Cardiac ischemic stress: Ca^{2+} and sex scenarios

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Important sex differences exist in cardiovascular heart disease, and much of this differential is cardiac specific. Pre-menopausal women are protected from ischemic heart disease compared with age-matched men, but prevalence increases steadily post-menopause. There is growing awareness of the extent to which cardiac function can be influenced by sex and sex hormones, however the fundamental mechanisms responsible for these sex differences are not well understood. Female and male cardiomyocytes exhibit markedly different calcium (Ca^{2+}) handling characteristics which reflect the influences of endogenous levels of sex steroids on myocyte Ca^{2+} transport mechanisms. Experimental studies show that, compared with males, female myocytes operate on a relatively low Ca^{2+} cycling load, with Ca^{2+} entry through L-type channels reduced and sarcoplasmic reticulum Ca^{2+} cycling downregulated. Overall, diastolic and systolic Ca^{2+} operational levels are higher in male myocytes – with endogenous estrogen and testosterone playing reciprocal regulatory roles in maintaining this difference. Ca^{2+} is a major causative factor in many of the pathologies associated with ischemia/reperfusion, including arrhythmogenesis, contractile dysfunction and multiple forms of cardiomyocyte death. Ca^{2+} overload triggers hypercontracture and activates calpain, leading to sarcolemmal rupture and a loss of cell integrity. It also promotes mitochondrial Ca^{2+} loading, causing the mitochondrial permeability transition pore to open. Subsequent mitochondrial swelling leads to cytochrome c release and caspase-mediated apoptosis. With more severe ischemic insults, an uncoupling of the mitochondria depletes ATP levels and necrotic injury occurs. Evidence suggests Ca^{2+} also triggers autophagy, though whether this is responsible for ischemia-induced autophagy is yet to be resolved. Limiting Ca^{2+} loading in ischemia/reperfusion substantially improves post-ischemic outcomes. The extent of Ca^{2+} overload is partly mediated by the actions of Ca^{2+}/calmodulin-dependent protein kinase (CaMKII). Responsive to fluctuations in Ca^{2+}, CaMKII functionally modulates many ion channels and transporters within the cardiomyocyte. Hence, an initial rise in Ca^{2+} levels during ischemia activates CaMKII, augmenting Ca^{2+} entry and increasing intracellular Ca^{2+}. Male only studies have shown that inhibiting CaMKII during ischemia/reperfusion reduces Ca^{2+} overload and attenuates apoptotic and necrotic cardiomyocyte death. We hypothesized that the lower operational levels of Ca^{2+} in female cardiomyocytes may limit the influence of CaMKII in ischemia/reperfusion injury and mediate the cardioprotection afforded to female hearts. We have recently shown CaMKII-mediated injury in simulated ischemia/reperfusion is attenuated in female myocytes. CaMKII inhibition (KN93) markedly enhanced male myocyte survival after a simulated ischemic event, but had only marginal effects on the more resilient female myocytes. Further studies will discern the fundamental mechanisms of this sex differential and how it may be modulated in complex disease settings (cardiac hypertrophy, diabetes).