A Novel Model of the Rabbit Atrial Myocyte for the Study of Ca\(^{2+}\) Mediated Arrhythmia

Maxx Holmes*, Alan P. Benson, Oleg V. Aslanidi, Michael A. Colman
University of Leeds, Leeds, United Kingdom

Atrial fibrillation (AF) and heart failure (HF) are two cardiac conditions with increasing incidence. Confounding the problem is that patients with HF frequently develop AF, and vice-versa. Dysfunction of the intracellular calcium (Ca\(^{2+}\)) handling system, which may involve remodeled channel expression and/or T-system morphological changes, has been conjectured to underlie both perturbed excitation-contraction coupling and an increase in arrhythmic events at the cellular scale; the role of T-system remodeling in the development of pro-arrhythmic cellular events such as spontaneous Ca\(^{2+}\) release and Ca\(^{2+}\) transient alternans remains unclear.

A contemporary model describing rabbit atrial electrophysiology (Aslanidi, et al., Biophys. J. 96(3):798-817, 2009) was integrated with our novel model describing stochastic spatio-temporal Ca\(^{2+}\) dynamics (Colman et al. PLOS Comp. Biol. 13, e1005714, 2017). Atrial T-system remodeling, associated with HF, was incorporated in isolation from other remodeling which may occur, through removal of the sarcolemmal ion-channel currents from individual CRUs, either assigned randomly or in pre-defined patches of varying sizes. Rapid pacing protocols were applied to induce Ca\(^{2+}\) transient alternans, and load the sarcoplasmic reticulum Ca\(^{2+}\) content.

The model reproduces rabbit atrial action potential and Ca\(^{2+}\) transient morphology associated with normal cardiac excitation. In isolation to other HF-related remodeling, variation in T-system density and organization showed an inverse correlation between density and susceptibility to two arrhythmogenic mechanisms: Ca\(^{2+}\) alternans and spontaneous release events; the former was determined by alternating successful and failed propagation of the Ca\(^{2+}\) into the regions without T-tubules; the latter was determined by an interaction of localized SR Ca\(^{2+}\) loading and reduced efflux, promoting successful Ca\(^{2+}\) wave propagation.

Conclusion: We have developed a novel model of rabbit atrial electrophysiology and Ca\(^{2+}\) handling. T-system remodeling in our atrial cell model suggests alterations to T-system morphology may play a role in the initiation and maintenance of AF in the presence of HF.