In Silico Prediction of Drug-induced Arrhythmogenic Events Through Tissue-level Simulations of Multichannel Pharmacology

Mengya Yuan[1,2], Pingan Zhao[1,2], Pan Li[1,2 #]

[1]Center for Public Health Informatics, Xinxiang Key Laboratory for Public Health Informatics, School of Public Health, Xinxiang Medical University, Henan, P.R.China
[2]Center for Biomedical Innovation, Yunmai Biomedical Research Institute, Henan, P.R.China
[#]Correspondence to: panli@xxmu.edu.cn

Drug-induced cardiotoxicity, e.g. potentially lethal torsades de pointes (TdP), has been a major concern since the early stage of novel drug development. In this study, we presented a one-dimensional (1D) tissue model of Purkinje-ventricular system (PVS) to predict drug-induced arrhythmogenic events using multichannel inhibition data. This 1D PVS tissue model is consisted of a group of electrically coupled cardiac cells, including Purkinje, endocardial, midcardial and epicardial cells. All drugs (68 in total) were applied at their effective free therapeutic plasma concentrations (EFTPC), and simulated according to their multichannel inhibition effects. Through tissue-level simulations across all physiological pacing rates (1~5Hz), we identified a wide range of drug-induced arrhythmogenic events (Fig 1) with the application of these drugs, including Purkinje-ventricular junction blockade, action potential (AP) prolongation, AP alternans, early afterdepolarization (EAD) and unidirectional conduction blockade. Our results suggested that tissue-level simulation of PVS may serve as a valuable tool to quantitatively predict drug-induced arrhythmogenic risks, and to provide mechanistic insights into these arrhythmogenic events.

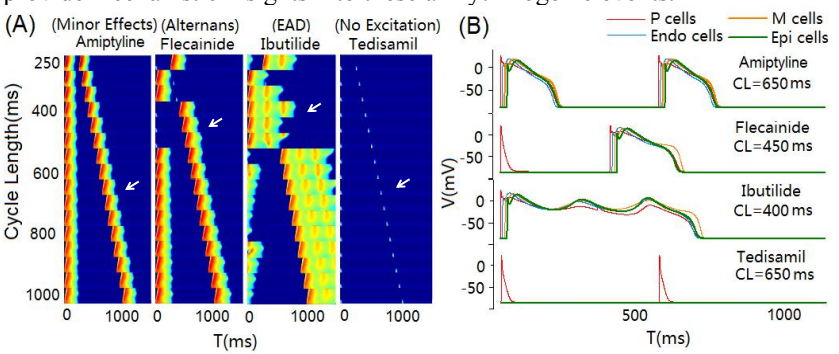

Fig 1 (A) in silico prediction of drug-induced tissue-level excitation patterns across all physiological pacing rates; (B) Drug effects on action potential morphologies of P-, Endo-, M-, Epi cells at different simulation conditions (white arrows in (A)).