TIME COURSE OF CARDIAC ELECTRICAL OSCILLATORY BEHAVIOR IN RESPONSE TO ENHANCED SYMPATHETIC ACTIVITY AND RELATION TO ARRHYTHMOGENESIS

D. A. Sampedro-Puente[1*], J. Fernandez-Bes[1], P. Taggart[3], E. Pueyo[1,2],

[1]*BSICoS, I3A, IIS Aragón, Zaragoza, Spain*
[2]*CIBER-BBN, Spain*
[3]*Dept. of Cardiovascular Sciences, University College, London, UK*

Background: Recent in vivo studies in patients have shown that cardiac electrical response exhibits a low-frequency oscillatory pattern following enhanced sympathetic activity, which has been related with arrhythmic risk. The mechanisms underlying such oscillatory pattern are explained by differential phosphorylation kinetics of IKs and ICaL currents upon beta-adrenergic stimulation as well as calcium cycling and the action of stretch-activated channels in response to mechanical stretch. The appearance of these oscillations in the cardiac action potential duration (APD) is, however, not immediate.

Objective: This work seeks to: 1) quantify the time lapse for APD oscillations to develop in response to sympathetic provocation; 2) ascertain the underlying mechanisms; 3) establish a link to arrhythmogenesis under disease conditions.

Methods: A representative set of physiologically feasible human ventricular AP models coupling electrophysiology, calcium dynamics, beta-adrenergic signaling and mechanics was built. Sympathetic provocation was modeled via phasic adrenergic and stretch actions. Disease conditions were simulated in association with reduced repolarization reserve and Ca2+ overload.

Results: In response to sudden sympathetic provocation, the mean time for low-frequency APD oscillations to develop was of around 4 minutes, due to slow phosphorylation of cellular substrates. This time lapse was significantly reduced provided adrenoceptors had already been stimulated to some extent. The key ionic factor determining the time for development of APD oscillatory behavior following sympathetic provocation was the very slow IKs phosphorylation kinetics as compared to other cellular substrates, causing APD transient response. Under diseased conditions, low-frequency APD oscillations following increased sympathetic activity developed notably earlier and, in some instances, early afterdepolarizations ensued.

Conclusions: Human cardiac cells present low-frequency electrical oscillatory behavior that develops in varying time lapses following sympathetic provocation. The major mechanism underlying the amount of time for oscillations to develop was identified and a link to occurrence of pro-arrhythmic events under diseased conditions was established.