Aromatase expression in human/rat myocardium and pericardial adipose – a potential mechanistic link between obesity and myocardial disease onset?

J.R. Bell,[1] G.B. Bernasochi,[1] W.T.K. Ip,[1] W.C. Boon,[2] S. Pepe,[3] S.B. Harrap[1] and L.M.D. Delbridge,[1]
[1]Department of Physiology, University of Melbourne, Parkville, VIC 3010, Australia, [2]The Florey Institute of Neuroscience University of Melbourne, Parkville, VIC 3010, Australia and [3]Murdoch Children's Research Institute, Department of Paediatrics, University of Melbourne, Parkville, VIC 3010, Australia.

Sex steroids are crucially implicated in cardiac disease development. Fundamental effects of sex and sex steroids on cardiac structure and function are evident, yet understanding of the pathophysiology of sex steroid involvement in cardiac disease and the identification of targets for potential therapeutic intervention has not been resolved. 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 subcutaneous 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 demonstrated aromatase expression in the mouse heart and shown that genetic aromatase disruption/overexpression alters post-ischemic functional outcomes. There is emerging evidence that pericardial adipose depots can exert important paracrine actions on the heart. Indeed, increased myocardial fat infiltration may increase the propensity for atrial fibrillation in obesity by an unknown mechanism. The aim of this study was to identify aromatase expression in both the myocardium and pericardial adipose, and to thus provide evidence of a potential role for pericardial fat-derived aromatase in regulating local cardiac sex steroid balance and arrhythmia propensity.

Human tissue samples were obtained from coronary artery bypass patients (all patients were consented and specimens collected in accordance with study protocols approved by the Alfred Hospital Human Research Ethics Committee for Discarded Tissue, Alfred Hospital, Melbourne). In parallel studies, heart and pericardial fat were excised from anaesthetized male/female Sprague Dawley (SpD) rats, and from Hypertrophic Heart Rats (HHR) and control Normal Heart Rats (NHR). Samples were homogenized and analysed for aromatase expression by Western immunoblotting. Aromatase was detected in both human and rat myocardium and pericardial adipose. In SpD rats, aromatase expression was greater in female myocardium (female *vs* male, arb. units; 1.30 *vs* 0.97, n=5, $P<0.05$) and pericardial adipose (1.68 *vs* 0.75, n=6, $P<0.05$), compared with male counterparts. In both male and female rats, aromatase levels were approximately 30-fold greater at 50wks (aged) *vs* 8wk young adult controls (50wk *vs* 8wk, arb. units; female 2.139 *vs* 0.044, n=8-9, $P<0.05$; male 1.022 *vs* 0.033, n=8-9, $P<0.05$). Furthermore, aromatase levels at 8wks were approximately half of that observed in neonatal (p2) rats (8wk *vs* p2; arb. units; female 0.040 *vs* 0.115, n=8-9, $P<0.05$; male 0.033 *vs* 0.085, n=8-9, $P<0.05$). In a setting of pathological hypertrophy, only female hearts (HHR) exhibited a significantly lower levels of aromatase (HHR *vs* NHR, arb. units; female 1.158 *vs* 2.139 n=9, $P<0.05$; male 1.218 *vs* 1.022, n=9, p=ns) compared with NHR controls.

This is the first study to show aromatase expression in atrial and pericardial adipose tissue. The data suggest that the heart may be subject to paracrine actions of locally-synthesized estrogens originating from both the myocardium and pericardial adipose depots, and that the relative importance of aromatase action may vary according to sex, age and disease state. These findings indicate that increased pericardial adipose deposition (*i.e.* in aging & obesity) provides for increased steroid conversion capacity through elevated levels of aromatase. The paracrine actions of locally synthesized estrogens in the heart may exert important influence on contractility and myocyte viability signaling, as well as atrial conduction properties and arrhythmia vulnerability.