Impaired post-ischemic functional recovery in primary cardiac hypertrophy is accentuated in female rats

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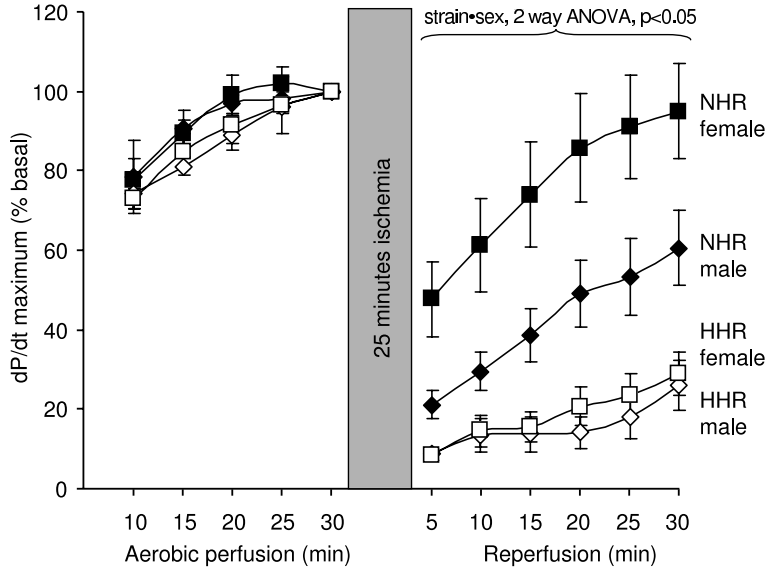
Pathological cardiac hypertrophy is associated with impaired cardiac function and a heightened vulnerability to ischemia/reperfusion injury. Sex differences have been reported in the characteristics of left ventricular remodeling and the susceptibility of these hearts to ischemia/reperfusion injury. Much of the evidence in this field derives from animal models exhibiting adaptive cardiac hypertrophy secondary to genetic hypertension or experimental haemodynamic loading. This study investigated the susceptibility of the hypertrophic heart rat (HHR), a normotensive model of primary cardiac hypertrophy, to post-ischemic cardiac dysfunction and evaluated sex-specific effects.

Male and female HHR and control Normal Heart Rats (NHR), aged 12 weeks (n = 8-10 per group), were anaesthetized (halothane). Hearts were rapidly excised and retrogradely perfused in the Langendorff mode with oxygenated (95% O2, 5% CO_2) bicarbonate buffer (37˚C) at a constant pressure of 73mmHg. Left ventricular pressure was monitored continuously with an isovolumic, intraventricular balloon inflated to give an end diastolic pressure of 4mmHg. Hearts were aerobically perfused for 30 min prior to 25 min global ischemia and 30 min reperfusion.

In HHR hearts, ventricular weight index was significantly higher than NHR controls (4.6 ± 0.1 *vs.* 5.6 ± 0.2 mg/g, male NHR vs HHR, and 4.8 ± 0.1 *vs.* 7.9 ± 0.5 mg/g, female, both $p < 0.001$). No significant differences were observed between NHR and HHR in basal cardiac function (left ventricular developed pressure (LVDP), coronary flow, heart rate, rate pressure product (RPP), dP/dt max and min), though females in both strains had reduced dP/dt max and min compared with males. HHR hearts exhibited a substantial decrease in contractile recovery during post-ischemic reperfusion compared with NHR controls in both males (LVDP at end of reperfusion: 31.7 ± 7.1% *vs.* 70.3 ± 8.32%, $p < 0.005$) and females (LVDP: 38.2±7.4% *vs.* 84.7±9.2%, $p < 0.005$). Heart rates were not different. Analysis of ectopy in the first 10 minutes of reperfusion also revealed increased incidence of arrhythmias in HHR hearts for males (59.4 ± 7.6% *vs.* 28.6 ± 6.0%, HHR vs NHR, $p < 0.01$) and females (46.9 ± 10.0% *vs.* 15.8 ± 5.0%, HHR *vs.* NHR, $p < 0.05$).

In NHR females, a significantly greater improvement in post-ischemic recovery of dP/dt max compared with males was observed. This sex difference in post-ischemic recovery was not evident in HHR (strain•sex, 2 way ANOVA, $p < 0.05$, see Figure). A similar pattern was observed in other parameters measured, including LVDP, RPP, and dP/dt min.



In conclusion, primary cardiac hypertrophy exacerbates the left ventricular dysfunction associated with ischemia/reperfusion and obviates the cardioprotection observed in non-hypertrophic females. Further studies are required to elucidate the signaling mechanisms responsible for this functional difference and to examine the role of sex steroids in the apparent loss of cardioprotection in the female HHR.