Modeling Circadian Rhythmicity of Cardiac Arrhythmias

Casey Diekman
Department of Mathematical Sciences
New Jersey Institute of Technology

The cardiomyocyte circadian (~24-hour) clock influences multiple intracellular processes, including transcription and contractile function, and has recently been linked to ventricular arrhythmias in mice [1]. Circadian rhythms have also been observed in transient outward potassium current (I_{to}), a current that dominates mice action potential (AP) repolarization. We used mathematical modeling to study the dynamical mechanisms underlying secondary oscillations during the repolarization phase of the AP. These oscillations, called early afterdepolarizations (EADs), have significance because they are associated with heart failure and arrhythmias. It can be shown numerically and analytically that EADs arise from a Hopf bifurcation and that this can occur for certain ranges of the I_{to} conductance [2]. We investigated how variation of calcium and I_{Ks} potassium conductances affects the range over which EADs occur. This allows us to predict the role circadian regulation of currents other than I_{to} could play in cardiac activity. Finally, we compare our results on daily rhythms in EADs to existing data on the times of day that humans are most likely to suffer sudden cardiac death.

Simulations were performed on ARCS resources (Kong) using the software packages MATLAB, XPPAUT [3], and CHASTE [4].

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