Cellular Mechanisms of Triggered Arrhythmias: Insights from Multiscale Insilico Modeling

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In this talk, I will survey recent advances in computational modeling of life-threatening cardiac arrhythmias. I will focus particularly on progress made to understand the origin of "triggered activity" at the cellular level. Triggered activity can be manifested in the form of early afterdepolarizations, as in the setting of the long QT (LQT) syndrome, or delayed afterdepolarization (DADs) in the setting of catecholaminergic polymorphic ventricular tachycardia. EADs and DADs have been traditionally assumed to result from distinct instabilities of membrane voltage and Ca^{2+} cycling dynamics, respectively. I will present results that challenge this dogma by showing that altered Ca^{2+} cycling can also have a direct causal relationship on EAD formation in the setting of LQT. The results are obtained using a multi-scale in-silico virtual ventricular mycoyte Markov model that describes both the spatially distributed and stochastic nature of Ca^{2+} release as well as its effect on key Ca^{2+} sensitive membrane ionic currents. I will highlight how including those realistic features is key to understanding triggered activity beyond the limitations of traditional low dimensional "common pool" models of Ca^{2+} cycling.