

# Alternans and 2-D Spiral Wave Dynamics in Human Atria with Short QT Syndrome Variant 3: A Simulation Study

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## Abstract

*The short QT syndrome (SQTS) is a genetic disease of heart which leads to an increased risk of atrial arrhythmias and sudden cardiac death. Cardiac alternans and high-frequency spiral waves are believed to be strongly associated with atrial arrhythmias. The present study aims to use computational models to investigate the alternans and re-entrant spiral wave in SQTS.*

*The Colman-Zhang (CZ) human atria cell model was implemented for simulation. Newly developed  $I_{K1}$  formulations describing the wide type (WT) and two SQTS mutations (D172N and E299V) were incorporated. Alternans was studied in rapid heart beat rate conditions, and the S1-S2 protocol was used to initiated re-entrant excitation wave in 2D tissue.*

*Alternans were found in the intracellular calcium concentration  $[Ca^{2+}]_i$  traces from basic cycle length (BCL) of 250 to 300 ms, and no alternans was observed in E299V mutation condition. In contrast, alternans emerged when BCL was smaller than 410 ms in WT condition. The minimal spatial lengths of S2 stimulus required to initiate re-entry was reduced by the mutations. Therefore, our findings show that there is a decreased observation of alternans phenomena and the spatial vulnerability to re-entry significantly increased in SQTS conditions.*

## 1. Introduction

The short QT syndrome (SQTS) is a genetic disorder which may causes serious heart problems such as atrial fibrillation and sudden cardiac death [1]. The third variant of the SQTS (SQT3) is linked to the inward rectifier potassium current  $I_{K1}$ . Identified by Priori et al.

in 2005, the D172N mutation is the first SQT3 mutation reported [2], in which a significant increase of outward  $I_{K1}$  was observed, whilst the abnormally large outward  $I_{K1}$  presented by the E299V mutation was resulted from the impaired inward rectification [3].

Cardiac alternans, defined as beat-to-beat oscillation in muscle contraction strength, action potential duration (APD) and intracellular  $Ca^{2+}$  concentration, has been reported to be associated with the long QT syndrome (LQTS) [4]. Although the emergence of alternans in SQTS patients is rare (negative T-wave alternans testing in 12 of 13 SQTS patients) [5], the alternans study in SQTS remains important.

In the present study, computational models were utilized to investigate the alternans in SQTS and assess the spatial vulnerability as a supplement research for our previous study on pro-arrhythmic effects of SQT3 mutations [6].

## 2. Methods

### 2.1. Model development

The Colman-Zhang (CZ) human atria cell model was employed for simulation in this study [7]. Modified from the Courtemanche-Rafael-Nattel (CRN) model [8], newly proposed  $I_{K1}$  formulations for D172N and E299V mutation, which was developed in our previous study, were incorporated [6]. The heterozygous mutations were defined as the conditions in which  $I_{K1}$  fomulations consist of half WT and half SQT3 mutation.

In single cell modelling, the right atria (RA) cell was paced with 100 uniform stimuli of amplitude  $-20$  pA/pF and duration 2.0 ms to reach the steady state. The basic cycle length (BCL) was set to range from 190 to 1000 ms for alternans examination, in which important currents

and concentration traces were checked.

## 2.2. 2D tissue simulations

The propagation of excitation wave in tissue simulation was described by the monodomain equation:

$$\frac{\partial V_m}{\partial t} = \nabla \cdot D \nabla V_m - \frac{I_{ion}}{C_m},$$

where  $V_m$  is the membrane potential,  $D$  is the diffusion tensor,  $I_{ion}$  is the total ionic current, and  $C_m$  is the cell capacitance.

An idealised 2D  $700 \times 700$  nodes sheet of isotropic RA tissue with diffusion coefficient  $D = 0.21 \text{ mm}^2/\text{ms}$  was simulated. The spacing between nodes was set to 0.25 mm. S1-S2 protocol was utilized to initiate the re-entrant wave. S1 stimulus was paced on the lower edge of the sheet with a spatial width of 10 nodes, followed by the S2 stimulus paced in the centre of the sheet. The spatial width of S2 stimulus was also 10 nodes.

## 3. Results

### 3.1. Alternans study

Table 1 summarized the emergence of alternans in action potential (AP) profiles, effective refractory period (ERP) restitution, intracellular calcium concentration  $[\text{Ca}^{2+}]_i$  and ionic current traces, suggesting that the observations of alternans were reduced in SQT3 mutation conditions. The onset BCL of alternans in the setting of wide type (WT) was found to be around 410 ms (alternans exist when BCL is lower than 410 ms), whilst in E299V mutation conditions, no alternation phenomenon was observed even in very small BCL condition (190 ms). Similar results were obtained for D172N mutation, no alternans was observed except for the alternans in  $[\text{Ca}^{2+}]_i$  trace from BCL of 250 ms to BCL of 300 ms, indicating the presence of  $\text{Ca}^{2+}$  transient (CaT)

alternans without the existence of APD alternans.

The APD restitution curves for WT and two mutations are shown in Figure 2. The restitution curve in WT condition splits into two branches at small diastolic interval (DI), demonstrating the emergence of APD alternans. In contrast, although the slope of restitution curve of D172N mutation is relatively steep, the APD restitution curves in the setting of both SQT3 mutation conditions are not bifurcated.

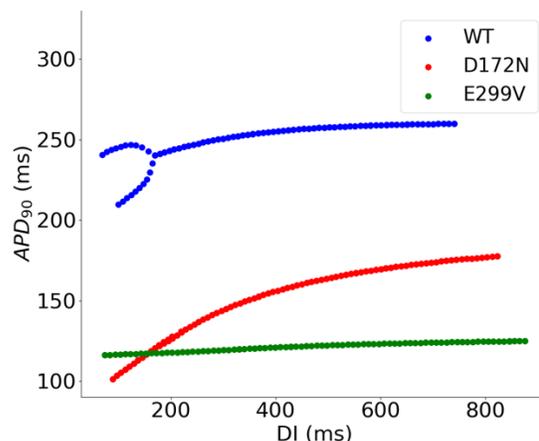


Figure 1. The action potential duration (APD) restitution curves of wide type (WT) and SQT3 mutations.

### 3.2. Spiral wave dynamics in 2D model

Figure 2 shows the snapshots of re-entry and rotor trajectories. The spiral excitation wave in the setting of WT sustained for 3 seconds with unstable trajectories, whilst the spiral wave in both the heterozygous and homozygous E299V mutation conditions were relatively stable. Although the excitation wave of homozygous E299V mutation only sustained for 1 second, the wave of heterozygous E299V mutation lasted for 5 seconds. As

Table 1. A summary of formation of alternans in action potential (AP) profiles, effective refractory period (ERP) restitution, intracellular calcium concentration  $[\text{Ca}^{2+}]_i$  and important current traces (rapid delayed rectifier  $\text{K}^+$  current  $I_{Kr}$ , slow delayed rectifier  $\text{K}^+$  current  $I_{Ks}$ , inward rectifier  $\text{K}^+$  current  $I_{K1}$ , fast  $\text{Na}^+$  current  $I_{Na}$ , L-type  $\text{Ca}^{2+}$  current  $I_{CaL}$ ).

Alternans	WT	E299V	D172N
AP	Observed	Not observed	Not observed
ERP	Observed	Not observed	Not observed
$[\text{Ca}^{2+}]_i$	Observed	Observed	Not observed
$I_{Kr}$	Observed	Not observed	Not observed
$I_{Ks}$	Observed	Not observed	Not observed
$I_{K1}$	Observed	Not observed	Not observed
$I_{Na}$	Observed	Not observed	Not observed
$I_{CaL}$	Observed	Not observed	Not observed

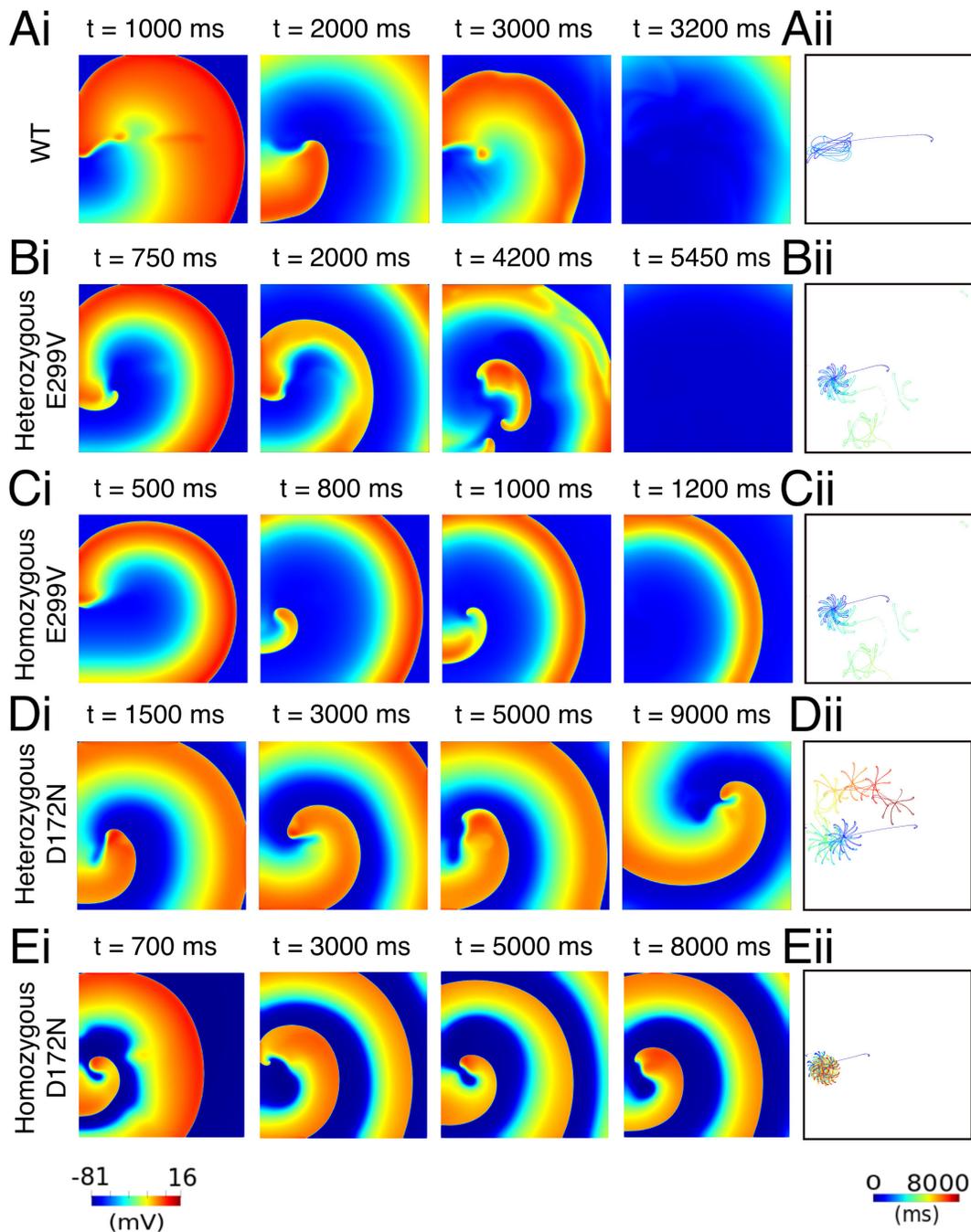


Figure 2. The snapshots of spiral waves (i) and the rotor trajectories (ii) in 2D model.

for D172N mutation, the excitation waves were more stable and meandered for a long time (more than 10 seconds), suggesting that the life-span of re-entry in the setting of D172N mutation was significantly prolonged, and the induced spiral waves were stabilized. The life-span of the E299V mutation was shortened and that of WT-E299V was prolonged.

The minimal spatial lengths of S2 stimulus required to

initiate re-entry of each gene type are shown in Figure 3. The longer spatial length of S2 stimulus needed for re-entry, the larger spatial vulnerability exhibited, since a smaller spatial length of S2 can initiate the re-entry means the re-entry can be induced more easily. Figure 3 shows that mutations significantly increased the spatial vulnerability, and half of the length of WT is sufficient for the homozygous mutations to initiate re-entry. Notably, the minimal length for heterozygous mutations

were larger than the homozygous mutations, and the E299V mutation had a shorter minimal length than the D172N mutation.

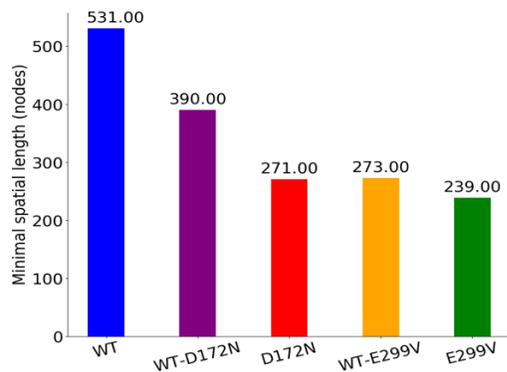


Figure 3. The minimal spatial length to initiate the re-entry.

#### 4. Discussion and conclusion

The main findings in this study are: (i) A decreased observation of alternans phenomena in SQT3 conditions. (ii) The spatial vulnerability to re-entry is augmented by the SQT3 mutations.

Our previous study have reported different effects on APD shortening caused by D172N and E299V mutation [6]. In the present study, the emergence of alternans was investigated in fast heart beat rate conditions. The study of fast heart beat rate conditions is of great significance. For example, it is common for an athlete to reach the heart beat rate of up to 180 bpm to 200 bpm during exercise [9].

The reduced observation of alternans is mainly caused by the shortened APD. Since alternans is usually induced by the fast heart beat rate, when the APD was shortened, although other pro-arrhythmic effects might be triggered, the required pace threshold for emergence of alternans were also reduced, leading to the reduced observation of alternans. In contrast, the long QT syndrome (LQTS) provides an inverse effect on the formation of alternans. Therefore, cardiac alternans has been demonstrated to be highly associated with the LQTS [4]. Previously, the SQT3 mutations were proved to augment the temporal vulnerability [6]. This study further confirmed the increase of spatial vulnerability.

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