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To cite this article: Cunjin Luo et al 2017 Physiol. Meas. 38 1859

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Modelling the effects of quinidine, disopyramide, and E-4031 on short QT syndrome variant 3 in the human ventricles

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Received 22 April 2017, revised 13 August 2017
Accepted for publication 16 August 2017
Published 21 September 2017

Abstract
Objective: Short QT syndrome (SQTS) is an inherited cardiac channelopathy, but at present little information is available on its pharmacological treatment. SQT3 variant (linked to the inward rectifier potassium current \(I_{K1}\)) of SQTS, results from a gain-of-function mutation (Kir2.1 D172N) in the \(KCNJ2\)-encoded channels, which is associated with ventricular fibrillation (VF). Using biophysically-detailed human ventricular computer models, this study investigated the potential effects of quinidine, disopyramide, and E-4031 on SQT3. Approach: The ten Tusscher et al model of human ventricular myocyte action potential (AP) was modified to recapitulate the changes in \(I_{K1}\) due to heterozygous and homozygous forms of the D172N mutation. Wild-type (WT) and mutant WT-D172N and D172N formulations were incorporated into one-dimensional (1D) and 2D tissue models with transmural heterogeneities. Effects of drugs on channel-blocking activity were modelled using half-maximal inhibitory concentration (IC50) and Hill coefficient (nH) values. Effects of drugs on AP duration (APD), effective refractory period (ERP) and QT interval of pseudo-ECGs were quantified, and both temporal and spatial vulnerability to re-entry was measured. Re-entry was simulated in the 2D ventricular tissue. Main results: At the single cell level, the drugs quinidine, disopyramide, and E-4031 prolonged APD at 90% repolarization (APD90), and decreased maximal transmural voltage heterogeneity (\(\delta V\)); this
caused the decreased transmural dispersion of APD90. Quinidine prolonged the QT interval and decreased the T-wave amplitude. Furthermore, quinidine increased ERP and reduced temporal vulnerability and increased spatial vulnerability, resulting in a reduced susceptibility to arrhythmogenesis in SQT3. In the 2D tissue, quinidine was effective in terminating and preventing re-entry associated with the heterozygous D172N condition. Quinidine exhibited significantly better therapeutic effects on SQT3 than disopyramide and E-4031. 

**Significance:** This study substantiates a causal link between quinidine and QT interval prolongation in SQT3 Kir2.1 mutations and highlights possible pharmacological agent quinidine for treating SQT3 patients.

**Keywords:** short QT syndrome, computational modelling, arrhythmia, quinidine, disopyramide, E-4031

Supplementary material for this article is available online (Some figures may appear in colour only in the online journal)

**Introduction**

Short QT syndrome (SQTS) is a disorder in the electrical function of the heart, and it is associated with high risk of arrhythmias and sudden cardiac death (SCD) (Gussak et al 2000, Gaita et al 2003, Schimpf et al 2005). The SQTS phenotype is characterized by less than 360 ms with a range of 220–360 ms and a higher, symmetrical T-wave amplitude on the electrocardiogram (ECG). The ‘short QT interval’ was first discovered as a new clinical entity by Gusssk et al (2000) in 2000 and first described with arrhythmias and a high incidence of SCD in families with SQTS by Gaita et al (2003) in 2003. The basis for SQTS associated with various mutations in 6 different genes have been found: KCNQ2 (Brugada et al 2004), KCNQ1 (Bellocq et al 2004), KCNJ2 (Priori et al 2005), CACNA1C (Antzelevitch et al 2007), CACNB2b (Antzelevitch et al 2007), and CACNA2D1 (Templin et al 2011). Among these mutations, either a gain-in-function of the potassium channel (linked to KCNQ2, KCNQ1, and KCNJ2 gene) or a loss-in-function of the calcium channel (linked to CACNA1C, CACNB2b, and CACNA2D1 gene) has been observed.

Among the mutations is a pair of complementary nucleotide bases substitute from aspartic acid (also known as aspartate) to sparonate at position 172 in KCNJ2 (which encodes the Kir2.1 channel protein) in patients exhibiting a history of palpitations, presyncope, and syncope symptoms (Priori et al 2005). Analysis of wild-type (WT) Kir2.1, of Kir2.1 D172N mutation under heterozygous (WT-D172N) homozygous (D172N) conditions, revealed the mutation led to changes in the inward rectifier potassium current (IK1) channels, which results in a gain-in-function, producing an increase of IK1 (Priori et al 2005). Previous studies have been shown that increased IK1 in SQT3 shortened the action potential duration (APD) and the effective refractory period (ERP), and stabilized rotors in computational models of human ventricular electrophysiology (Adeniran et al 2012).

The current first-line treatment for SQTS patients is an implantable cardioverter-defibrillator (ICD) device, but there is an increased risk of inappropriate treatment due to tachycardia, atrial fibrillation and, above all, of T-wave oversensing (Schimpf et al 2003). Moreover, the QT interval does not fall within the normal range over time by using the ICD. Clinical trials from Gaita et al (2004) concurrent with the in vitro findings demonstrated the antiarrhythmic
effectiveness of quinidine in patients with SQTS. They reported hydroquinidine administration prolonged the QT interval to the normal range. Moreover, quinidine also restored the QT interval/heart rate (QT-RR) relationship towards the normal range (Wolpert et al. 2005). In a one-year follow-up, the SQT1 patients who treat hydroquinidine remained asymptomatic, and no further episode of arrhythmias was detected. However, the mechanisms by which quinidine prolongs QT interval and terminates and prevents arrhythmias in SQTS have still not yet been fully elucidated. However, possibly due to a lack of phenotypically accurate experimental models, there has hitherto not been any detailed investigation of how the quinidine prolongs QT interval and terminates and prevents ventricular arrhythmias in SQTS. Therefore, this study aimed to evaluate and compare the potential effects of quinidine in comparison to disopyramide and E-4031 on ventricular depolarization and repolarization and susceptibility to re-entrant excitation waves in SQT3, by using multi-scale models of human ventricular electrophysiology. These results may provide theoretical insights into the possible pharmacological agent for treating SQT3 patients.

Methods

$I_{K1}$ and human ventricular cell models

A contemporary human ventricular cell action potential (AP) model developed by ten Tusscher and Panfilov (2006) was used for the simulations in this study. The original equations for $I_{K1}$ in the ten Tusscher et al model was modified to incorporate the previously reported changes in $I_{K1}$ for WT, mutant D172N and WT-D172N conditions (Priori et al. 2005). The derived equation of $I_{K1}$ for WT, WT-D172N and D172N conditions (McPate et al. 2008) is available in the supplementary materials (stacks.iop.org/PM/38/1859/mmedia).

In a single myocyte, the electrophysiological behavior can be described using the following ordinary differential equation (ODE):

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

where $V$ is the cell membrane potential; $t$ is time; $C_m$ is the membrane capacitance per unit area; $I_{stim}$ is the external stimulus current; $I_{ion}$ is the sum of membrane currents. Particularly, the component of the late sodium current ($I_{NaL}$) from the ORd model (O’Hara et al. 2011) was incorporated. Equation (1) was numerically integrated using the forward Euler method with a time step of 0.02 ms. APs were elicited with an S1-S2 protocol consisting of 20 S1 stimuli and an S2 stimulus. The S1 was applied at a basic cycle length (BCL) of 800 ms and -52 pA/pF strength for 1 ms. The S2 was applied at varying diastolic intervals (DI) after the AP evoked by the last S1. The ERP was measured as the smallest DI for which the overshoot of the AP evoked by the S2 reached 80% of the AP evoked by the 20th S1.

Modelling the interactions between drugs and ion channels

A ‘simple pore block’ theory (Brennan et al. 2009) was implemented to model drug-ion channel binding interactions. The reduced maximum conductances of the targeted channels in the presence of quinidine, disopyramide, and E-4031 were shown in tables 1–3, respectively. E-4031 is a specific blocker of delayed rectifier current ($I_{Kr}$) (Izumi et al. 2010), and it does not affect sodium and calcium inward currents (Wettwer et al. 1991). However, quinidine and disopyramide are multi-channel blockers (Sanchez-Chapula 1999, Gaita et al. 2004). In this
study, several doses (4, 7, and 10 µM for quinidine; 13 and 100 µM for disopyramide; 4, 100, and 1000 nM for E-4031) were selected to assess the pharmacological effects on SQT3.

Effects of a combined action of blocking of multiple currents in the presence of quinidine at 4, 7, and 10 µM doses together with different theoretical (5% and 10%) and experimental (13.5%) blocking of \( I_{NaCa} \).

Multicellular tissue simulations

Propagation of APs in multicellular tissue was described by using the monodomain equation:

\[
\frac{\partial V}{\partial t} = \frac{I_{\text{ion}} + I_{\text{stim}}}{C_m} + \nabla \cdot (D \nabla V) \tag{2}
\]

where \( \nabla \) is the gradient operator; \( D \) is the diffusion parameter modelling the intercellular electrical coupling via gap junctions. \( D \) was set to a value of 0.0008 cm\(^2\) ms\(^{-1}\) that gave a conduction velocity (CV) of a planar wave at 52 cm/s, close to the experimental CV of ~50 cm s\(^{-1}\) through one-dimensional (1D) strand (Weingart 1977, Taggart et al 2000), except for a 5-fold decrease at the MIDDLE-EPI junction (Gima and Rudy 2002). The strand had a total length of 15 mm, with space step 0.15 mm, which is close to the cell length of a human ventricular myocyte (80–150 µm). The corresponding length of each subregion was 3.75 mm for 25 ENDO cells, 5.25 mm for 35 MIDDLE cells, and 6 mm for 40 EPI cells of the strand. The total length and proportion of each sub-region reliably reproduced a positive T wave (Zhang

### Table 1. Conductivities (% of the original value) in the presence of 4100, and 1000 nM E-4031.

| Current | IC\(_50\) nM | nH | Conductivity | Source |
|---------|---------------|----|--------------|--------|
| \( I_{Kr} \) | 15.96 ± 0.04 nM | 0.74 ± 0.05 | 80.0/22.1/2.9% | McPate et al (2006, 2008) |

### Table 2. Conductivities (% of the original value) in the presence of 13 and 100 µM disopyramide.

| Current | IC\(_50\) µM | nH | Conductivity | Source |
|---------|---------------|----|--------------|--------|
| \( I_{Kr} \) | 10.66 ± 0.04 µM | 1.07 ± 0.05 | 39.1/5.4% | McPate et al (2006, 2008) |
| \( \text{Na} \) | 168.4 µM | 1.09 | 95/63.6% | Yasuda et al (2015) |
| \( \text{h} \) | 259 µM | 1.07 | 94.3/75.5% | Sanchez-Chapula (1999) |
| \( I_{CaL} \) | 1036.7 µM | 1.0 | 98.7/90.9% | Yasuda et al (2015) |

### Table 3. Conductivities (% of the original value) in the presence of 4, 7, and 10 µM quinidine.

| Current | IC\(_50\) µM | nH | Conductivity | Source |
|---------|---------------|----|--------------|--------|
| \( I_{Kr} \) | 0.62 ± 0.03 µM | 0.93 ± 0.06 | 17.0/10.0/7.0% | McPate et al (2006, 2008) |
| \( \text{Na} \) | 4.899 µM | 1.4 | 56.9/37.5/27.0% | Crumb et al (2016) |
| \( \text{h} \) | 3.487 µM | 1.3 | 45.6/28.8/20.3% | Crumb et al (2016) |
| \( \text{Na} \) | 14.6 µM | 1.22 | 83.0/71.1/61.4% | Kramer et al (2013) |
| \( I_{CaL} \) | 14.9 ± 1.5 µM | 1.1 ± 0.1 | 83.2/72.9/61.29% | Zhang and Hancox (2002) |
| \( \text{NaCa} \) | Not given | Not given | 95.0/90.0/86.52% | Zhang and Hancox (2002) |
| \( \text{NaL} \) | 12.0 ± 0.7 µM | 1.0 | 71.7/62.3/47.7% | Wu et al (2008) |
et al 2008, Adeniran et al 2011, 2012). The pseudo-ECG was computed by using the Gima and Rudy approach (Gima and Rudy 2002). The electrode was placed at a site located 2.0 cm from the ENDO distal end. The pseudo-ECG morphology is consistent with the clinical data (Priori et al 2005).

A two-dimensional (2D) model was modelled by expanding the 1D strand (length of 15 mm- x direction, 100 cells) into a sheet with a width (y direction, 1000 cells) of 150 mm (or with a larger size in order to measure the critical size of the tissue to support the formation and maintenance of re-entry). The spatial and time steps were the same as used in the 1D strand. Re-entry was initiated in 2D tissue by an S1–S2 protocol. An S1 (amplitude: $-52 \text{ pA/pF}$; duration: 1 ms) was applied at ENDO distal end of the 2D tissue (length: 15 mm along the x- direction; width: 150 mm in the y- direction) to evoke a planar wave. During the vulnerable window (VW), an S2 with the same amplitude and duration as S1 was applied to the MIDDLE-EPI junction to evoke a unidirectional wave propagation. The S2 has variable spatial sizes. The critical size of the tissue to support re-entry was quantified as the minimum length of S2 that supports the formulation and maintenance of re-entry, which provides a reciprocal index of the spatial vulnerability of ventricle to re-entry: the smaller the critical size, the easier the initiation of re-entry (Zhang et al 2008).

**Results**

**Effects of quinidine, disopyramide, and E-4031 on SQT3 in the single cell APs**

The ten Tusscher et al human ventricular cell model (ten Tusscher and Panfilov 2006) incorporating SQT3 $I_{K1}$ formulations (Adeniran et al 2012) gave AP characteristics which were in excellent agreement with experimental data from human ventricular myocytes (Priori et al 2005). Alternations to $I_{K1}$ due to SQT3 mutations accelerated the repolarization phase of APs as shown in figure 1. The D172N mutation resulted in shortening of APD, with the D172N condition exerting a more profound effect than the WT-D172N condition. The measured APD$_{90}$ was 302 ms for the ENDO (figure 1(a)), 406 ms for the MIDDLE (figure 1(d)), and 304 ms for the EPI (figure 1(g)) in WT, which was shortened, respectively, to 273, 357, and 274 ms in WT-D172N and to 261, 341, and 262 ms in D172N condition. The abbreviated APD resulted largely from increased $I_{K1}$ during the late phase of AP repolarization as shown by the time course of $I_{K1}$ and the $I–V$ phase plot in figures 1(b), (c), (e), (f), (h) and (i).

The effects of drug interactions simulated on APD prolongation from representative ENDO myocytes under WT-D172N and D172N condition are summarized in figure 2. APD$_{90}$ in WT-D12N condition was prolonged to 278, 293, 299, 288, 291, 321, 340, and 341 ms in the presence of 4, 100, and 1000 nM E-4031, 13 and 100 $\mu$M disopyramide, and 4, 7, and 10 $\mu$M quinidine, respectively, and in D172N condition was prolonged to 266, 279, 284, 274, 276, 303, 319, and 320 ms, respectively. Quinidine produced a significant prolongation of APD$_{90}$, bringing it much closer to that in WT condition. The observed resting membrane potential (RP) values were $-84.65, -85.61, -85.42, -86.06,$ and $-85.97$ mV for the WT, WT-D172N, WT-D172N + 4 $\mu$M quinidine, D172N, and D172N + 4 $\mu$M quinidine conditions, respectively.

**Effects of quinidine, disopyramide, and E-4031on SQT3 in the 1D strand model**

The simulated effects of all drug interactions simulated on pseudo-ECG are shown in figure 3. Supra-threshold stimulus ($-52 \text{ pA/pF}$) was applied to the ENDO distal end, initiating electrical excitation propagation towards MIDDLE and EPI parts in figure 3(a) (for WT-D172N
condition), (b) (for WT-D172N + 4 µM quinidine condition), (e) (for D172N condition), and (f) (for D172N + 4 µM quinidine condition). From this electrical excitation wave, pseudo-ECG traces were computed as shown in figures 3(c) and (g). In these simulation results, quinidine, disopyramide, and E-4031 prolonged the QT intervals on the ECGs and reduced the T-wave amplitude. The QT interval was prolonged from 322 ms in WT-D172N condition to 328, 346, 347, 353, 360, 395, and 397 ms in the presence of 4, 100, and 1000 nM E-4031, 13, and 100 µM, and 4, 7, and 10 µM quinidine, respectively, and from 318 ms in the D172N condition to 323, 328, 333, 338, 364, 371, 375 ms, respectively. Then we further measured the rate dependence of ventricular CV (shown in supplementary materials). It shows that quinidine decreased ventricular conduction. At a rate of 75 b.p.m. (Pacing Cycle Length (PCL) = 800 ms), the measured CV was 52 cm s⁻¹ for the WT, 51 cm/s for the WT-D172N, 47 cm/s for the D172N, 41 cm s⁻¹ for the WT-D172N + 10 µM quinidine, and 36 cm/s for the D172N + 10 µM quinidine conditions. The decreased CV was due to the blocked sodium current as shown in table 2, as no change in the intercellular coupling was considered.

In order to explain the decreased T-wave amplitude seen in figure 3(c), we examined the effects of quinidine on the membrane potential heterogeneity (δV) during APs, as well as transmural APD dispersion across the strand. Figures 4(a) and (b) show simulated ENDO, MIDDLE, and EPI APs for WT-D172N, and WT-D172N + 4 µM quinidine conditions whilst figures 4(c) and (d) show corresponding time-course plots of the δV between different cell types. The δV maximal between both MIDDLE-EPI and ENDO-MIDDLE APs was smaller with actions of drugs than before (see figures 4(e) and (f)). Figure 5(a) shows the distribution of APD₉₀ for WT, WT-D172M and WT-D172N + 4 µM quinidine conditions.
Quinidine decreased APD\textsubscript{90} dispersion of APD\textsubscript{90} in the 1D strand in figure 5(b). Figures 5(c) and (d) show the maximal spatial gradient of APD\textsubscript{90} in drug-in-action conditions. The ERP was prolonged in all drug-in-action conditions compared to the mutant conditions (see figure 6). ERP restitution (ERP-R) in the presence of quinidine showed a rightward shift, with decreased maximal slopes, which is associated with decreased instability of re-entrant excitation waves (Xie \textit{et al} 2002), indicating antiarrhythmic effects of quinidine on D172N mutation. Then we quantified the vulnerability of tissue to unidirectional conduction block. Results of bidirectional conduction block, unidirectional conduction block, and bi-directional conduction are shown in figures 6(e)–(g), respectively. Figures 6(h) and (i) demonstrate the width of the VW. The VW decreased from 15 ms in WT-D172N to 7 ms in WT-D172N + 4 \mu M quinidine condition, and from 36 ms in D172N to 11 ms in D172N + 4 \mu M quinidine condition.

**Effects of quinidine, disopyramide, and E-4031 on SQT3 in 2D model**

Further simulations were performed utilizing an idealized area of the 2D model to investigate the effects of quinidine, disopyramide, and E-4031 on the dynamic behaviours of re-entrant excitation waves. The results are shown in figure 7, in which snapshots of re-entrant excitation
waves from WT, WT-D172N, and WT-D172N + 4 \( \mu \)M quinidine conditions are shown. In WT condition (see figures 6(a)–(d)), re-entrant waves were unstable and non-stationary as the tip of the re-entry meandered out of the tissue boundaries leading to self-termination, whereas augmented \( I_{K_1} \) in the WT-D172N condition (see figures 6(f)–(i)) helped to sustain re-entrant excitation waves. Snapshots of simulated pharmacological effects of quinidine on re-entry in WT-D172N condition are shown in figures 6(k)–(n). Quinidine terminated re-entrant excitation waves in the WT-D172N condition. Figures 6(e), (j) and (o) show a recording of the evolution of the AP of an EPI cell in the tissue in WT, WT-D172N, and WT-D172N + 4 \( \mu \)M quinidine conditions, respectively.
We then proceeded to measure the minimal spatial length of a premature S2 stimulus that provides a sufficient substrate for the formulation and maintenance of re-entry. Quinidine, disopyramide, and E-4031 prolonged the minimal length of S2; the minimal length was prolonged from 78 mm in WT-D12N condition to 79, 81, 82, 85, 107, 110, and 112 mm in the presence of 4, 100, and 1000 nM E-4031, 13 and 100 µM disopyramide, and 4, 7, and 10 µM quinidine, respectively. Prolongation of APD due to the action of drugs increased the wavelength of the wave and thus increased the minimal length of S2, which supports the notion that in SQT3 tissue with the application of quinidine, re-entrant excitation waves occur harder than in the drug-free SQT3 tissue.

**Figure 4.** Membrane potential heterogeneity ($\delta V$) between ENDO, MIDDLE, and EPI cells. (a) and (b) ENDO, MIDDLE, and EPI APs in WT-D172N and WT-D172N + 4 µM quinidine conditions, respectively. (c) and (d) Corresponding plots of $\delta V$ against time. (e) and (f) Maximal $\delta V$ during repolarization process between MIDDLE-EPI cells.
Summary of the major findings

The proband with the KCNJ2 D172N mutation had a QTc interval of 315 ms, where her 35-year-old father had a QTc of 320 ms (Priori et al 2005). There is clinical evidence to demonstrate the efficacy of quinidine in patients with SQTS (Gaita et al 2004, Wolpert et al 2005, Kaufman, 2007, Milberg et al 2007). Gaita et al reported that hydroquinidine prolonged a QT interval, which increased from 263 ± 12 ms to 362 ± 25 ms (calculated QT from 290 ± 13 ms to 405 ± 26 ms). Wolpert et al described that quinidine was an effective drug for SQTS with a mutation in HERG by restoring normal rate dependence of the QT interval and rendering ventricular tachycardia (VT)/ventricular fibrillation (VF) non-inducible. In the present study, with the use of quinidine, mimicking the effects on SQT3, we found that the QT interval extended from 322 ms to 380, 395, and 397 ms in the presence of 4, 7, and 10 μM quinidine, which is within the normal range of QT interval between 363 and 421 ms.

Our major findings are as follows. (i) Quinidine prolonged APD of the ventricular cells. (ii) Quinidine prolonged ventricular cell APD90 inhomogeneously across the strand, thereby decreased the maximal membrane potential heterogeneity ($\delta V$) and decreased transmural...
dispersion, which combined to contribute the decreased T-wave amplitude. (iii) Quinidine increased ERP and reduced temporal and increased spatial vulnerability to initiate and sustain re-entry, resulting in a reduced susceptibility of ventricular tissue associated with SQT3 to arrhythmogenesis. (iv) Quinidine prevented and terminated re-entrant excitation waves.
Quinidine exhibited significantly better therapeutic effects on SQT3 than disopyramide and E-4031.

Antiarrhythmic mechanisms of quinidine on SQT3

Our data constitute new evidence that the anti-arrhythmic effects of quinidine on SQT3 associated with Kir2.1 D172N mutation involve both decrease tissue susceptibility to the initiation of re-entry and prevention and termination of re-entry (terminating VF). An increase in ERP generated by actions of quinidine prolonged the wavelength of ventricular excitation waves and less likelihood for re-entrant excitation wave to be formed in a limited ventricular tissue mass. We found that, once formed, re-entry was unstable in the presence of quinidine.

Tissue susceptibility to the genesis of re-entry can be indexed by its temporal and spatial vulnerability. In our simulations, quinidine prolonged ventricular repolarization time due to the prolongation of APD and ERP, and subsequently resulted in a decreased temporal vulnerability (the width of VW). However, prolongation of ERP markedly increased the critical size of the re-entrant substrate, leading to an increased spatial vulnerability to re-entry. This provides a means for decreased ventricular tissue susceptibility to re-entry with the use of quinidine.
Limitations

The ten Tusscher and Panfilov (2006) model was used here to simulate cellular electrical AP of human ventricular myocytes; potential limitations of this model have been discussed elsewhere (ten Tusscher and Panfilov 2006, Zhang et al 2008, Adeniran et al 2011, 2012). This study aimed to predict the effects of drugs on SQT3 by using purely cellular electrophysiology, and as such did not consider the effects of electrical remodelling or fibrosis. Evidence of electrical remodelling in SQTS is currently lacking; nevertheless, this may play important roles in re-entrant arrhythmias in SQTS. On the other hand, our model did not consider cardiac mechanical contraction, which has previously been suggested to be affected in SQTS patients (Schimpf et al 2008, Adeniran et al 2013, Frea et al 2015), and may affect the pharmacological effects of drugs on SQTS.

Another limitation is that the action of drugs at the ion channel level did not incorporate voltage-, state-, frequency-dependent block effects. Regarding the experimental conditions, many factors, including oxygen, the concentration of ions, temperature, and pH (Cardona et al 2010, Mirams et al 2012), which influence the binding of drugs to ion channels would be required and modelled. Nevertheless, whilst it is useful to make potential limitations of the present study explicit, there are not anticipated to change the fundamental conclusions drawn in our study.

Conclusion

Alterations in $I_{K1}$ have previously been implicated in genesis and maintenance of VF associated with SQT3. Significantly, previous studies demonstrated the efficacy of quinidine in patients with SQTS. Our data indicate that quinidine not only helps to terminate re-entry but also decreases the susceptibility of human ventricular tissue to the genesis of re-entry. Our study identifies distinct factors at cell and tissue levels that underlie these antiarrhythmic changes. In conclusion, the findings of this simulation study add to the growing weight of evidence that quinidine may be a potential therapeutic agent for SQT3.

Acknowledgments

The authors thank Dr Ismail Adeniran for useful discussions and thank the editors and the anonymous reviewers for their constructive comments. Financial support was provided by the China Scholarship Council (CSC) (to CL) and the National Natural Science Foundation of China (NSFC) under Grants No. 61571165 and No. 61572152 (to KW and HZ).

Author contributions

KW and HZ: Conceived and designed the experiments. CL: Performed the experiments. LC, KW, and HZ: Analyzed the data. CL: Wrote the manuscript. KW and HZ: Reviewed and edited the manuscript. All authors approved the work for publication.

Conflict of interests

The authors declare that there are no competing interests.
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