

EFFECTS OF ISCHEMIC METABOLITES AND CHRONIC EXERCISE ON CARDIAC MYOCYTE POWER OUTPUT

Aaron Curtis Hinken

Dr. Kerry S. McDonald, Dissertation Supervisor

ABSTRACT

During times of low blood flow (ischemia), concentrations of wastes increase in tissues, which can lead to decreased striated muscle contractile function. Acute cardiac contractile dysfunction during ischemia is likely mediated by build-up of inorganic phosphate (P_i) and protons (i.e., decreased pH). The focus of this dissertation is examination of the myofibrillar mechanisms by which ischemic metabolites alter the work capacity of cardiac myocytes, which ultimately comprise ventricular pump function. In addition, contractile properties and changes thereto with metabolite concentration were investigated in myocytes expressing either of the two isoforms of myosin heavy chain (α -MyHC and β -MyHC), that show altered expression in response to chronic ischemia. Studies demonstrated differential response to metabolites with P_i and H^+ alone and together decreasing power generating capacity of α -MyHC while only in combination did they diminish β -MyHC myocyte power. The greater tolerance toward ischemic conditions in β -MyHC myocytes was attributed to a P_i and H^+ induced increase in the velocity of loaded shortening. In contrast to ischemia, changes following exercise training are thought to improve cardiac function. A pig model of exercise training was examined to determine if changes intrinsic to the myofilaments were partially responsible for changes in global cardiac function. Increased peak power generating capacity was observed in myocytes from exercise trained animals as compared to sedentary controls, which coincided with an increase in PKA-induced phosphorylation of myofibrillar proteins. Overall, these results provide evidence for myofibrillar mechanisms that, in part, underlie changes in myocardial performance associated with acute and chronic ventricular stress.