Gender and Age Based Differences in Risk of Proarrhythmia by Dofetilide : A Computational Model Study

Rodolfo Gonzalez*, Julio Gomis-Tena, Alberto Corrias, Jose Maria Ferrero, Blanca Rodríguez and Javier Sáiz

i3bh, Universidad Politecnica de Valencia, Valencia, Spain

Male/female differences in cardiac electrophysiology have long been noted, but only in recent years has there been an increased awareness and appreciation of the influence of a patients sex on presentation of various cardiac arrhythmias. Women have higher resting heart rates than do men, but a longer rate-corrected QT (QTc) interval. However, young boys and girls have similar QTc. Many drugs associated with acquired long QT syndrome have a greater risk of inducing torsades de pointes (TdP) arrhythmia in women than in men. The aim of this study was to investigate the risk of proarrhythmia by dofetilide in gender and age based differences using action potential duration (APD) and dispersion of repolarization (DOR). Left ventricular epicardial, midmyocardial and endocardial action potentials were simulated using a modified Luo Rudy model. Sex, age and regional differences in current densities and voltage dependent parameters for ICaL, IKr, IKs, and Ito were incorporated into the model. A model of dofetilide was developed and included into a ventricular cell model. Dofetilide concentrations used were 30 and 100 nM. DOR was defined as the delay in final repolarization between shortest and longest action potential. Results shown that in all cell types, adult female cells had longer action potentials and a higher susceptibility to early afterdepolarizations (EAD) than adult male cells under control and drug induced conditions. On the other hand, young male cells had longer action potentials and higher susceptibility to EADs than young female cells under drug induced conditions. In conclusion, this study has demonstrated that gender and age based differences in ionic currents and drug induced action of dofetilide might explain in part the higher susceptibility of EADs and prevalence of TdP in adult females and the higher risk of cardiac events in males than females during childhood.