THE EFFECT OF TROPONIN I PHOSPHORYLATION ON THE STEEPNESS OF THE FRANK-STARLING RELATIONSHIP

Timothy Cornell

Dr. Kerry McDonald, Thesis Advisor

ABSTRACT

Heart failure begins with a reduction in the contractile strength of the cardiac myocytes (systolic dysfunction.) Cardiac myofibrils compensate via sympathetic activation to maintain adequate cardiac output. Beta-adrenergic stimulation has long been known as a cardiac inotropic agent, whereby it increases ventricular contractility yielding greater stroke volume (and more power output) for a given end diastolic volume, commonly known as the Frank-Starling Relationship. The purpose of this study was to investigate a potential molecular mechanism by which cardiac myofilaments augment ventricular contractility. Recent work in our laboratory has shown that PKA-mediated phosphorylation of cardiac myofilaments steepens the sarcomere length tension relationship, and it appears that phosphorylation of cTnI was both necessary and sufficient to mediate this biophysical response. The goal of this study was to investigate whether these biophysical/biochemical results translate to the organ (heart) level. The hypothesis was tested that the steepness of the left ventricular power-preload relationship would correlate with the phosphate content of cTnI. This was tested by direct comparison of cTnI phosphate content and ventricular function curves of the same isolated rat heart. The finding that these two parameters were highly correlated suggests that shifts in length-tension relationships at the myofilament level by covalent modulation of cTnI translate to ventricular function and may be a key molecular mechanism underlying the steepness of the Frank-Starling relationship.