Available online at www.sciencedirect.com
ScienceDirect
Progress in Biophysics and Molecular Biology 96 (2008) 112–131
Progress in Biophysics & Molecular Biology
www.elsevier.com/locate/pbiomolbio

Original Article

Repolarisation and vulnerability to re-entry in the human heart with short QT syndrome arising from KCNQ1 mutation—A simulation study

Henggui Zhang[a,*], Sanjay Kharche[a], Arun V. Holden[c], Jules C. Hancox[b,**]

[a]*Biological Physics Group, School of Physics and Astronomy, The University of Manchester, Manchester M13 9PL, UK*
[b]*Department of Physiology and Cardiovascular Research Laboratories, School of Medical Sciences, University Walk, Bristol BS8 1TD, UK*
[c]*Institute of Membrane and Systems Biology, The University of Leeds, Leeds LS2 9JT, UK*

Available online 11 August 2007

Abstract

Idiopathic short QT syndrome (SQTS) is a recently identified, genetically heterogeneous condition characterised by abbreviated QT intervals and an increased susceptibility to arrhythmia and sudden death. This simulation study identifies mechanisms by which cellular electrophysiological changes in the SQT2 (slow delayed rectifier, I_{Ks}, -linked) SQTS variant increases arrhythmia risk. The channel kinetics of the V307L mutation of the KCNQ1 subunit of the I_{Ks} channel were incorporated into human ventricular action potential (AP) models and into 1D and 2D transmural tissue simulations. Incorporating the V307L mutation into simulations reproduced defining features of the SQTS: abbreviation of the QT interval, and increases in T wave amplitude and T_{peak}–T_{end} duration. In the single-cell model, the V307L mutation abbreviated ventricular cell AP duration at 90% repolarisation (APD_{90}) and increased the maximal transmural voltage heterogeneity (δV) during APs; this resulted in augmented transmural heterogeneity of APD_{90} and of the effective refractory period (ERP). In the *intact* tissue model, the vulnerable window for unidirectional conduction block was also increased. In 2D tissue the V307L mutation facilitated and maintained reentrant excitation. Thus, in SQT2 increases in transmural heterogeneity of APD, δV, ERP and an increased vulnerable window for unidirectional conduction block generate an electrical substrate favourable to reentrant arrhythmia.

Keywords: Arrhythmia; Death; Sudden; Ion channels; Fibrillation ventricular; Short QT syndrome

Contents

*Corresponding author. Tel.: +44 161 200 3966.
**Also author for correspondence. Tel.: +44 117 928 9028; fax: +44 117 928 8923.
E-mail addresses: henggui.zhang@manchester.ac.uk (H. Zhang), jules.hancox@bristol.ac.uk (J.C. Hancox).

0079-6107/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pbiomolbio.2007.07.020

1. Introduction

Disorders of ventricular repolarisation leading to QT interval prolongation have been the subject of intensive investigation and, in a number of cases, are linked to defects in cardiac potassium channel genes (Mitcheson and Sanguinetti, 1999; Keating and Sanguinetti, 2001; Kass and Moss, 2003). In contrast, relatively little is known about genetic disorders leading to QT interval shortening. However in recent years some patients have been identified with idiopathic shortening of the QT interval. The 'short QT syndrome' (SQTS) is characterised by shortening of the QT interval in the absence of structural heart disease and, in susceptible families, by a history of sudden cardiac death and arrhythmic events (Gussak et al., 2000; 2002; Gaita et al., 2003). Gussak et al. (2002) suggested that the idiopathic SQTS could involve defects to genes encoding ion channels carrying the rapid and slow delayed rectifier K^+ currents (I_{Kr} and I_{Ks} respectively), ATP-sensitive K^+ current $I_{K,ATP}$ or acetyl-choline activated K^+ current $I_{K,ACh}$.

Subsequently, three genetic variants of the SQTS have been identified, involving gain-in-function mutations to genes encoding different K^+ channel subunits. The SQT1 variant involves mutations to *hERG*, which encodes the α-subunit of the I_{Kr} channel (Brugada et al., 2004). The SQT2 variant has been associated with mutations in *KCNQ1,* the gene responsible for the (KCNQ1) α-subunit of the I_{Ks} channel (Bellocq et al., 2004; Hong et al., 2005). The SQT3 variant is associated with a defect to the KCNJ2 gene responsible for Kir2.1 (inwardly rectifying, I_{K1}) K^+ channels (Priori et al., 2005). Although the changes to I_{Kr}, I_{Ks} and I_{K1} observed with these mutations are anticipated to shorten action potential duration (APD) and, thereby, refractoriness (Brugada et al., 2004; Bellocq et al., 2004; Priori et al., 2005), the precise mechanism(s) leading to increased arrhythmic risk in the SQTS are not known. A recent experimental study has utilised a canine ventricular wedge model and the $I_{K,ATP}$ opener pinacidil to demonstrate heterogeneous APD shortening and increased susceptibility to polymorphic ventricular tachycardia with QT interval shortening (Extramiana and Antzelevitch, 2004). However, the resulting SQT phenotype, with T wave inversion, is distinct from that seen clinically (tall upright T waves) with SQT K^+ channel mutations (Extramiana and Antzelevitch, 2004). A second possible pro-arrhythmic substrate, suggested by Cordeiro et al. (2005) on the basis of action potential (AP) clamp experiments on SQT1 mutant hERG channels, is increased heterogeneity between ventricular and Purkinje fibre (PF) APs, which might underpin U-waves seen in some SQTS patients and which might increase vulnerability to extrasystoles.