Multi-scale Cardiac Modelling Reveal Tachyarrhythmias Induced by Abrupt Rate Accelerations in Long QT Syndrome

Jieyun Bai, Kuanquan Wang, Henggui Zhang
School of Computer Science and Technology
Harbin Institute of Technology, HIT
Harbin, China

Dec. 15, 2016, Shenzhen, China.
Outline

I. Background

II. Methods

III. Results

IV. Conclusion

V. Acknowledgement
Long QT syndrome (LQTS) is a rare congenital and inherited or acquired heart condition which delayed repolarization of the heart following a heartbeat increases the risk of episodes of ventricular arrhythmias.

The long-QT syndromes (LQTS) are characterized by:
- action potential (AP) prolongation in single cells.
- a prolonged QT interval on the electrocardiography (ECG), and ventricular arrhythmias in patients.

Although molecular and genetic changes of the individual ionic channels were addressed, it is relatively unclear for the exact tissue-level electrophysiological mechanism for arrhythmias as a result from cellular disorder.
Background

- The mechanisms by which this bradycardia-dependent phenomenon contributes one to rapid arrhythmias are worthy to be studied and important for preventing and managing sudden cardiac death.

- Multi-scale mathematical modeling provides an alternative method for understanding the development of cardiac arrhythmias.

Fig. 1 Early afterdepolarizations (EADs) often occurred at slow heart rates and ventricular arrhythmias are characterized by excessively high heart rates.
Background

- Experimental studies in animal ventricle have suggested that acceleration of heart rate can induce transient EAD activity (Burashnikov, et al. and Nuyens, et al.).

- This study sought to test the hypothesis that EADs induced by abrupt rate accelerations can occur and investigate how this abrupt rate accelerations is related to the mechanisms of reentrant excitations.

- A human ventricular cell was modified to model experimental conditions in LQTS. Then, the normal and EADs cell models were incorporated into homogeneous multicellular 1D and 2D tissue models to study the mechanism underlying the generation of reentrant events.


Methods

The TP06 model for the human ventricular AP, which was suggested that it can be used for ventricular arrhythmias under pathological conditions, was developed by using the human experimental data.

Thus, the TP06 model was modified to simulate EADs at the cellular level based on experimental data.

Fig. 2 A human ventricular model (upper) and ventricular arrhythmias (bottom) were studied by using the TP06 model.
Methods

Part II

- The modified human ventricular cell model was governed as follows

\[
\frac{C_m \partial V}{\partial t} = -I_{ion} + I_{stim}
\]

\[
I_{ion} = I_{Kr} + I_{Ks} + I_{K1} + I_{to} + I_{Na} + I_{bNa} + I_{CaL} + I_{bCa} + I_{NaK} + I_{NaCa} + I_{pCa} + I_{pK} + I_{NaL}
\]

where \( C_m, V, t, I_{stim} \) and \( I_{ion} \) are the membrane capacitance, the membrane potential, the time and the stimulus current and the sum of transmembrane ionic current, respectively.

Table 1. Changes of parameters for simulating EADs based on experimental data (Vandersickel, et al.).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>( G_{Kr} )</td>
<td>0.5fold (↓)</td>
</tr>
<tr>
<td>( G_{CaL} )</td>
<td>5 fold (↑)</td>
</tr>
<tr>
<td>( Tau )</td>
<td>2 fold (↓)</td>
</tr>
</tbody>
</table>

Methods

- We constructed a 1.5cm cable (100 cell with cell length 0.015cm) with an EADs region containing 10 cells (from 45 to 55) in the center of the fiber. The distance between the center of the EADs region and the fiber end is about ~7.5 mm, which is similar to that observed by Vijayakumar et al.

- For our 2D simulations, a square tissue of 15 mm×15 mm, which contains a 7.5 mm×7.5 mm EADs region (similar to ionic heterogeneity measured by Glukhovet et al., is developed to investigate the dynamics of spiral waves.

![Diagram](image.png)

Fig. 3 1D (left) and 2D(right) idealized human tissue model.

Methods

- Action potentials were simulated by changing pacing rate from 0.5Hz to 2Hz, recording and analyzing ionic currents and concentrations changes. The stimulus strength is with the amplitude of -52pA/pF and the duration of 1 ms. APD90 was measured as the duration of APs at 90% repolarization.

- **Dispersion** of repolarization (DOR) was computed as the time difference of repolarization time along the 1D tissue. APD spatial gradient was computed as rate of APD changes per unit length, which provides a measure of the extent to conduction block of cardiac tissue.

- The temporal vulnerable window (VW) was computed as the time window for unidirectional conduction block.
During fast pacing (2Hz), the content of SR calcium $[\text{Ca}^{2+}]_{\text{SR}}$ increased from 3.64 to 4.58 mM and spontaneous calcium release ($I_{\text{rel}}$) occurred before completed repolarization. EAD was triggered by a sodium-calcium exchange current not the $I_{\text{CaL}}$.

Fig. 4. The development of EADs for abrupt rate accelerations. The pacing rate was changed from 0.5Hz to 2Hz and EAD was initiated by spontaneous calcium release ($I_{\text{rel}}$) from SR and a sodium-calcium exchange current ($I_{\text{NCX}}$), depolarizing inward current.
Results

- Compared with the normal condition, DOR under LQTS condition excessively was increased by 473% (from 15 ms to 86 ms) and caused by the EAD region. Prolonged APD in the EAD region was paralleled by an abrupt rise in DOR from 1 ms/m to 63.3 ms/mm, producing steep spatial gradients of repolarization that was directly responsible for unidirectional conduction block.

Fig. 5. DOR under Normal and local LQT conditions.
Results

- For the normal condition, bidirectional block ($T=332$ ms), unidirectional conduction block (from $T=333$ to $333.5$ ms, $0.5$ ms) and bidirectional conduction ($T=333.6$) were observed. But unidirectional conduction block (from $T=348$ to $362$ ms) for the LQTS condition is $14$ ms. Compared with the normal condition, a marked increase (from $0.5$ ms to $14$ ms, $2800\%$) in VW demonstrated a notable increase in tissue susceptibility to arrhythmogenesis.

Fig. 6. Space-time plot of propagating excitation wave in response to a premature test stimulus at various time interval ($T$) between S1 and S2 stimulus under normal (A) and LQTS (B) conditions.
For the normal condition (Fig. 7, Normal), an abrupt pacing stimulus produced bidirectional conduction leading to genesis of plane waves without breaking up. For the LQTS condition (Fig. 7, LQTS), an abrupt pacing stimulus produced unidirectional conduction block leading to genesis of a reentrant excitation resulted from local plane waves block.

Fig. 7. Simulation of spiral waves in a 2D ventricular tissue under normal and LQTS conditions.
Conclusion

- Abrupt rate acceleration prolonged action potential duration, caused premature beats and induced EADs in LQTS cells.

- The changes in cellular electrophysiology modulated ventricular conduction and increased tissue temporal and spatial vulnerability. The local LQT region increased spatial vulnerability and prolonged APD in local LQT cells increased temporal vulnerability, producing steep spatial repolarization gradients that was directly responsible for unidirectional conduction block.

- An abrupt pacing stimulus produced unidirectional conduction block leading to genesis of reentrant excitations, but the reentry wave for the LQTS condition was unstable and promoted self-termination in idealized 2D tissue. Local LQTS region with a longer wavelength is responsible for self-termination of the reentry wave.
Conclusion

- Although EADs in LQTS classically occurred at slow heart rates, some experimental studies suggested EADs may be induced at the fast heart rates, which provided a potential link between bradycardia-dependent AP prolongation and tachycardia-dependent ventricular arrhythmias. The present study provided direct evidences that support the hypothesis EADs induced by abrupt rate accelerations can transform into ventricular arrhythmias (EADs increased regional repolarization dispersion that contributed to the genesis of tachyarrhythmias in LQTS).
Acknowledgement
Any questions?