

Electrotonic Coupling Effect on Pharmacological Cardiotoxicity Assessment in Atrial Tissue

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In the last decade, considerable efforts have been dedicated to change the cardiac proarrhythmia safety paradigm. In literature, several studies who shed light to the electrophysiological mechanisms, that stands behind the pharmacological cardiotoxicity, have been carried out by considering just isolated cells; the scope of this work is that of including in the analysis the electrotonic coupling, enabling the cells to mutually interact, aiming to assess how the risk of inducing potentially fatal arrhythmias could be affected.

To include variability in the model, atrial populations obtained from Courtemanche model have been generated by means of population of model technique, defining stable cardiac action potentials. They have been properly clusterized according to the most relevant atrial anatomical regions; among all the action potentials, a final population of 2989 left atrium action potentials has been randomly chosen to assess the pharmacological effect of 10 different drugs which have been identified as Pro-arrhythmic drugs, safe drugs and borderline drugs.

The simulations have been firstly on isolated cells and later on tissue preparations to consider the electrotonic coupling. A parallelepiped with fibers along the longitudinal direction was considered as the tissue model. Both cases have been conducted at a frequency of 1.25 Hz comprising 500 stimuli with a Basic Cycle Length of 800 ms. The assessment of torsadogenic risk has been quantified by a TdP risk score based on the presence of repolarization abnormalities i.e., presence of early after depolarization or excessive APD prolongation, or alternans for isolated cells model and tissue model. Results show that the electrotonic coupling related to the atrial tissue (The right panel) demonstrates that it decreases the torsadogenic risk.

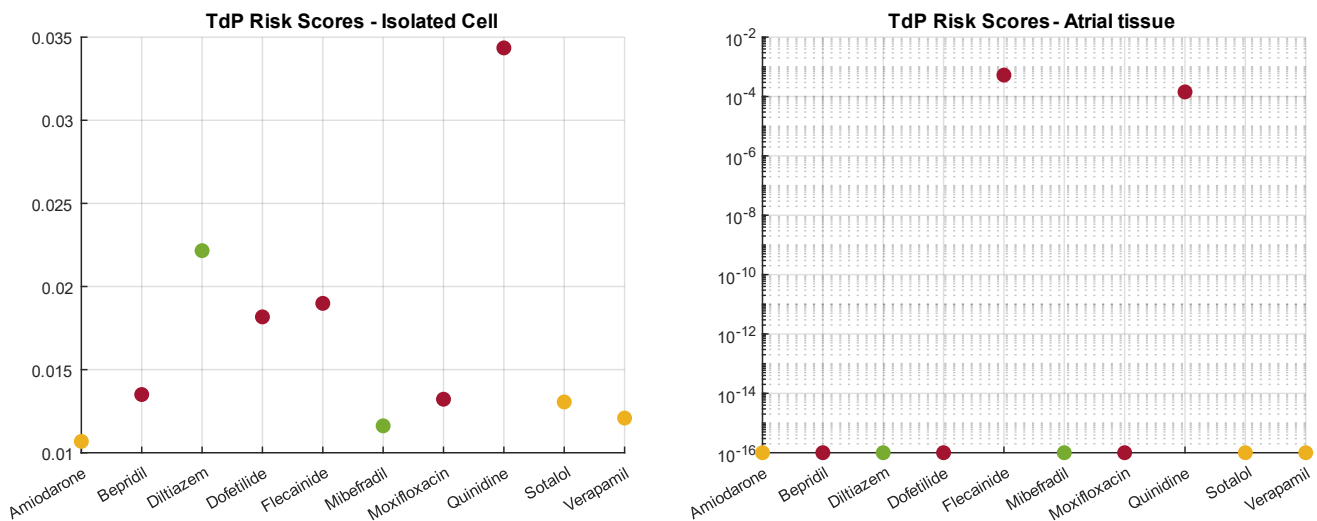


Figure 1 – Two TdP Risk Score plots have been reported. The first one is related to the isolated cell model, on the contrary the second one shows TdP Risk Score concerning the atrial tissue in which the electrotonic coupling is considered. The second plot is depicted in a logarithmic scale to better appreciate the level of torsadogenic risk. It can be seen how the electrotonic coupling lowers the torsadogenic risk associated to the drugs investigated in this study. The green color is related to the anti-arrhythmic drugs, the red one to pro-arrhythmic drugs and yellow to the borderline ones.