Cardiac adipose, aromatase and arrhythmia vulnerability

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For both sexes, cardiovascular disease is the leading cause of death and disability. Observational studies of the sex demographics of cardiovascular disease have supported the conventional view of estrogen ‘protection’ (inference testosterone ‘liability’). Clinical trial outcomes have not demonstrated definitive benefit of estrogen supplementation in women – instead the findings of the Women’s Health Initiative trial, which began reporting over 10 years ago provided qualified evidence of increased risk for some women. It is clear that sex steroids can exert both protective and adverse actions depending on context. It is also clear that sex steroids are implicated in disease causation - but how, when and where? Levels of estrogen and testosterone are reciprocally regulated by the P450 enzyme, aromatase (CYP19a1), which synthesizes estrogens from androgen precursors. Aromatase is known to be expressed in non-gonadal tissues – including adipose, brain and placenta. Wherever it is expressed, aromatase utilizes available androgen substrate to synthesize estrogens and this conversion shifts the local testosterone-estrogen balance. We have previously reported aromatase expression in the mouse heart and demonstrated that aromatase transgenic and knockout animals exhibit cardiac sex specific phenotypes. Our studies showed that altered aromatase expression produces sex-specific arrhythmogenic and cardiomyocyte functional impacts. Building on these findings, our goal now is to demonstrate that the modulation of local cardiac sex steroid levels, through aromatase action, plays an important role in cardiac disease etiology though the regulation of myocardial viability and electromechanical function.