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Cellular Simulation of Startle-induced Early Afterdepolarizations in Long QT Syndrome 2

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Abstract— **Computational cardiac models are an emerging technology that can offer unique insight into the field of medicine. However, much progress remains to be made before they can be used in standard clinical practice. One significant challenge is in representing an individual's particular disease presentation with standardized models. It is necessary to overcome this challenge in order for cardiac models to be practically beneficial to patients in a healthcare setting. In this study, we modify a computational cardiac model to observe the electrophysiological characteristics of a specific cardiac condition: long QT syndrome 2 (LQT2). We simulate the baseline cellular effects of LQT2 as well as the startle response that often triggers life-threatening arrhythmias in patients displaying this condition. Finally, a potential line of therapy for LQT2 is simulated, and significant changes in the cardiac cell action potentials are observed. The approach used demonstrates not only the feasibility of parametrizing cardiac models for disease states but also the benefit that cardiac models can offer to the current healthcare paradigm.**

Keywords— **Cardiac simulation, Long QT Syndrome, LQT2, Startle, Calcium channel blockers**

I. Introduction

Cardiac simulation models are a powerful tool that can offer unique insight into the field of medicine; however, they are still not considered to be a standard method of practice in clinical settings [1]. Parametrizing mathematical models for specific disease traits can be a tedious and difficult task, and there is often variation between outputs from the various models. Although there is no immediate fix to these challenges, we aim to demonstrate here the feasibility and benefit of parametrizing cardiac models for one particular disease: the long QT syndrome 2 (LQT2) channelopathy.

Long QT syndrome (LQTS) is a family of diseases affecting various ion channels involved in action potential propagation in the heart [2]. The identifying characteristic is a delay in ventricular repolarization, indicated by a prolongation of the interval between the Q and T waves on an electrocardiogram [3]. Individuals with LQTS are susceptible to a serious arrhythmia called torsades de pointes (tdP), syncope, and potentially cardiac arrest, usually brought about by a triggering event [2].

LQT2 is caused by a mutation in the KCNH2 gene, which encodes the α-subunit of the voltage-gated potassium channel that conducts the rapidly activating delayed rectifier potassium current, I_{Kr} [4]. The specific event that triggers LQT2 arrhythmias is not always easy to identify; however, one trigger that is largely associated with the LQT2 phenotype is a sudden auditory stimulus (such as an alarm clock, a siren, etc.) that induces a sympathetic surge as the individual is startled [5, 6]. This surge contributes to the rapid acceleration and deceleration of the heart rate as seen in [7] and, at the cellular level, has the effect of increased calcium activity, particularly the L-type calcium current, I_{Ca}, which is an inward current that must be balanced by an outward current to maintain stability in the coordination of action potentials [6]. In LQT2 syndrome, because one of the major outward currents, I_{Kr}, is attenuated, the coordination of action potentials is delicate, even at a baseline level. When there is also a sudden increase in inward current caused by a sympathetic surge, the lack of balance between inward and outward current becomes even more pronounced.

In addition to the variation in triggering events among patients, the standard LQT2 treatment is not as effective as it is with LQT1 [5]. Currently, the standard therapy is β-blockers [8], although there is still a high incidence of recurring cardiac events after therapy [5, 8]. Several studies have been done on the effects of an alternative pharmacological approach, such as calcium channel blockers [3, 4].

Cardiac simulations have proven to be a helpful tool for analyzing the underlying electrophysiological dynamics in various disease conditions [9]. The study we perform here examines the cellular basis of LQT2-induced arrhythmias through the lens of a cardiac simulation. We apply a mathematical model of the cardiac action potential to one ventricular myocyte, and after emulating the disease at a baseline level, we simulate a startle response and observe the effects on the action potentials in the cell. We then simulate calcium channel blockers and observe the ensuing change. Through these experiments, we demonstrate the unique insight that is

gained by parametrizing and simulating specific cardiac conditions that are risky or impossible *in vivo* in order to understand pathological mechanisms and potential drug therapies.

II. Materials and Methods

The mathematical model used in all simulations was developed by Grandi et al. and may be found in the supplementary material of [10]. The model is a system of 38 differential equations describing the dynamics of ionic currents and ion concentrations in a human ventricular cardiomyocyte during the course of an action potential. The cell model was obtained from the CellML repository [11]. All simulations were carried out in Matlab using its `ode15s` solver [12].

The experimental data used to validate our simulations were obtained from Itzhaki et al. [4]. Their experiments were performed using human induced pluripotent stem cells that were acquired from an individual with congenital LQT2 syndrome. The patient had a missense mutation in the KCNH2 gene (A614V) affecting the pore region of the voltage-gated I_{Kr} channel. The measurements used for reference were APD90 and I_{Kr} current density (Fig. 3b,d in [4]). Relative differences between Control and LQTS values were calculated; then the I_{Kr} conductance, g_{Kr}, was changed such that the current density acquired from our simulations matched the measured values of Itzhaki et al. (i.e., between 27% and 42% of control). The resulting change in APD90 seen in our simulations was calculated and again compared with [4], and it was found to be within the reported range (i.e., 236-260% of control for ventricular cells).

To simulate the cardiac startle response, the original model code was modified to allow variable stimulus period lengths throughout the simulation. The stimulus periods correspond to the lengths of time between successive applied stimuli, i.e., corresponding to the pacing of the sinoatrial node. Period lengths were then adjusted to match data on the cardiac response to startle, as found in [7].

The process of being startled involves rapid and intense activation of the sympathetic nervous system [6]. This is caused by a sudden increase in the quickly activating L-type calcium current, I_{Ca}, while the slower-activating mediating current I_{Ks} has not yet caught up [6]. To represent this phenomenon, pCa, a calcium transport constant in the model of Grandi et al. (Table 2.8 of [10], Suppl.), was increased by a factor of 1.4. In addition to this, changes were made to the algebraic equations governing I_{Ca} to reflect a negative shift in voltage dependence: gating variables d_{ss} and f_{ss} and activation and inactivation time constants, τ_d and τ_f, respectively. (Eqs. 62–65 of [10], Suppl.) The changes made were similar to those made by Shannon et al. in [13] to their original model. (See Table 8; Eqs. 79–82 of [14] for original equations.)

To model the attenuating effect of calcium channel blockers, pCa was reduced to 86% of the original value used in both baseline and startle conditions.

III. Results

A. Baseline LQT2 activity

We now present the results of our simulations. To represent baseline LQT2 activity, the conductance, g_{Kr}, of the potassium current I_{Kr} was reduced to 35% of the original value. This change resulted in a reduction of I_{Kr} peak current to 35% of its original (healthy control) value, shown in Fig. 1. This agrees with the measurements of Itzhaki et al. and is well within the range of other findings as well (e.g., [15]).

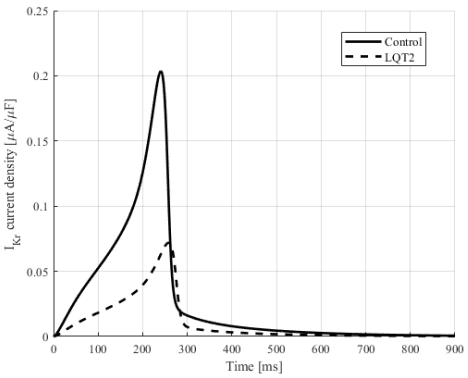

Fig. 1: I_{Kr} current density plot during one simulated action potential. The solid line represents a healthy cell and the dashed line represents a cell with LQT2. In the LQT2 plot, the I_{Kr} peak current is reduced to 35% of that of a healthy cell.

B. Effect of adrenergic surge on LQT2 action potential

In Fig. 2, a single simulated action potential is shown under different conditions. At a baseline level, the LQT2 action potential duration up to the point of 90% repolarized (APD90) is prolonged by a factor of 1.08. After introducing the sympathetic changes to the model as described in Section II, this factor becomes 2.45, which is in the range of the APD90 values reported in [4]. The abnormal imbalance between inward and outward currents is seen in the extended length of time it takes for the membrane to repolarize to a resting potential. For this reason, an increased action potential duration is considered a hallmark feature of Long QT syndrome, and it is also closely associated with the distance between the Q and T waves on an ECG [3].

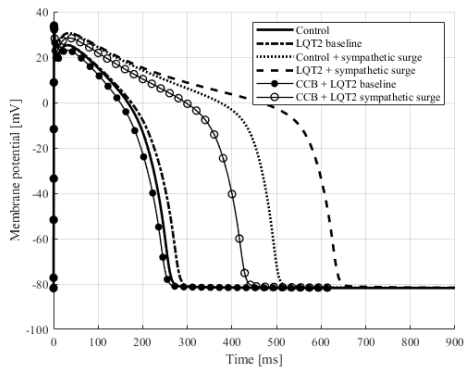

Fig. 2: Changes in action potential duration under six conditions. The reduction in I_{Kr} from LQT2 slightly prolongs the APD at baseline levels. When sympathetic activity is simulated at the same time, the prolonging effect becomes much more pronounced. After calcium channel blockers are added, the APD returns to approximately the control length.

C. Startle response and drug simulation

Adjustments were made to the cell model code to allow for varying stimulus period lengths, so that a dynamic cardiac startle response could be elicited. In combination with the previously mentioned changes to I_{Kr} and I_{Ca}, the stimulus period length was set to 983.6 ms (i.e., 61 beats per minute) as an initial value, and changes to it were made according to the values reported by Ramirez et al. [7]. The entire response lasted 70 seconds.

Fig. 3A shows the action potentials during the startle response of a healthy control; Fig. 3B is a patient with LQT2 undergoing the same response. It can be observed in Fig. 3B*a* that some action potentials are skipped, and early after-depolarizations (EADs) are seen throughout. (See Fig. 3B*b* compared to Fig. 3A*b* for detail.) These changes are especially apparent close to the end of the response, when the heart rate is at its fastest.

Calcium channel blockers (CCBs) have been studied for their potential anti-arrhythmic properties in various LQT syndromes, including LQT2 [3]. The rationale behind this is that I_{Ca} plays a significant role in the duration of the action potential; therefore, if the calcium current can be reduced, this may allow for faster repolarization, and thus more stability in the coordination of action potentials [3]. To simulate this, the calcium dynamics that brought about the sympathetic surge were diminished. Other than that, a startle response was initiated in the same way.

Fig. 2 shows the normalizing effects of CCBs on the APD of a LQT2 patient, both at a baseline level and with a sympathetic surge. Fig. 3C shows these effects on a larger scale during the startle response. The incidence of EADs is greatly reduced, and it appears much more similar to the control (3A).

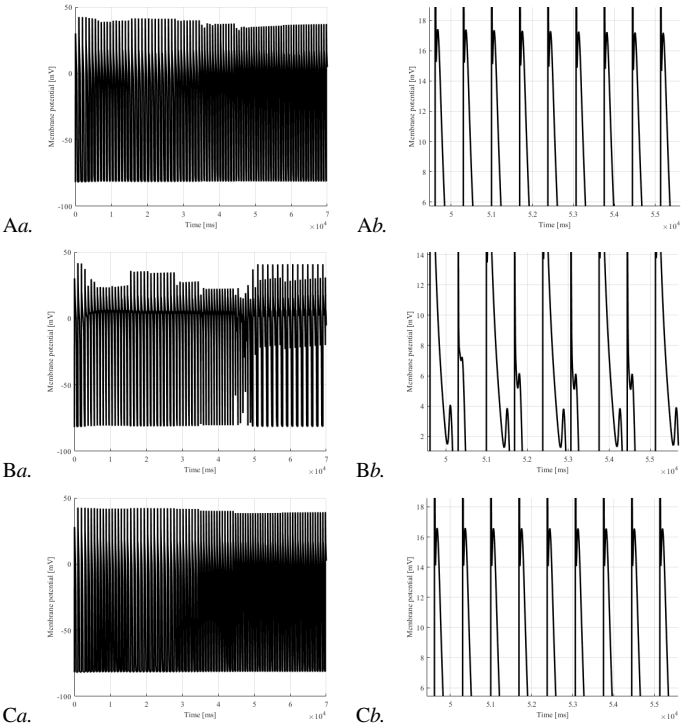

Fig. 3: Action potential traces of simulated startle response under three different conditions. Traces are over the course of 70 seconds, with a varying heart rate and sympathetic surge parameters. A*a*: Startle response of control cell. A*b*: Enlarged for clarity. B*a*: Startle response of cell with LQT2-induced I_{Kr} block. Action potentials are less dense, as some are skipped due to delayed repolarization. B*b*: Enlarged for clarity. Extra peaks represent early after-depolarizations (EADs), the abnormal electrical activity characteristic of LQT syndrome. C*a*: LQT2 startle response with calcium channel blockers applied. Traces appear nearly the same as A*a*. C*b*: Enlarged for clarity. EADs no longer present.

IV. Discussion

The results presented in this paper are representative of other simulation studies of potassium current blocks. In [16], Zeng and Rudy use the Luo–Rudy model [17] to simulate the effects of a potassium current block in tandem with various calcium parameters, and similar results were obtained. EADs of amplitude 3mV were precipitated in the presence of cesium (to block I_K) and increased $[Ca]_o$. The amplitude of EADs produced in our study is also 3 mV (Fig. 3B*b*). In addition, in the presence of an I_K block, a reduction of I_{Ca} produced a shortened APD, as well as fewer EADs. A similar outcome was demonstrated by the consequences of our CCB simulation. However, a much larger I_{Ca} block was needed in [16] to remove all EADs, whereas in our simulations, the I_{Ca} was still above baseline levels when EADs ceased.

A significant difference between [16] and this study is the magnitude of the prolonged action potential. In [16], the APD

was increased from 260 ms to 900 ms. This is upwards of a 300% increase. However, in the original paper by Grandi et al., the APD was increased by only 27% in response to a full I_{Kr} block [10]. This second result is more in line with our study, which showed an 8% increase with a partial I_K block. Accordingly, these differences can be attributed to the difference in models employed.

Detailed simulations of LQT syndromes such as the one in this study and others mentioned above offer significant advantages for patient care in clinical settings. The most noteworthy that we have shown is the capacity to observe different sets of conditions. Modelling the sudden sympathetic activity and the cardiac startle response in tandem with the LQT2 I_{Kr} block resulted in a dynamic and detailed visualization of the resulting arrhythmia that might not otherwise be seen on an ECG or other clinical tests because it is both difficult and dangerous to literally startle a patient thought to have LQT2. The combination of simulating baseline disease conditions with potential triggering events would be a valuable addition to the field of cardiology.

The other capability demonstrated in this study is the simulation of a drug therapy. This is an important aspect of cardiac simulations in clinical settings as well because it could allow for greater precision in treatment determination. Once the calcium channel blocker was applied, the EADs previously present in the startle response did not show up despite the continued block of I_{Kr}, pointing to the potential success of CCBs in the treatment of this form of LQT2.

V. Conclusion

In this study, we have demonstrated the benefits and feasibility of simulating LQT channelopathies, in particular, LQT2. Through the parametrization of an existing mathematical model, we modelled a sympathetic surge and heart rate pattern distinctive of the startle response as well as the effects of a therapeutic approach. The mechanisms underlying many cardiac arrhythmias are still not fully understood, nor are the best ways to treat them. Cardiac simulation models stand as a useful lens through which to view these questions.

Conflict of Interest

The authors declare that they have no conflict of interest.

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