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

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Dec. 15, 2016, Shenzhen, China.

Outline

Background

Part I

- 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

Part I

- 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.

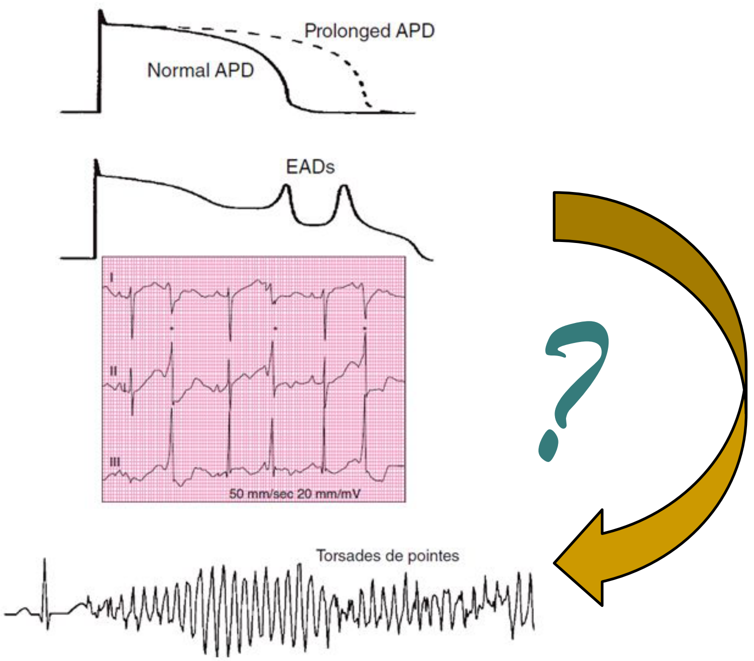


Fig. 1 Early afterdepolarizations EADs often occurred at slow heart rates and ventricular arrhythmias are characterized by excessively high heart rates.

Background

Part I

- 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.

Burashnikov, *et al*. (1998). *Journal of cardiovascular electrophysiology.* 9**,** 934-948.
Nuyens, *et al*. (2001). *Nature medicine.* 7**,** 1021-1027.

Methods **Part II**

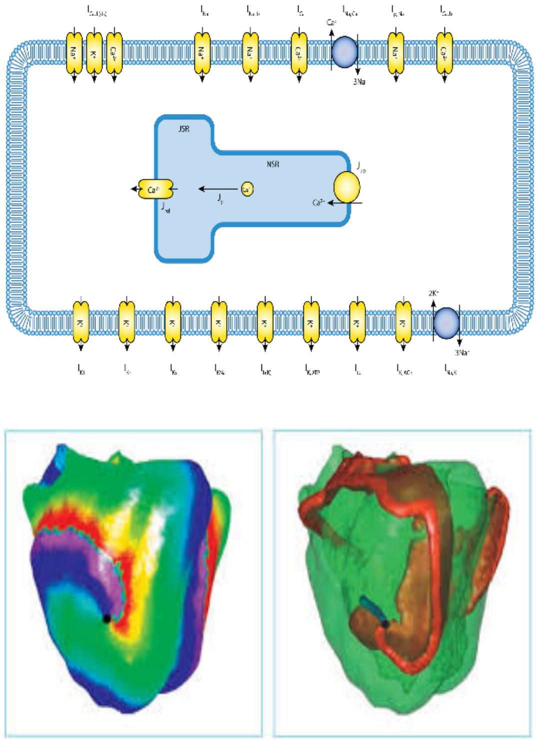


Fig. 2 A human ventricular model (upper) and ventricular arrhythmias (bottom) were studied by using the TP06 model.

- 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.

Methods **Part II**

- The modified human ventricular cell model was govern as follows

$$C_m \, \partial V/\partial t = -I_{ion} + I_{stim}$$

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

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.).

Parameters	Percentage
G_{Kr}	0.5fold (↓)
G_{CaL}	5 fold (↑)
Tau	2 fold (↓)

Vandersickel, *et al*. (2014). *PloS one*. 9, e84595.

Methods

Part II

- 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.

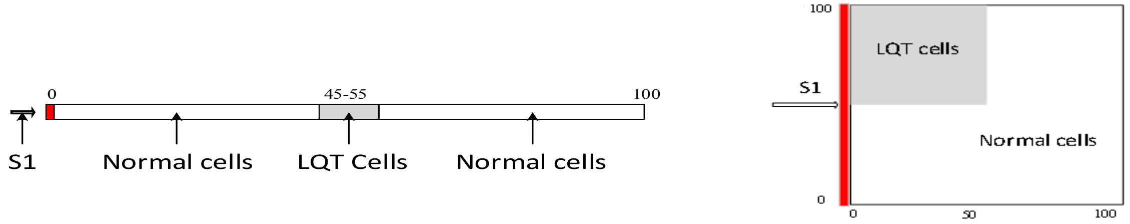


Fig. 3 1D (left) and 2D(right) idealized human tissue model.

Vijayakumar et al.(2014). *Circulation.* 130, 1936-1943.
Glukhovet et al.(2010). *Circulation research. 106,* 981-991.

Methods

Part II

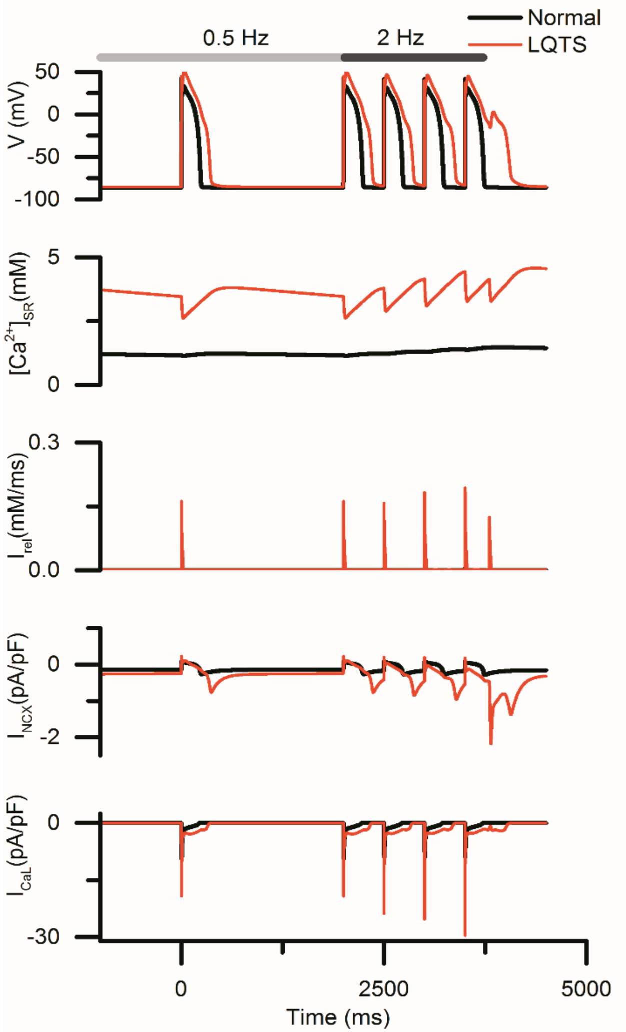
- Action potentials were simulated by changing pacing rate from 0.5Hz to 2Hz, recording and analyzing ionic currents and concentrations changes. The stimulus strength is with the amplitude of -52pA/pF and the duration of 1 ms. APD90 was measured as the duration of APs at 90% repolarization.

- 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.

Results

Part III



- During fast pacing (2Hz), the content of SR calcium [Ca2+]SR increased from 3.64 to 4.58 mM and spontaneous calcium release (Irel) occurred before completed repolarization. EAD was triggered by a sodium-calcium exchange current not the ICaL.

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 (Irel) from SR and a sodium-calcium exchange current (INCX), depolarizing inward current.

Results

Part III

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

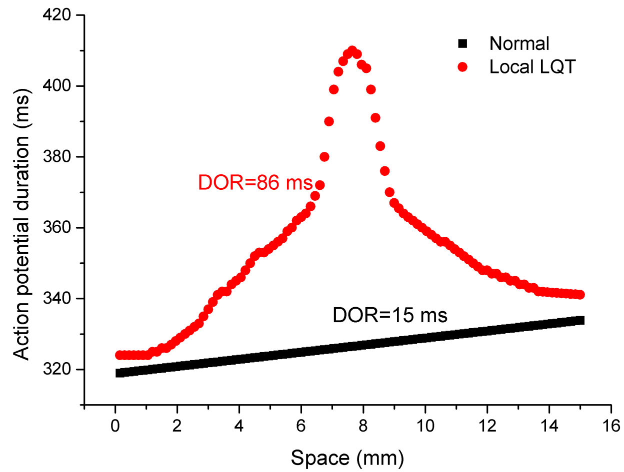


Fig. 5.DOR under Normal and local LQT conditions.

Results **Part III**

- For the normal condition, bidirectional block (T=332 ms), unidirectional conduction block (from T=333 to 333.5ms, 0.5ms) and bidirectional conduction (T=333.6) were observed. But unidirectional conduction block (from T=348 to 362ms) 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.

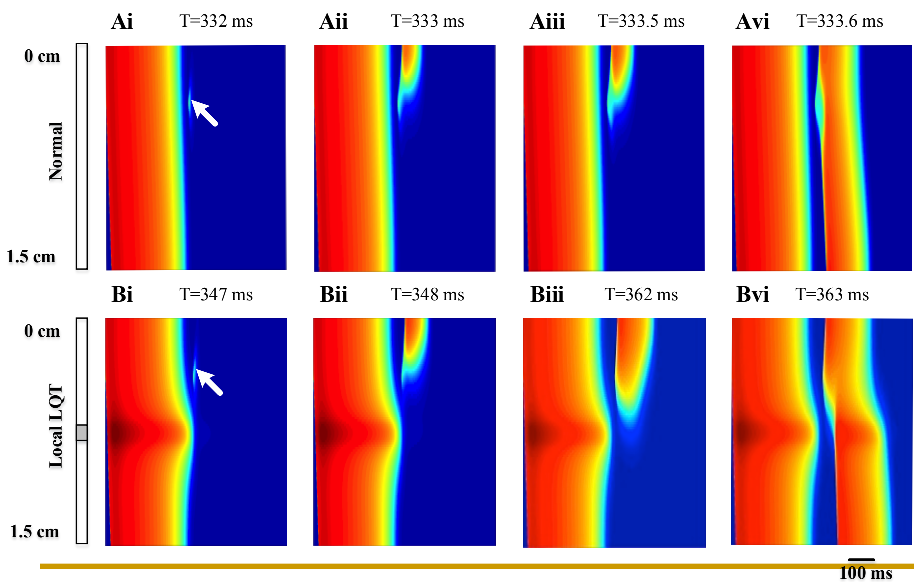


Fig. 6. Space-time plot of propagating excitation wave in response to a premature test stimulus at various time interval (T) between S1 and S2 stimulus under normal (A) and LQTS (B) conditions.

Results

Part III

- 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.

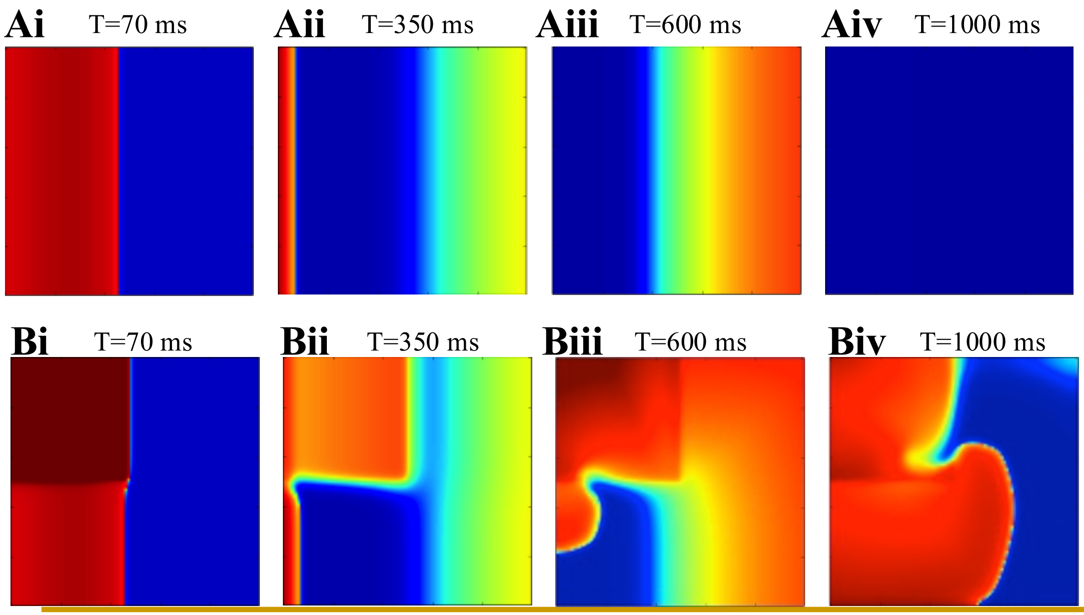


Fig. 7. Simulation of spiral waves in a 2D ventricular tissue under normal and LQTS conditions.

Conclusion

Part IV

- 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

Part IV

- 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

Part V

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国家留学基金管理委员会
CHINA SCHOLARSHIP COUNCIL

MANCHESTER
1824
The University of Manchester

国家自然科学基金委员会
National Natural Science Foundation of China

Any questions ?