Multi-Scale Systems Models of Murine Heart Failure

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Alterations in myocyte neurohumoral regulation, ion currents, calcium (Ca^{2+}) handling, and contractility, accompanied by ventricular hypertrophy and structural remodeling all contribute to heart failure. Understanding the interactions of these complex biochemical and biophysical functions requires quantitative systems models that also integrate over multiple physical scales. Well-characterized and readily perturbed experimental systems are needed to validate computational models. Ca^{2+}-calmodulin dependent protein kinase (CaMKII) is upregulated and more active in heart failure, and is a key regulator of cellular subsystems contributing to acute mechanical and electrical dysfunction as well as chronic cardiac remodeling in heart failure. CaMKII overexpression leads to heart failure in mice, while CaMKII knockout or inhibition can protect against failure. We are using a closely integrated combination of novel experimental and computational studies to test the overall hypothesis that Ca^{2+}-CaMKII signaling controls multiple multi-scale processes that synergize in maladaptive electrophysiological, Ca^{2+} handling, contractile and hypertrophic remodeling leading to heart failure. Here we summarize selected progress to date including: (1) We have developed a new model of excitation-contraction coupling in the murine ventricular myocyte that integrates the CaMKII and PKA signaling pathways [1]. The model was validated against the experimentally observed frequency response of Ca dynamics, $[Na]_i$, AP shape, dependence of AP duration on cycle length. (2) We have now merged the Soltis-Saucerman [2] model with PKA/CAMKII crosstalk pathways with the Grandi-Bers ionic model. We are also now adding HF changes into this model (all from human data), so that we will have a fairly comprehensive model of human HF with key pathways. (3) Cardiac-specific CaMKIIδC transgenic mice (TG) and WT littermates were studied at 8-9 weeks of age to determine whether CaMKII-overexpression promotes electrophysiologic instability prior to overt HF [3,4]. Unlike in established for HF, superimposing βAR stimulation upon CaMKIIδC overexpression elicited early afterdepolarizations (EADs) without delayed afterdepolarizations (DADs) and spontaneous SR Ca^{2+} release. The myocyte model recapitulated the observed AP prolongation and EAD genesis, but only when CaMKII- and PKA-mediated effects were combined. *In-silico* EADs were sensitive to computational ablation of SR calcium release, or CaMKII-mediated induction of $I_{Na,L}$. (4) We have made some preliminary progress in modeling β-adrenergic regulation of cardiac thin filament dynamics based on a Markov model of cardiac thin filament activation. The new model has been developed to account for increased Ca^{2+} dissociation rate from cardiac troponin C due to phosphorylated N-terminal extension (NE) of cardiac troponin I (cTnI) and for accelerated crossbridge kinetics by phosphorylation of cardiac myosin binding protein C.

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