

Multiscale Modeling of Impulse Propagation in the Heart**Beaumont J., Bayer J., Chen M.****Upstate Medical University of the State University of New York at Syracuse, Syracuse, NY, USA**

Problem: To date it is well accepted that vortices of electrical waves are responsible for the most severe arrhythmias. Our modelling of vortex activity has enabled to: accurately reproduce experimental results, elucidate the origin of high frequencies (cycle length briefer than the refractory period) observed during lethal arrhythmias, explain their spatial distribution, and determine that contrary to current beliefs prolongation of the impulse duration through a block of the time-dependent potassium channels is not efficient to terminate vortex activity (Biophys. J. 75(1998), pp. 1-15). Instead repolarizing time-independent currents (Samie et al. Circ. Res. 89(2001) pp. 1216-1223) or currents activated early during the plateau (Samie et al. Circ. Res., 86(2000) pp. 684-691) have a much greater influence on vortex dynamics and may be better targets for antiarrhythmic drugs.

Models and Methods: From macroscopic simulations in realistic heart models we identify drug targets and specify how their bioelectric properties should be altered in order to terminate arrhythmias. With bioinformatics and molecular modelling techniques we find binding sites on the targets, ligands, and conditions which enable to alter current kinetics in a manner suitable to terminate arrhythmias.

Results: Recently we have developed a vortex dynamics model which clarify the role played by various membrane channels in the control of the frequency of rotation of vortices of electrical waves (Beaumont et al. Biophys. J. submitted). From the latter, we derive three mechanisms leading to the termination of vortex activity. They consist in a specific alteration of the membrane current kinetics of the: sodium, calcium and inward rectifier (I_{K1}) channels.

The I_{K1} is formed by heteromerization of three different isoforms (Kir2.1, Kir2.2, and Kir2.3). Each one is abundant in the heart and exhibits a different current voltage relation ($I(V)$). We have developed an homology model of each isoform which are stable in a cardiac membrane. Simulations show that polyamines, which is responsible for the rectification of $I(V)$ binds differently to each isoform.

While the findings are interesting and accurate up to some extent (experiment showed that ventricular fibrillation can in fact be terminated in the guinea pig by I_{K1} block, Warren et al. J. Cardiovasc. Electr., 14(2003) pp. 1-11), we here show that the situation is much more complex when considering heart geometry, and tissue microstructure. Vortices of electrical waves that normally drift in an uniform medium, stabilize in regions where fiber arrangements exhibit a radial configuration similar to the one encountered where papillary muscles and left ventricle or the septum merge. The opposite is also true, vortices that are stable at high frequency in an uniform medium may drift in arrangements that exhibit feather like patterns that are encountered in the free wall of the left ventricle. Similar finding holds for the geometry. Nonuniform curvature induce drift, and highly convoluted geometries can induce stabilization.

Conclusion: We have already made innovative and reliable predictions as to how to terminate ventricular fibrillation. Cardiac arrhythmia is multifactorial phenomenon, and integrative modelling may be the most efficient way to approach this problem.