JOHNS HOPKINS
BIOMEDICAL ENGINEERING

Monday, April 13, 2009, 1:00 PM Rome Room, Clark 110
(Homewood campus)
Light lunch will be provided at 12:15

"New Insights Into How Early Afterdepolarizations Cause Cardiac Arrhythmias"

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Hosted by Dr. Natalia Trayanova

Abstract In acquired and congenital long QT syndromes, reduced repolarization reserve predisposes the heart to early afterdepolarizations (EADs) and lethal ventricular arrhythmias. Although there is a strong association between EADs and ventricular arrhythmias, how EADs at the cellular level cause ventricular arrhythmias in well-coupled tissue is poorly understood. We combined experimental and modeling approaches to address this issue. Isolated patch-clamped rabbit ventricular myocytes exposed to H2O2 (0.2–1mM) for 5-15 min consistently developed EADs and triggered activity, which were suppressed by tetrodotoxin and nifedipine, as well as the CaMKII inhibitors KN-93 and AIP (2 μM), but not the inactive analog KN-92. In addition to inducing late INa (as reported previously), H2O2 also enhanced both peak and late ICa,L, consistent with CaMKII activation by oxidative stress. EADs occurred with each action potential (AP) at long pacing cycle lengths (PCL) >6s, were suppressed completely at short PCL <2s, but occurred irregularly at intermediate PCL 3-5 s. A deterministic rabbit ventricular AP model produced similar findings, indicating that irregular EAD behavior is dynamical chaos. In electrically homogeneous tissue models, chaotic EADs synchronized globally when the tissue was smaller than a critical size. However, when the tissue exceeded the critical size, electrotonic coupling could no longer globally synchronize EADs, resulting in regions of partial synchronization which shifted in time and space. This process created multiple "shifting" foci on successive beats resembling polymorphic ventricular tachycardia. Shifting foci encountering shifting repolarization gradients also resulted in localized wavebreaks leading to reentry and fibrillation. As predicted by the theory, rabbit hearts exposed to H2O2 exhibited multiple shifting foci causing polymorphic tachycardia and fibrillation. By generating propagating triggered activity and dispersion of refractoriness at slow heart rates, as observed clinically in long QT syndromes, this novel mechanism of chaos synchronization explains how collective cellular behavior integrates at the tissue scale to produce lethal cardiac arrhythmias.

Upcoming Seminars
April 20, 2009: Eric Grimson, MIT
April 27, 2009: Jason Burdick, UPenn
April 29, 2009: Betsy Nabel, NIH
May 11, 2009: Gaudenz Danuser, Scripps

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