Impaired postischemic contractile recovery in male mice overexpressing aromatase

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The pathological characteristics of ischemic heart disease differ between men and women, though the mechanisms responsible are poorly understood. There is a growing awareness of the extent to which sex and sex steroids can influence both cardiac function and stress responses. Aromatase catalyses the conversion of testosterone to estrogen and has been shown to exert important local actions in some extragonadal tissues (*e.g.*, brain and bone). We have shown aromatase is expressed in the heart, and disrupting aromatase activity (high testosterone, low estrogen) increases cardiac functional recovery and tissue salvation postischemia. This challenges the conventional view that estrogen is protective and testosterone a liability (Bell *et al.*, 2011). The aim of this study was to further assess the influence of aromatase on ischemic vulnerability using a model of transgenic aromatase overexpression.

Animals were anesthetised using intraperitoneal injection of sodium pentobarbitone in combination with heparin (200 mg/kg and 200 IU/kg respectively). Hearts from male wild type (WT) and aromatase transgenic overexpression mice (AROM+, high estrogen/low testosterone) were isolated, Langendorff-perfused with Krebs-Henseleit bicarbonate buffer (n = 7-8; 37°C, 80mmHg) and electrically paced (580bpm). Following aerobic perfusion (30mins), hearts were subjected to 25 minutes global ischemia and 60 minutes reperfusion. Left ventricular (LV) pressure was continuously measured using an intraventricular balloon.

Basal contractile function in the AROM+ was suppressed compared to WT (WT *vs* AROM+; dP/dt max, 4991±283 *vs* 4121±225 mmHg/s, $P < 0.05$), consistent with a suppressive action of estrogen on cardiomyocyte contractility. In ischemia, amplitude of contracture was lower in AROM+ hearts (55±4 *vs* 43±3 mmHg, $P < 0.05$), indicating less systolic calcium loading. However, in reperfusion AROM+ hearts recovered poorly. In the first 5 minutes of reperfusion, the severity of ventricular fibrillation was greater in the AROM+ hearts (duration, 103±22 *vs* 197±12 s, $P < 0.05$). Additionally, systolic functional recovery was reduced (LV developed pressure, 56±5 *vs* 39±6 % basal, $P < 0.05$) and diastolic relaxation impaired (LV end diastolic pressure, 24±2 *vs* 36±4 mmHg, $P < 0.05$) in the AROM+ (*vs* WT) at the end of 60 minutes reperfusion.

These observations indicate that the estrogen-androgen balance has a complex role in modulating ischemia/reperfusion injury. High estrogen levels in AROM+ mice may enhance resistance to ischemic damage, but paradoxically fail to support a robust inotropic recovery in reperfusion. Suppression of aromatase at the time of reperfusion may therefore assist longer term recovery/prognosis post-infarction. Molecular studies are required to establish the mechanisms underlying the detrimental role of aromatase on postischemic functional recovery.

Bell JR, Mellor KM, Wollermann AC, Ip WT, Reichelt ME, Meachem SJ, Simpson ER & Delbridge LMD. (2011) *Endocrinology* **152**, 4937-47.