Evaluating Body Surface ECG Differences of Simulated Long-QT Syndromes

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Abstract

Congenital Long-QT Syndrome (LQTS) is a genetic disorder affecting the repolarization of the heart. The most prevalent subtypes of LQTS are LQT1-3. In this work, we aim to evaluate the differences in the T-waves of simulated LQT1-3 in order to identify markers in the ECG that might help to classify patients solely based on ECG measurements. For LQT1, mutation S277L was used to characterize I_{Ks} and mutation S818L in I_{Kr} for LQT2. Voltage clamp data were used to parametrize the ion channel equations of the ten Tusscher and Panfilov model of human ventricular electrophysiology. LQT3 was integrated using an existing mutant I_{Na} model. The monodomain model was used in a transmural and apico-basal heterogeneous model of the ventricles to calculate ventricular excitation propagation. The forward calculation on a torso model was performed to determine body surface ECGs. Compared to the physiological case with a QT-time of 375 ms, this interval was prolonged in all LQTS (LQT1 423 ms; LQT2 394 ms; LQT3 405 ms). The T-wave amplitude was changed (Einthoven lead II: LQT1 108%; LQT2 91%; LQT3 103%). Also, the width of the T-wave was enlarged (full width at half maximum: LQT1 111%; LQT2 125%; LQT3 109%). At the current state of modeling and data analysis, the three LQTS have not been distinguishable solely by ECG data.

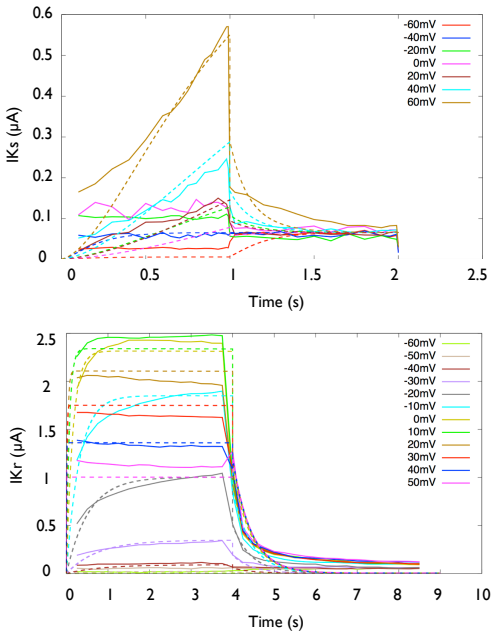

Figure 1. Voltage clamp data (solid lines) and simulated traces after fitting procedure (dashed lines) for mutation S277L in I_{Ks} (top) and mutation S818L in I_{Kr} (bottom). Colors indicate different step voltages during clamping.

1. Introduction

Congenital Long-QT Syndrome (LQTS) is a genetic disorder affecting the repolarization of the heart. Genes that encode the various cardiac ion channels or regulatory proteins of these channels are mutated, which leads to a prolonged ventricular action potential duration (APD). Thus, it leads to a propensity for ventricular arrhythmias. It affects up to 1 out of 2500 people and it is a common cause of sudden cardiac death among children.

Currently, LQTS is classified according to 12 types of ion channel mutation (LQT1-12) but the first three, LQT1-3, are the most prevalent and most studied. LQT1 occurs in 30-35%, LQT2 in 25-30%, LQT3 in 5-10%, LQT4 in 1-2%, and LQT5 in 1% of cases. LQT6-12 are all rare.

Despite the significant increase regarding the understanding of this heart disease in the past years, some gaps related to the diagnosis and sub-typing methods are still existent. Genetic testing can identify the responsible genes in patients with known disease, but there are some important limitations to LQTS genetic testing. First of all, they are still not affordable for a significant part of the population. Besides the financial aspect, the currently available genetic test will not be able to identify the LQTS-causing mutation in all of the patients. New technologies are continually being developed to better identify the still

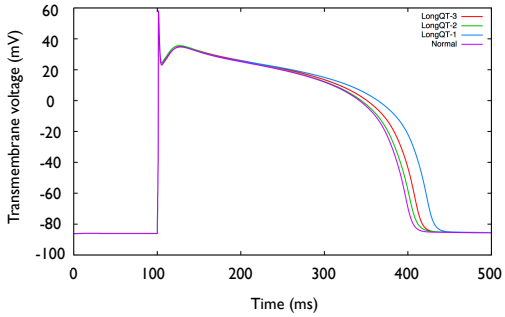

Figure 2. Action potential of the physiological case (purple), LQT1 (blue), LQT2 (green) and LQT3 (red).

unknown mutations and, as these defects are characterized and validated, they must be incorporated into the commercially available testing. Therefore, it is of great importance to investigate and to develop alternative methods, in order to provide higher accuracy regarding the diagnosis and sub-typing of LQTS.

The experimental and clinical possibilities for studying cardiac arrhythmias in human ventricular myocardium are very limited. Animal hearts used for empirical studies may differ significantly from human hearts and cardiac arrhythmias are three-dimensional phenomena, whereas experimental observations are still largely constrained to surface recordings. For these reasons, experimental cardiac electrophysiology has been increasingly complemented by computational models of membrane excitability over the last 50 years. The mentioned models, combined with computational simulations can be used to test and generate hypotheses that are difficult to address experimentally.

The objective of this work is to investigate alternative methods to distinguish between the first three types of the Long-QT syndrome by looking for differences in simulated Body Surface Potential Maps (BSPM). A model of human ventricular myocytes was adapted to represent the behavior of the mutated channels and BSPM were simulated including the subtypes.

2. Materials and methods

In order to simulate excitation propagation in the human heart, a geometrically accurate model in combination with a heterogeneous electrophysiological model was used. The transmural and apico-basal electrophysiological heterogeneity was optimized in such a way that the differences between measured and simulated multi-channel ECG data were minimized [1]. The heterogeneous model TM35_30_A2B1 was used (see [1]). Activation and repolarization were calculated using the ten Tusscher model [2] of human ventricular electrophysiology in combination with the monodomain approach. An endocardial stimu-

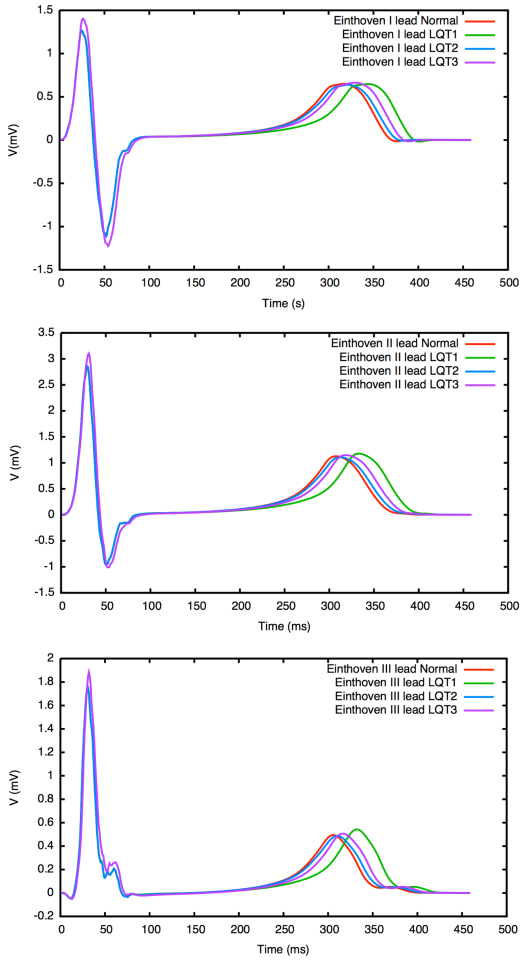

Figure 3. Simulated Einthoven I (top), II (middle) and III (bottom) ECGs for the physiological case (red), LQT1 (green), LQT2 (blue) and LQT3 (purple).

lation protocol was used to mimick Purkinje-muscle junctions and to activate the tissue. The body surface potentials were calculated using the bidomain model on the corresponding anatomical torso model of a volunteer generated on the basis of MRI data. Details about the used models and methods can be found in [3].

Data from voltage clamp recordings of mutated LQT1 [4] and LQT2 [5] channels co-expressed with wild-type channels were used in order to integrate the effects of these mutations into the model. For LQT1, mutation S277L was used to characterize I_{Ks} (Fig. 1 top) and mutation S818L in I_{Kr} for LQT2 (Fig. 1 bottom). The data was used to parametrize the ion channel equations of the ten Tusscher model [2]. The parameters were found by minimizing the root mean squared error between measured and simulated current traces using a trust region reflective method [6]. LQT3 was integrated using an existing mutant I_{Na} model of Clancy and Rudy [7]. In order to represent

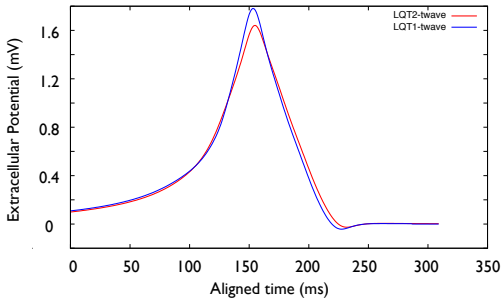

Figure 4. Differences between LQT1 and LQT2 T-wave on the body surface node with the largest differences in the signals. The two T-waves were aligned to eliminate time shifts.

co-expressed mutant I_{Na}, half of the physiological I_{Na} was mixed to half of the mutant I_{Na}.

3. Results

The optimization of the channel model parameters to the measured voltage clamp data lead to the following parameters in the model equations:

$$I_{Ks} = 0.159 x_s^2 (V_m - E_{Ks})$$
$$x_{s,\infty} = \frac{1}{1 + e^{(-32.8719 - V_m)/14}}$$
$$\alpha_{xs} = \frac{1400}{\sqrt{1 + e^{(-19.3863 - V_m)/0.2885}}}$$
$$\beta_{xs} = \frac{1}{1 + e^{(V_m - 27.7474)/22.2581}}$$
$$\tau_s = \alpha_{xs}\beta_{xs} + 80$$

$$I_{Kr} = 0.125\sqrt{\frac{K_o}{5.4}} x_{r1} x_{r2} (V_m - E_K)$$
$$x_{r1,\infty} = \frac{1}{1 + e^{(-43.96 - V_m)/7.251}}$$
$$\alpha_{xr1} = \frac{450}{1 + e^{(-15.7865 - V_m)/13.8433}}$$
$$\beta_{xr1} = \frac{6}{1 + e^{(V_m + 44.0902)/10.5209}}$$
$$x_{r2,\infty} = \frac{1}{1 + e^{(V_m + 95.463)/25.977}}$$
$$\alpha_{xr2} = \frac{3}{1 + e^{(55.3022 - V_m)/20}}$$
$$\beta_{xr2} = \frac{1.12}{1 + e^{(V_m - 60)/20}}$$

The corresponding simulated voltage clamp protocol traces are depicted in Fig. 1 (top) for LQT1 and in Fig. 1 (bottom) for LQT2.

Integrating these modified ion channel equations and the LQT3 model of Clancy and Rudy [7] into the ten Tusscher model, revealed a prolongation of the APD for all three LQTS seen in Fig. 2. The prolongation of the APD corresponds also to the prolongation of the T-wave in the simulated ECGs (Fig. 3). Compared to the physiological case with a QT-time of 375 ms, this interval was prolonged in all LQTS (LQT1 423 ms; LQT2 394 ms; LQT3 405 ms). Additionally,the T-wave amplitude was changed (Einthoven lead II: LQT1 108%; LQT2 91%; LQT3 103%). Also, the width of the T-wave was enlarged (full width at half maximum: LQT1 111%; LQT2 125%; LQT3 109%).

For further investigation of the T-wave differences in the LQTS, the T-waves of all body surface nodes of the torso model were aligned and the maximum differences were extracted. Fig. 4 shows the node with the largest difference in signal between LQT1 and LQT2. Only small differences in signal morphology were visible.

Additionally to the signal morphology, the signal pattern on the whole body surface might be changed in LQTS. The signal pattern of the T-Wave differences for 6 time instances are shown in Fig. 5. There seems to be a signal pattern difference, but the changes are again 1-2 magnitudes smaller than the signal amplitude itself.

4. Discussion

Aim of this work was to evaluate the body surface ECG differences in simulated LQTS. Therefore, the effects of LQT1-3 on the ion channels were integrated in the ten Tusscher model of human ventricular electrophysiology. Using reaction-diffusion systems, the excitation spread and BSPM was calculated. The differences in the signals were analyzed and quantified.

The adaptation of the ion current equations to the measured data delivered an appropriate fit (see Fig. 1), although the effects of the mutations could only reconstruct the behavior phenomenologically rather than mechanistically. For a mechanistically appropriate description, Markov chain models of ion channels would be a better choice and would additionally deliver an even better fit.

The prolongation of the QT-interval for the three LQTS is significant but does not reconstruct the clinically measured prolongation. One reason might be, that we did not correct the QT-interval for the heart rate. Another more important reason is, that we only included biophysical changes of the ion channel in the parameter optimization but not amplitude differences. Additionally to the biophysical changes, there might be loss-of-function effects that we were not able to extract from the voltage clamp data. These effects will prolong the QT-interval further. One way to solve this issue would be to adjust the maximum conductance of the effected channel in such a way, that the QT-interval prolongation is equivalent to the mea-

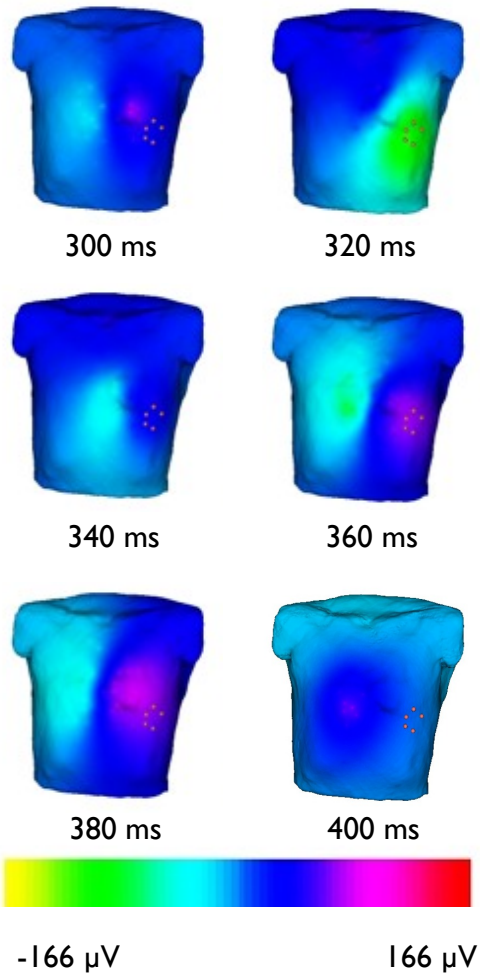

Figure 5. Temporal evolution of the signal amplitude difference between LQT1 and LQT2 during the T-wave on the body surface.

sured one. It is possible, that these T-waves could be distinguished more easily.

Additional to the presented measures of difference, further parameters of T-wave morphology and T-wave pattern have to be evaluated and applied to the data. The final goal of this research is to find specific non-standard leads on the body surface with which a sub-typing of LQT patients solely based on ECG data would be possible.

In sum we can say, that the presented version of the model can partly reconstruct QT-interval prolongation for the three main forms of long QT syndrome. Nevertheless, we were not able to find yet any descriptor that would distinguish the LQTS from each other solely with our simulated body surface ECGs.

Acknowledgements

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References

[1] Seemann G, Álvarez de Eulate M, Dössel O, Keller D. Variation of human ventricular IKs heterogeneities to reconstruct measured multi-channel ECG data. Biomedical EngineeringBiomedizinische Technik 2013;Epub ahead of print.

[2] ten Tusscher KHWJ, Panfilov AV. Alternans and spiral breakup in a human ventricular tissue model. American Journal of Physiology Heart and Circulatory Physiology 2006; 291:H1088–100.

[3] Keller DUJ, Weiss DL, Dössel O, Seemann G. Influence of I(Ks) heterogeneities on the genesis of the T-wave: a computational evaluation. IEEE Trans Biomed Engineering 2012; 59:311–322.

[4] Scholz EP, Niemer N, Hassel D, Zitron E, Burgers HF, Bloehs R, Seyler C, Scherer D, Thomas D, Kathofer S, Katus HA, Rottbauer WA, Karle CA. Biophysical properties of zebrafish ether-a-go-go related gene potassium channels. Biochemical and Biophysical Research Communications 2009; 381:159–164.

[5] Berecki G, Zegers JG, Verkerk AO, Bhuiyan ZA, de Jonge B, Veldkamp MW, Wilders R, van Ginneken ACG. Herg channel (dys)function revealed by dynamic action potential clamp technique. Biophysical Journal 2005;88:566–578.

[6] Wilhelms M, Schmid J, Krause MJ, Konrad N, Maier J, Scholz EP, Heuveline V, Dössel O, Seemann G. Calibration of human cardiac ion current models to patch clamp measurement data. In Computing in Cardiology, volume 39. 9-12 Sept, Kraków, Poland, 2012; 229–232.

[7] Clancy CE, Rudy Y. Na(+) channel mutation that causes both brugada and long-QT syndrome phenotypes: a simulation study of mechanism. Circulation 2002;105:1208–1213.

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