Sex steroid balance plays a role in ischemic vulnerability

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Ischemic heart disease is the leading cause of death for men and women in Australia, though the characteristics/prognoses of an ischemic event differ between sexes. Much of this differential is cardiac specific, however, the fundamental mechanisms responsible for these sex differences are not well understood. The heart expresses androgen and estrogen receptors, which mediate both genomic and non-genomic actions on the cardiomyocyte, and there is growing awareness of the extent to which cardiac function can be influenced by sex and sex hormones. 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. 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. Estrogen levels are dependent on the availability of testosterone, which is converted into estrogen through the actions of the cytochrome P450 enzyme, aromatase. We have recently shown that aromatase is expressed in the adult heart, supporting the notion of a local androgen-estrogen system, analogous to the well-established intracardiac renin-angiotensin system. Inotropic actions of sex steroids are supported by our studies in the aromatase transgenic overexpression mouse heart (Arom+; high systemic estrogen, low testosterone). Basal contractile function was lower in male AROM+ hearts *vs* wild-type controls, though to what extent this is related to changes in underlying cardiomyocyte Ca^{2+} handling has yet to be investigated. Interestingly, 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, and the influence of sex and sex steroids on acute ischemia/reperfusion injury have been studied in detail.

Experimental manipulation of systemic sex steroids has led to a conventional viewpoint that estrogen is cardioprotective and testosterone a liability, though there is increasing evidence challenging this pre-conception. We have shown improved post-ischemic recovery in female aromatase knockout mouse (AromKO; low systemic estrogen, high testosterone) hearts, contrasting with a poor recovery in male Arom+ hearts. This indicates testosterone may have beneficial actions in ischemia/repefusion and that striking the right balance between estrogenic myocyte salvage and androgenic inotropic support is key to determining post-ischemic outcomes. Further studies are required to fully elucidate the mechanisms responsible for these actions, though cardiomyocyte Ca^{2+} management in ischemia/repefusion is undoubtedly involved. We have focused on the contribution of Ca^{2+}/calmodulin dependent kinase II (CaMKII) to ischemia/repefusion pathologies, particularly reperfusion arrhythmias, and how this may differ in males and females. Responsive to fluctuations in cytosolic Ca^{2+}, CaMKII phosphorylates and upregulates numerous ion channels known to exacerbate myocyte Ca^{2+} loading in ischemia/reperfusion. We were the first to show that CaMKII inhibition substantially reduces the incidence of lethal arrhythmias in reperfusion (male only model). However, contrary to our hypothesis, CaMKII recruitment in female hearts subjected to ischemia/reperfusion was augmented (*vs* males), despite substantially less arrhythmias in the females.

Our subsequent studies have determined that differential post-translational modifications of CaMKII may influence its arrhythmogenic properties, and that the female heart may be protected from reperfusion arrhythmias by a particular susceptibility to autophosphorylation of the putatively cardioprotective CaMKIIdB splice variant. Further studies are required to discern how this is influenced by sex steroids and complex disease settings (cardiac hypertrophy, diabetes).