ABSTRACT FORM DEADLINE: December 15, 2021

Association of University Cardiologists
January 19-21, 2022
Belmond Charleston Place
Charleston, SC

Dysregulation of Ca^{2+} Homeostasis in Hypertrophic Cardiomyopathy

Jil C. Tardiff, M.D., PhD
University of Arizona

Hypertrophic Cardiomyopathy (HCM) is the most common genetic cardiomyopathy, and its clinical manifestations are near protean, vastly complicating clinical management and the development of new therapeutics. One of the few common findings is varying degrees of impairment of cardiac relaxation, though the etiologies are likely complex, given that symptoms are not always directly related to the degree of LV hypertrophy, an observation that suggests a primary myocellular mechanism. Moreover, decreased ventricular compliance contributes to an increase in LV filling pressures that can promote adverse left atrial remodeling and increases the risk of atrial fibrillation and stroke, poor prognostic indicators in patients with HCM. Our group focuses on the structure, biology and pathobiology of the cardiac thin filament (CTF). Given the primary role of the CTF as the transducer of oscillatory myocellular [Ca^{2+}] into mechanical work (sarcomeric contraction), our primary hypothesis is that HCM-linked CTF mutations disrupt the kinetics of Ca^{2+} association and dissociation at the myofibrillar Ca^{2+} "axis" and lead to complex downstream alterations in Ca^{2+} signaling that contribute to progressive pathogenic remodeling and eventually impaired relaxation in HCM. We have developed an integrated *in silico – in vitro – in vivo* approach that facilitates coupling between molecular level biophysical mechanisms and whole heart function via transgenic mouse models. Building on our original myocyte-level observations that revealed mutation-specific differences in Ca^{2+} homeostasis in CTF mutant mice and a potential nodal role for CaMKIIδ (the latter recently validated in human samples), more recently we have focused on using our all-atom computational model of the CTF to predict the mechanisms whereby mutation-specific allosteric modulation of Ca^{2+} association and dissociation kinetics at Site II of cTnC potentially alters the local [Ca^{2+}] domain, leading to the auto-activation of CaMKIIδ. We propose that this modulation is regulated by a mutation-driven disruption of the physical orientation of the N- terminus of cTnI that physically alters the efficiency of Ca^{2+} association/release from cTnC Site II. Of note, this region of cTnI contains the PKA-mediated substrate site that coupled CTF function to beta-adrenergic signaling. The complexity of this proposed mechanism likely contributes to the phenotypic variability observed in patients and provides a potential target for therapeutic modulation that may have broader applicability.

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Jul C. Tardif MD PhD

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