THICK FILAMENT REGULATION OF MYOCARDIAL CONTRACTION

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ABSTRACT

The ability of the heart to function as a pump is governed by mechanisms intrinsic to individual cardiac myocytes. The experiments in this dissertation were designed to examine the effects of sarcomere length and thick filament protein isoform expression on the contractile properties of single skinned cardiac myocytes. Myosin binding protein-C ablation (MyBP-C$^{-/-}$) increases the rate of force development, loaded shortening velocity, and power output in mouse skinned cardiac myocytes, implying that MyBP-C regulates myocardial contractility by limiting crossbridge cycling. We also examined the effects of SL on mechanical properties in rat skinned cardiac myocytes containing either α-MyHC or β-MyHC. Peak absolute and normalized loaded shortening velocity and power output was decreased at short SL in both α-MyHC and β-MyHC myocytes. Matching myocyte force between long and short SL, however, sped loaded shortening velocity and increased power output in α-MyHC myocytes to values greater than at long SL, but this did not occur in β-MyHC. Matching myocyte width between long and short SL sped loaded shortening velocity and increased power output to values greater than at long SL in both α-MyHC and β-MyHC myocytes. It is concluded that there is an increase in crossbridge cycling at short SL as compared to long SL, but increased lattice spacing at short SL decreases actomyosin interactions. The data are presented in terms of a model whereby shortening SL induces a conformational change in MyBP-C that removes its constraint on the myosin heads, allowing them to cycle faster.