Action Potential Alternans in LQT3 Syndrome: A Simulation Study

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Abstract—The long QT syndrome type-3 (LQT3) is an inherited cardiac disorder caused by mutations in the sodium channel gene SCN5A. LQT3 has been associated with ventricular arrhythmias and sudden cardiac death, specially at low heart rates. Based on computer simulations and experimental investigations, analysis of the morphology of the Action Potential (AP) has shown that it undergoes early afterdepolarizations (EADs) and spontaneous discharges, which are thought to be the trigger for reentry-like activity. However, dynamic characteristics of cardiac tissue are also important factors of arrhythmia mechanisms. In this work, we propose a dynamical analysis of the LQT3 at cellular level. We use a detailed Markovian model of the ΔKPQ mutation, which is associated with LQT3, and we study beat-to-beat AP Duration (APD) variations by using a long-term stimulation protocol. Compared to wild-type (WT) cells, ΔKPQ mutant cells are found to develop APD alternans over a narrow range of stimulation frequencies. Moreover, the interval of frequency dependence of APD alternans is related to the degree of severity of the EADs present in the AP. In conclusion, dynamical analysis of paced cells is a useful approach to understand the mechanisms of rate dependent arrhythmias.

I. INTRODUCTION

The long QT syndrome type-3 (LQT3) is an inherited cardiac disease characterized by a delayed ventricular repolarization that manifests as prolongation of the QT segment in the electrocardiogram (ECG). LQT3 has been associated with complex ventricular arrhythmias and ventricular fibrillation (VF), preferentially at low heart rates, during rest or sleep periods [1]. LQT3 is caused by mutations in the cardiac sodium channel gene SCN5A. Deletion of the amino acids KPQ (ΔKPQ) in SCN5A is one of the most severe mutations associated with the LQT3, as it disrupts the inactivation process [2]. Mutant channels continue to reopen at depolarized membrane potentials, hence inducing a small persistent inward current which prolongs the action potential duration (APD) and leads to a QT lengthening [2], [3]. Prolongation of the APD, as well as the presence of early afterdepolarizations (EADs) has been confirmed in in-vitro experiments in ΔKPQ transgenic mice [4], [5]. EADs are thought to be the trigger of cardiac arrhythmia in the settings of LQT3, however, the mechanisms by which they promote an arrhythmogenic behavior are not fully understood.

Complementary to in-vitro experiments, computer models have been also used to understand the mechanisms of cardiac arrhythmia in the LQT3 syndrome. Clancy and Rudy developed a cellular AP model of the ΔKPQ, by means of a Markovian description of the wild-type (WT) and ΔKPQ mutant (MT) channels [6]. Their results showed bradycardia-dependent delayed repolarization that may lead to EADs. Based on an analysis of the AP morphology, this model has been used to link genetic cardiac mutations to its cellular manifestation [7], [8], and to evaluate the effects of drug therapy to manage cardiac arrhythmias [9]. However, besides anomalies in the AP morphology due to EADs, abnormal beat-to-beat phenomena, like APD alternans, are important factors and predictors of cardiac arrhythmia [10]. Therefore, the aim of this study is to analyze with detail the beat-to-beat variations of the ΔKPQ-LQT3 model. We characterize dynamically both the WT and the ΔKPQ MT cells by a long-term stimulation protocol. Simulations show that MT cell exhibit APD alternans. Furthermore, these APD alternans are found at stimulation frequencies where intermittent EADs are present, thus generating unstable beat-to-beat AP changes.

In the following sections, we first introduce the computer model and simulation protocol. Secondly, we investigate the dynamic properties of the LQT3-ΔKPQ model and we present our main results. Thirdly, we discuss the principal findings. Finally, we summarize our results and propose future research.

II. METHODS

A. Single Cell Model

Single cell behavior was simulated by using the Luo-Rudy model (LRd) of the ventricular AP for the guinea pig [11]. The AP is reconstructed according to the following differential equation:

\[
\frac{dV_m}{dt} = - \frac{1}{C_m} \cdot (I_{ion} + I_{st})
\]

which relates the rate of change of the transmembrane potential \(V_m\) to the total ionic transmembrane currents \(I_{ion}\) and the stimulation current \(I_{st}\). \(C_m\) represents the membrane capacitance and is set to 1 \(\mu F/cm^2\). The LRd computes the AP from voltage-gated ionic channels, pumps, and exchangers. The model also accounts for processes that regulate intracellular concentration changes of sodium...
(Na\(^+\)), potassium (K\(^+\)), and calcium (Ca\(^{2+}\)) ions. All the ionic currents, except for the fast sodium current (\(I_{\text{Na}}\)), are formulated according to the Hodgkin-Huxley formalism. A detailed description of each current can be found in the original paper [11].

B. Markovian Model of the \(I_{\text{Na}}\)

The gating behavior of the sodium channel is represented as a continuous-time Markov model. This Markovian representation of the \(I_{\text{Na}}\) is integrated into the single cell model, yielding a computer model that simulates the \(\Delta\)KPQ mutation associated with the LQT3 syndrome (see [9] for more details). The \(\Delta\)KPQ-LQT3 model accounts for both WT and \(\Delta\)KPQ channels, so the total output macroscopic sodium current can be expressed as

\[
I_{\text{Na}} = \alpha \cdot I_{\text{Na-MT}} + (1 - \alpha) \cdot I_{\text{Na-WT}} \tag{2}
\]

where \(I_{\text{Na-MT}}\) is the current produced by MT channels, \(I_{\text{Na-WT}}\) the current produced by WT channels, and \(\alpha\) is the penetrance index, i.e. the proportion of WT and MT channels, in such a way that:

- \(\alpha = 0\) represents a WT cell;
- \(\alpha = 0.5\) represents a heterozygous cell;
- \(\alpha = 1\) represents a homozygous MT cell.

The accuracy of this model has been thoroughly tested and validated according to experimental data [6]–[9].

C. Simulation conditions

All simulations were performed on a desktop PC (3GHz, 2GB RAM), using C/C++. The integration time step was taken to be \(\Delta t = 0.005\) ms. The APD is defined as the interval between the AP upstroke and the repolarization potential of \(-70\) mV, which is approximately the APD at 90\% repolarization.

D. Stimulation protocol

In this paper, beat-to-beat APD variations are characterized by using a long-term stimulation protocol. Starting from an initial Basic Cycle Length (BCL) \(B_0\), both WT and \(\Delta\)KPQ cells are paced at decreasing BCLs (\(B\)). For each cycle length \(B\), cells are stimulated for 60 seconds. After that, \(B\) is decreased in \(\Delta\) ms, so \(B_{\text{new}} = B_{\text{old}} - \Delta\). The protocol is repeated until the minimum value of \(B\) for which an APD can be elicited for each given stimulus is attained. By means of this protocol, the temporal evolution of the APD can be obtained (Fig. 1). This is a useful representation, since it shows how the APD accommodates [12] in response to step decrements in \(B\). Abrupt changes in the APD result at time instants where decrements in \(B\) take place (vertical dotted lines). Then, as time goes by, the APD slowly reaches the steady-state, until another stimulation rate is used.

III. RESULTS

A. Stimulation protocol of the WT

Fig. 1 illustrates the results of applying the stimulation protocol to a WT cell. As the value of \(B\) was changed, the WT cell responded in a stable 1:1 manner. This response pattern corresponds to a normal behavior, in which APD variations from one beat to the other are negligible (for the same \(B\)).

B. Stimulation protocol of the MT

A very different behavior results when applying the stimulation protocol to a \(\Delta\)KPQ MT cell. The APD accommodation of a heterozygous cell (\(\alpha = 0.5\)) is plotted in Fig. 2 (a). As shown, for \(B = 800\) and \(700\) ms, the APD does not have a steady-state, rather it alternates between a discrete set of values. Thus, the APD oscillates from one of these values to the other on a beat-to-beat basis. An example of the beat-to-beat variation of the AP can be seen in Fig. 2 (b). Unstable EADs disrupt the balance between the APD and the preceding diastolic interval (DI). In consequence, the APD never reaches a steady state, giving rise to APD alternans. Pacing cycle intervals \(B\), for which no EADs (\(B = 600\) to 300 ms), or stable EADs (\(B = 1000\) and 900 ms) are present, do not show APD alternans (Fig. 3).

In a homozygous \(\Delta\)KPQ cell (\(\alpha = 1.0\)), APD alternans arises over a wider range of stimulation intervals when compared to a heterozygous cell (Fig. 4 (a)). In this case, there are no stable states until the 1:1 response returns at \(B = 300\) ms. It is also remarkable that the AP shows large EADs, thus indicating that the larger the EADs, the more unstable the APD.

We have found that the results presented above are not dependent on the values of \(B_0\) and \(\Delta\). Test values of \(B_0\) ranged between \(B_0 \pm 200\) ms of the original value (i.e \(B_0 = 1000\) for heterozygous cell). \(\Delta\) has been changed from small values (\(\Delta = 10\) ms), to larger values (\(\Delta = 500\) ms). Simultaneous variations of both \(B_0\) and \(\Delta\) also yielded similar results.

Fig. 1. Stimulation protocol for a WT cell. From a starting value of \(B_0 = 1000\) ms, cycle length was decreased until \(B = 300\) ms, with \(\Delta = 100\) ms. For each \(B\), the APD slowly reaches the steady-state (APD accommodation). Even if the APD seems not to reach a steady-state, longer stimulation periods -i.e. 120 s- has been studied showing that effectively it does.
IV. DISCUSSION

In the present study, we have analyzed the dynamic behavior of both WT and ΔKPQ cells, using a Markovian computer model of the ΔKPQ-LQT3 syndrome subjected to a long-term stimulation protocol. A picture of the time evolution of the APD identified APD alternans in MT cells over a narrow range of stimulation frequencies. This result may help to explain why patients with ΔKPQ mutation are likely to develop arrhythmias within different heart rate ranges compared with normals or other types of LQT syndrome [1]. More interestingly, APD alternans is also linked to T waves alternans [13], an ECG phenomenon associated with LQT syndrome that has been proposed as an important harbinger for ventricular arrhythmia [14]. On the other hand, presence of EADs is not a sufficient condition to generate alternans, as for very low stimulation intervals (i.e. $B > 900$ ms for a heterozygous cell) APs with stable EADs do not show APD alternans. However, in a narrow band of stimulation intervals, EADs generated in MT cells induce irregularities in the DI, leading to beat-to-beat irregularities in the APD. Further, as it was shown when comparing heterozygous and homozygous MT cells, large EADs produces irregularities (alternans) at the APD in wider range of stimulation frequencies.

V. CONCLUSIONS AND FUTURE WORK

Our simulations demonstrate that a dynamical analysis at the cellular level based on computer simulations is an useful approach to link molecular defects to mechanisms of rate dependent arrhythmias. We have also shown that potential mechanisms of LQT3 arrhythmias can not be attributed exclusively to EADs or APD alternans, but to a contribution of both factors. Future research should study the dynamic dependence between EADs and APD alternans. Extensions of the cellular model proposed here, to one-dimensional and two-dimensional ventricular tissue models,
would allow us to analyze further the mechanism of cardiac arrhythmia in terms of both EADs and spatially discordant APD alternans [15]. Finally, the predictions of this theoretical analysis based on computer simulations are readily testable in experiments using cardiac cells that express the ΔKPQ and other mutations that are relevant to the LQT syndrome.

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REFERENCES


