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

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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.