The long QT syndrome (LQTS) is a cardiac disease characterised by prolonged ventricular repolarisation and high risk of malignant arrhythmias. LQTS is divided into two groups: inherited and acquired forms. A great number of exogenous factors can cause acquired LQTS, usually by acting on the same ion channels implicated in the inherited LQTS. These factors include non-cardiac and heart-targeted drugs. Abnormal prolonged repolarisation of the cardiac action potential can be revealed on the electrocardiogram as an abnormal prolongation of the QT interval and it is one of the mechanisms that predisposes to arrhythmias.

One of the channels involved in the control of the repolarisation phase is the human ether-a-go-go (HERG) channel. HERG gene encodes a voltage gated potassium channel that mediates the rapid component of the cardiac delayed rectifier designated as Ikr. Due to the voltage-dependent properties of the HERG channel, Ikr displays peak activity during the repolarisation phase of the action potential. Drugs belonging to different chemical classes and with different therapeutic indications are able to produce cardiotoxic effects by means of HERG channel inhibition. One of the non-cardiac drugs acting on HERG channels and producing ventricular arrhythmias is the widely used prokinetic agent cisapride. For a better understanding of the mechanisms underlying cardiotoxic effects of cisapride, our study proposes new voltage protocols that simulate the cardiac action potential in in vitro conditions. In this study we used COS7 cells transiently transfected with HERG cDNA, and the whole cell patch-clamp technique to investigate the rate dependent block of HERG channels by cisapride. Simplified simulated cardiac action potential (SCAP) waveforms at varying rates (45, 60, 120 and 180 SCAPs/min) have been used for in vitro simulations of normal and high rate heartbeats. All experiments were carried out at 37°C.

In the presence of a therapeutic concentration of cisapride (200nM) there is no apparent effect on the initial phase of the HERG channel activation, however a clear rate dependent block of HERG channel was observed. The percentage of HERG current blockade increased 2 fold when the rate of SCAPs rose from 45 to 180 SCAPs/min. Our results suggest that cisapride should be taken with caution by athletes and patients with tachycardia, LQTS or when simultaneous medication with drugs that enhance the HERG channel block is used.