024(V - E_k)}} \quad (7)$$

$$G_{k1} = 4.8 ns/pF \quad (8)$$

WT-D172N:

$$\alpha_{k1} = \frac{0.1}{1 + e^{0.023(V - E_k - 199.9)}} \quad (9)$$

$$\beta_{k1} = \frac{3e^{0.0002(V - E_k + 100.4)} + e^{0.07(V - E_k - 9.8)}}{1 + e^{-0.02(V - E_k)}} \quad (10)$$

$$G_{k1} = 6.27 ns/pF \quad (11)$$

D172N:

$$\alpha_{k1} = \frac{0.1}{1 + e^{0.05(V - E_k - 199.9)}} \quad (12)$$

$$\beta_{k1} = \frac{3e^{0.0002(V - E_k + 100.1)} + e^{0.08(V - E_k - 10.3)}}{1 + e^{-0.06(V - E_k)}} \quad (13)$$

$$G_{k1} = 11.32 ns/pF \quad (14)$$

G_{K1} is the maximal channel conductance of I_{k1}, $x_{k1\infty}$ is the time-independent inward rectification factor, K_o is the extracellular potassium concentration.

The ECG (pseudo-ECG) formulation was computed as the followings [5]:

$$ECG = \int \frac{D\nabla V_m \cdot \vec{r}}{r^3} dV = -D\iint \frac{1}{r^3}\left((x - x_0)\frac{dV_m}{dx} + (y - y_0)\frac{dV_m}{dy}\right)dxdy$$
$$= -D \cdot \frac{1}{((x - x_0)^2 + (y - y_0)^2)^{3/2}} \cdot ((x - x_0) \cdot \frac{V_m(x+1,y) - V_m(x-1,y)}{2\Delta x}$$
$$+ (y - y_0) \cdot \frac{V_m(x,y+1) - V_m(x,y-1)}{2\Delta y}) \cdot \Delta x \Delta y \quad (15)$$

where V is the area of 2D ideal tissue, $\vec{r}$ is the vector from the recording electrode to a point in the tissue, and is $r=((x-x0)^2+(y-y0)^2)^{3/2}$ the distance from the recording electrode to the point, (x_0,y_0) is the coordinates of the electrode. In this paper, we placed the virtual electrode in the middle of the model at the left side, 2 cm distance off the endocardial layer cells.

We set the basic cycle length (BCL) of 800 ms, and dt is set to 0.02 ms. In order to make stable experimental results, we calculated the 20 basic cycles, that is to say, at the beginning of each cycle, we applied one S1 stimulation, finally, the 20th cycle of action potential is as our experimental result.

3. Result

3.1. Cellular simulation

Under the Kir2.1 D172N mutation and WT-D172N conditions, the action potential duration (APD) are shortened as compared to the WT condition. The APD shortening in the D172N condition is more remarkable than in that in the WT-D172N condition, but the resting membrane potential remains unchanged. Figure 1 shows the action potentials of endocardial cell, mid-myocardial cell, epicardial cell under WT, WT-D172N, D172N conditions, respectively.

In simulations, in the middle cell, WT-D172N's APD and D172N's APD are abbreviated by about 12.3%, 16.6%, respectively; in the endocardial cell and epicardial cell, WT-D172N's APD and D172N's APD are abbreviated by about 12.2%, 16.2%, respectively.

Current intensity of I_{K1} during the time course of action potentials is shown in Figure 2. D172N mutation and WT-D172N mutation lead to increased current intensity of I_{K1}, and D172N mutation current is much greater than WT-D172N mutation current. Besides, the activation time (i.e., the time for the current to reach its peak value) in D172N and WT-D172N conditions is advanced .

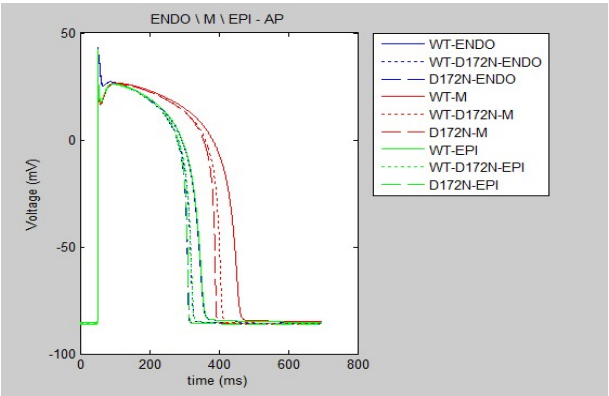


Figure 1. Cellular simulation of APs under WT, WT-D172N, and D172N conditions. ENDO: the endocardial APs; M: mid-myocardial APs; EPI: epicardial APs.

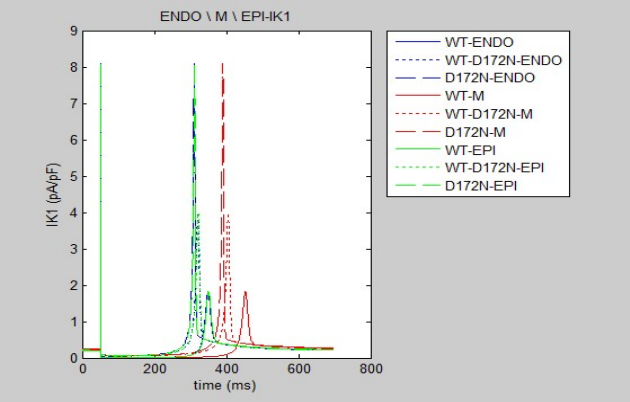


Figure 2. Current intensity of I_{k1} under WT, WT-D172N, and D172N conditions. ENDO: the endocardial I_{K1}; M: the mid-myocardial I_{K1}; EPI: the epicardial I_{K1}.

3.2. Changes induced by KCNJ2-linked short QT syndrome in the cellular depolarization and repolarization process

We designed a 2D idealized model of human ventricular tissue across the transmural ventricular wall. The model consisted of 100 cells in length and 40 cells in width. The 2D sheet model was further divided it into an endocardial region, mid-myocardial layer and an epicardial region with a proportion of cells of 25%, 35% and 40%, respectively. These proportions are the same as used in previous studies [3,6]. In order to simulate the functional impacts of the Kir2.1 D172N mutation on the depolarization and repolarization processes of the tissue, the model was stimulated by a sequence of external stimuli applied at the endocardial edge with a basic cycle length (BCL) of 800 ms. In the model, membrane potential is color represented with blue denoting -90 mV and red denoting +30 mV.

The 2D ideal human ventricular tissue model simulated electrical wave conduction under WT, WT-D172N and D172N conditions. From the perspective of our simulation results, D172N mutation and WT-D172N mutation can reduce the speed of depolarization, which are shown at 30ms clearly in Figure 3.

The mutation has great influence on ventricular repolarization process. It leads to earlier onset of repolarization at 300ms. The repolarization end up at 340 ms and 360 ms under D172N and WT-D172N conditions, as compared to 410 ms under WT condition.

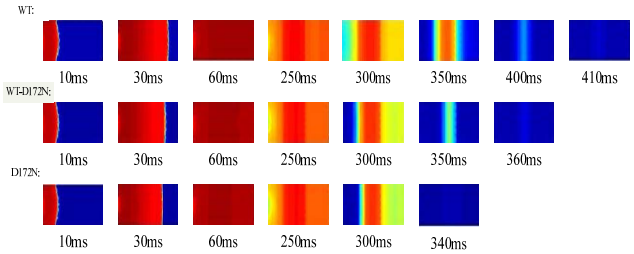
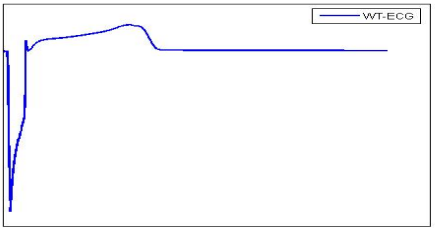


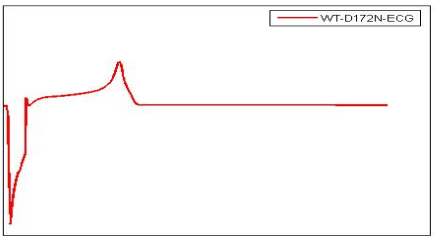
Figure 3. Depolarization and repolarization processes under WT, WT-D172N and D172N conditions.

3.3. Changes in the ECG induced by KCNJ2-linked short QT syndrome

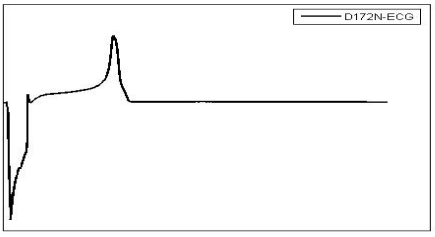
By using the integrated 2D idealised model under the WT, WT-D172N, D172N conditions, we simulated the effects of Kir2.1 D172N mutation on pseudo-ECG waveform. Figure 4 shows the pseudo-ECG computed from the 2D model. As compared to the WT condition, the pseudo-QT interval is shortened under the WT-D172N. In addition, the mutation produces an increased gradient of membrane potential across the ventricle tissue, leading to a taller T-wave with a sharper peak and steeper falling phase.



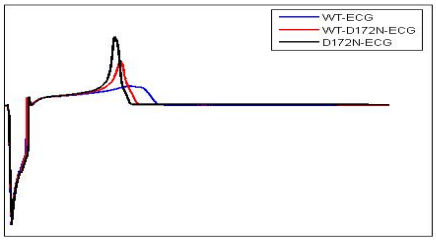
a) WT condition



b) WT-D172N condition



c) D172N condition



d) The whole 3 conditions

Figure 4. Pseudo-ECG under WT, WT-D172N and D172N conditions.

4. Conclusions

In conclusion, we have developed an integrated model for human ventricule in SQT3 condition. Using the model, we simulated the action potential, current intensity of I_{K1}, tissue's depolarization and repolarization processes, and the waveform of ECG under the WT, WT-D172N, D172N conditions. Our simulation results indicate that under Kir2.1 D172N mutation condition, action potential durations are reduced, current intensity of I_{K1} are increased, QT interval is shorter than in the WT condition. In particular, D172N mutation makes T-wave a higher amplitude, sharper and symmetrical. Further more, the mutation induced changes on cellular action potentials and ventricular wave excitation under the D172N condition are more remarkable than under the WT-D172N condition. In conclusion, our results demonstrated that the Kir2.1 D172N mutation affects ventricular tissue's excitability, which may be pro-arrhythmic.

Acknowledgements

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