

A Novel Mathematical Model of the Electrical Action Potential in a Canine Purkinje Fiber Cell

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Abstract

*Purkinje fiber (PF) cells exhibit action potential (AP) morphology and duration markedly different to those of ventricle myocytes. In order to study heterogeneity at the Purkinje-ventricular junction (PVJ), we construct a new AP model for the canine PF cell based on detailed experimental data of ion channel characteristics obtained by voltage clamp techniques. Single-cell PF model is incorporated into a 1D transmural strand model, which is used to simulate the AP conduction through the PVJ under physiological and short QT syndrome (SQTS) conditions. Simulations produced the APD dispersion patterns and pseudo-ECGs consistent with experimental data under physiological conditions. Incorporating changes to the activation kinetics and time constants of the I_{Ks} channel associated with the *KCNQ1* gene mutation resulted in the shortened QT interval characteristic of SQTS.*

1. Introduction

The conduction network of the Purkinje fibers (PFs) plays an important role in ensuring the synchronized timing and sequencing of ventricular contraction. However, action potential (AP) morphology and duration of the PF cells are markedly different to those of ventricle myocytes (VMs), which may result in excitation conduction abnormalities and genesis of arrhythmias under certain pathological conditions. Primarily, the AP heterogeneity at the Purkinje-ventricular junction (PVJ) can contribute to the initiation of reentry [1] and triggered activity [2].

Existing AP models of the PF cell, such as the DiFrancesco-Noble model [3], were based on incomplete and outdated experimental datasets. The aim of this work is to construct a biophysically detailed AP model of the canine PF cell using recent experimental data, and to study implications of the AP heterogeneity between the PF cells and VMs under the short QT syndrome (SQTS) conditions caused by a mutation of the *KCNQ1* gene [4].

2. Methods

The dynamics of the membrane potential in a 1D cardiac tissue strand can be described by the nonlinear partial differential equation (PDE) [5, 6]:

$$\frac{\partial V}{\partial t} = D \frac{\partial^2 V}{\partial x^2} - \frac{I_{ion}}{C_m} \quad (1)$$

Here, V is the membrane potential, t is time, x is the spatial coordinate, D is the diffusion coefficient characterising the electrotonic cell-to-cell coupling by gap junctions, C_m is the cell membrane capacitance and I_{ion} is the total membrane ionic current.

Our single PF cell model is based a modification of the canine VM model of Benson et al. [6], which is itself a derivative of the Hund-Rudy model [7]. Ion channel conductance, steady state activation, inactivation and time constants for all currents in the major model [6] – I_{Na} , I_{NaL} , I_{CaL} , I_{K1} , I_{Kr} , I_{Ks} and I_{to} – were modified based on recent voltage clamp data [8]. Two pacemaking currents, I_{CaT} and I_f , present in PF cells but absent in VMs, were introduced and fitted to available experimental data. Simulations of the voltage clamp experiments [8] for major ionic currents are illustrated in Fig. 1.

The 1D multicellular strand model consisted of 0.25 cm PF and 0.25 cm ventricular segments, each of which was discretised by a spatial resolution of 0.1 mm, forming 25 PF cells and 25 VMs (8 endocardial, 9 midmyocardial and 9 epicardial). Equation (1) was solved using a finite-difference PDE solver that implemented the explicit Euler method with time and space steps $\Delta t = 0.005$ ms and $\Delta x = 0.1$ mm, respectively. The strand was stimulated with a current pulse at the start of the PF region ($x = 0$), resulting in AP propagation through the PVJ into the ventricular tissue. As conduction velocity in the PFs is higher than in the ventricle [9-12], values of the diffusion coefficient D were chosen non-uniformly through the strand to produce experimentally observed velocities of 1.8 m/s in the PF and 0.5 m/s in the ventricular tissue.

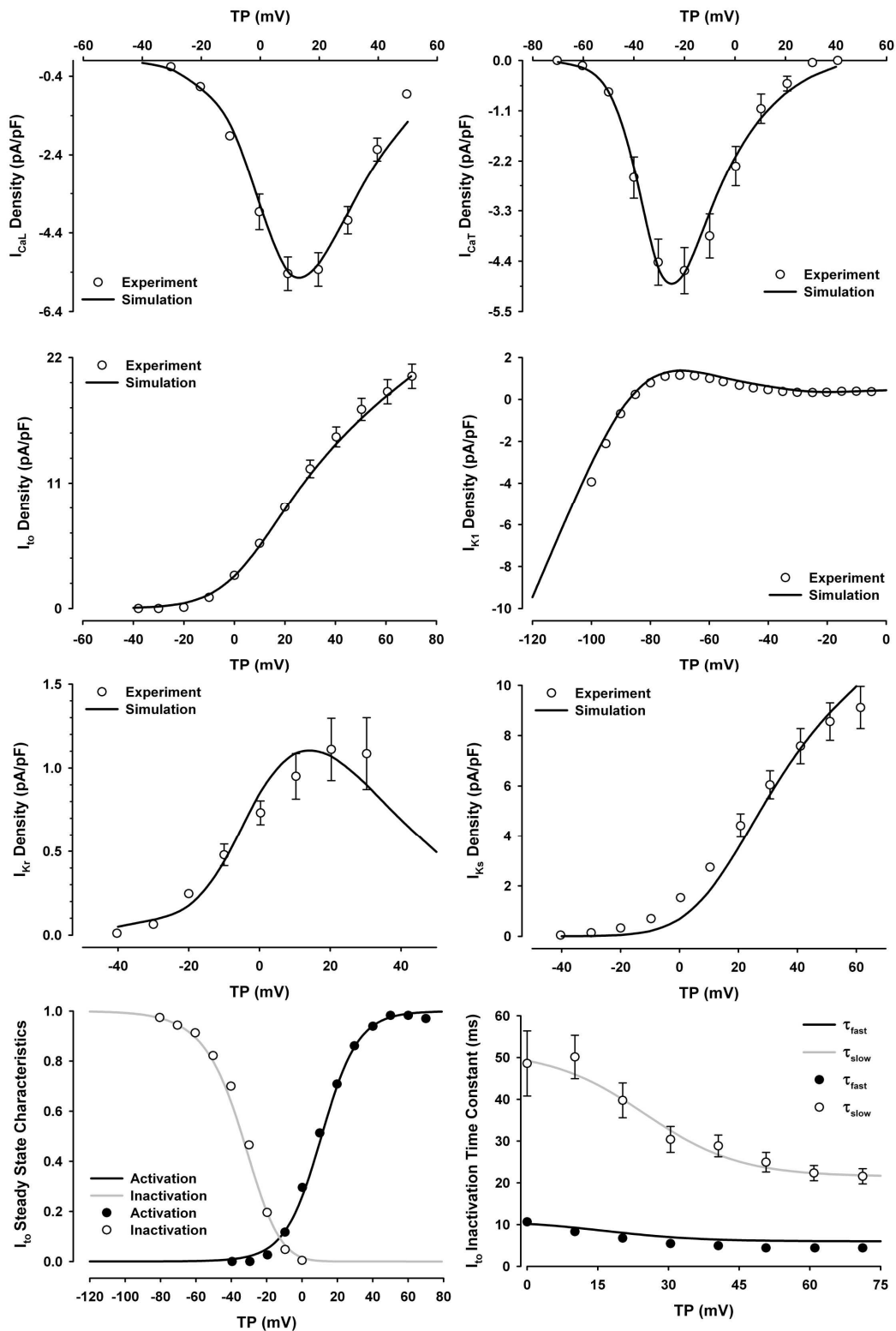


Figure 1. Fitting the PF cell model to the voltage clamp experimental data [8]. Ion channel current-voltage relationships (top 6 panels) are modelled by first fitting steady-state activation and inactivation curves (bottom, left) and time constants (bottom, right) to experimental data [8]. Here, I_{Io} is used as an illustrative example. TP is the voltage clamp test potential.

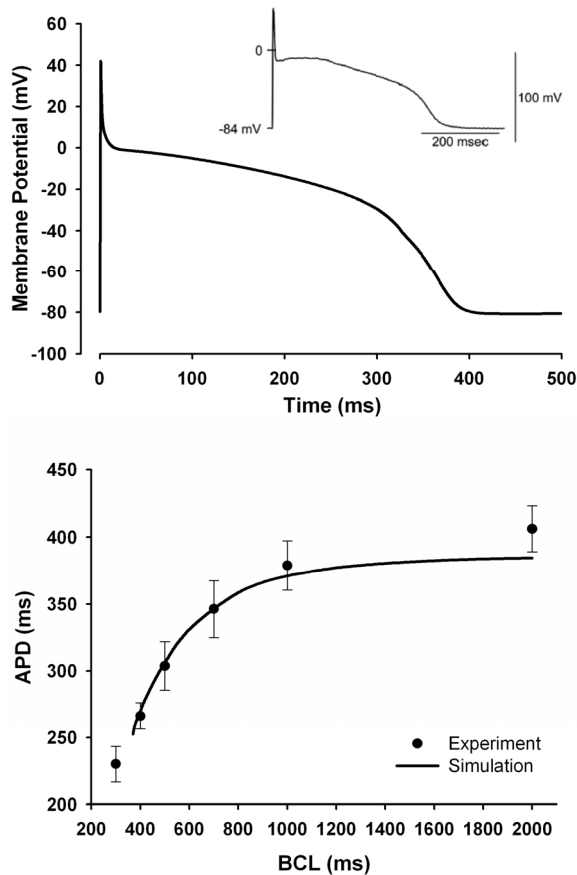


Figure 2. Simulated PF cell AP (top), as compared to the experimental recording (inset) [13]. The computed APD restitution curve (bottom), validated by experimental data [14].

3. Results

The AP produced by our PF cell model implementing the modified ion channel kinetics is shown in Fig. 2. The model reproduces the AP morphology and duration [13], with the action potential duration (APD) at 90% repolarisation of 371 ms (comparable to experimental data of 373 ms), and the plateau potential of about -10 mV (comparable to experimental data of -10 mV). Furthermore, the model reproduces experimental data [14] of the APD restitution at various basic cycle lengths (BCL), validating the model across the physiological range of pacing rates (Fig. 2).

The changes caused by the SQTS can be implemented into the model by modifying the kinetics of I_{Ks} – primarily, decreasing the slope of its steady-state activation by 8% and shifting it by -18.15 mV, as well as decreasing its time constant by 48% [4]. Fig. 3 shows the

APD abbreviation under the SQTS conditions – VMs are affected more than PF cells, with the APD shortened by 24% and 17% respectively.

Simulations of the 1D strand model resulted in feasible AP propagation patterns, the APD dispersions and pseudo-ECGs (Fig. 4). The SQTS conditions associated with the KCNQ1 mutation resulted in the QT interval shortening and increased T wave amplitude – two of the main characteristics of the short QT syndrome [4].

4. Discussion and conclusions

We have developed the first biophysically detailed mathematical model of the canine PF cell. Our model accurately reproduces the AP duration, morphology and restitution properties for the PF cells, as well as the AP conduction characteristics through the PVJ, and thus, provides a powerful tool for in silico investigation of the PVJ phenomena. Our 1D strand study of the SQTS demonstrates a causal link between the KCNQ1 mutation

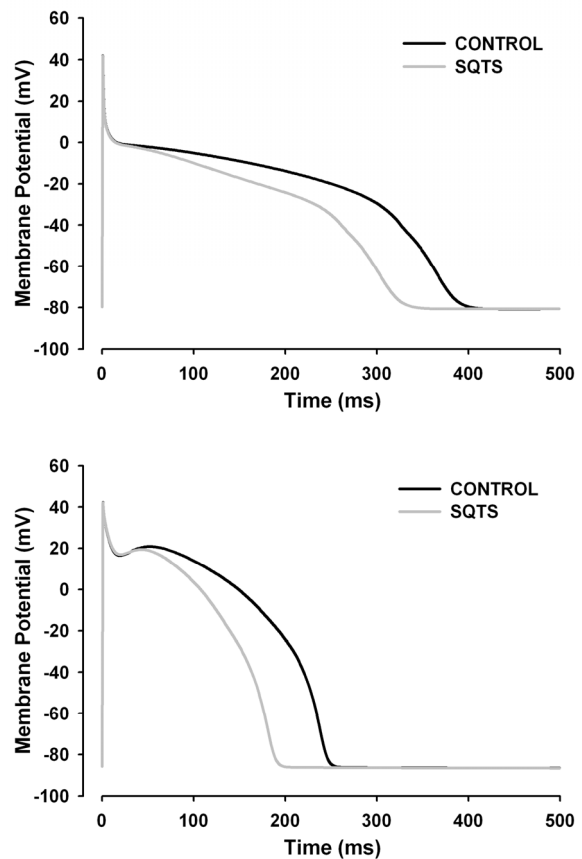


Figure 3. AP abbreviation in the PF cell (top) and VM (bottom) under the SQTS conditions.

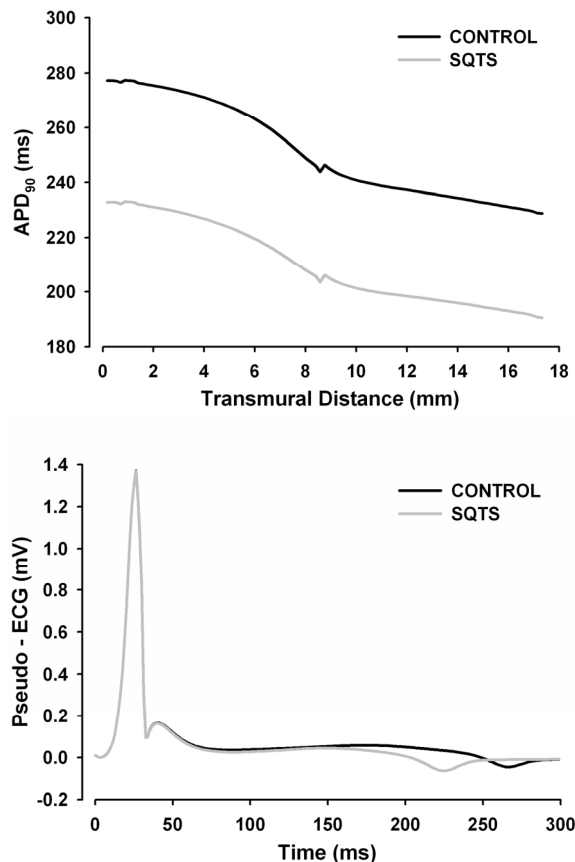


Figure 4. Simulated APD dispersions (top) and pseudo-ECGs (bottom) for control and the SQTs conditions.

and QT interval shortening due to changes in I_{Ks} . Further simulations with the 3D ventricular wedge models [6] are required to investigate whether changes at the PVJ under mutant conditions increases the risk of arrhythmia.

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