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Title: Heart failure related hyper-phosphorylation in the cardiac troponin I C-terminus has divergent effects on cardiac function in vivo

Clinical Perspective

Heart failure (HF) is associated with many adaptations in cardiac myocytes. Several laboratories noted altered phosphorylation of the sarcomere protein cardiac troponin I (cTnI) in HF. A recent quantitative proteomics study by the labs of Anne Murphy and Jennifer Van Eyk measured the changes in phosphorylation of known and newly identified cTnI phosphorylation sites in human failing hearts. Remarkably, one of the newly identified phosphorylation sites, cTnI Serine 199 (Ser199) had 2-fold more phosphorylation in HF compared to controls. Phosphorylation at Ser199 was also present in a model of dyssynchronous HF, and restored to normal with resynchronization. How increased phosphorylation of the newly identified site affects cardiac function was unknown. This study reports the *in vivo* cardiac impact of the pseudo-phosphorylation of Ser199 of cTnI. The study reveals that cardiac-specific expression of cTnI Ser200Asp in mice (equivalent to human Ser199), a phospho-mimic, is sufficient to depress diastolic but not systolic function at baseline with diminished systolic reserve under chronotropic and catecholamine stimulation. These findings resemble physiologic changes in human HF, in particular features of HF with preserved ejection fraction. In essence, the results indicate that excessive phosphorylation on human cTnI Ser199 reduces heart function likely through increased sensitivity to Ca^{2+} in the myocardial contractile apparatus and impact on the nuanced interactions between sarcomere proteins on the thin filament. The study provides new functional insights into the post-translational regulation of cTnI and the role of a post-translational modification observed in human HF might have impact in patients.