Salutary effects of pyruvate are more evident in female than male glut4-deficient mouse hearts

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The mechanisms involved in diabetic cardiac pathology are not well understood. Insulin resistance, defined as a decrease in the ability of insulin to stimulate cellular glucose uptake is often termed the "pre-diabetic" state. Insulin-stimulated glucose uptake in the heart is mediated by the glut4 transporter. It is known that alterations in substrate availability are associated with cardiac hypertrophy, reduced energy production and subsequent cardiac contractile dysfunction (Taegtmeyer *et al.*, 2002). There is some epidemiologic evidence indicating that diabetes has greater negative impact on cardiovascular morbidity and mortality in women than men (Sowers, 1998). The goal of this study was to investigate the metabolic basis for this sex-specific vulnerability in the heart. The inotropic actions of pyruvate, a metabolic product of glycolysis and an oxidizable fuel in the heart, were investigated in a genetic animal model of insulin resistance.

Hearts of age-matched female and male mice (22 week) from three genetic groups were evaluated: wildtype (WT), 'knock-down' (KD, 15% WT glut4) and 'knock-out' (KO, ≤ 5% WT glut4). Mice were anaesthetised with pentobarbitone sodium (70mg/kg, ip), and hearts excised and arrested in iced Krebs-Henseleit buffer. Hearts were perfused (Langendorff-mode) in normoxic conditions with Krebs-Henseleit bicarbonate buffer (37ºC). Left ventricular function was measured using a fluid-filled balloon interfaced to a pressure transducer (MLT884). 5mM glucose with 100uU/ml insulin was provided as the substrate for basal measurements. The perfusate was then supplemented with 5mM pyruvate.

Under basal conditions hearts of female and male glut4-KO mice exhibited significantly reduced developed pressure relative to WT. Hearts of female glut4-KD mice were significantly more functionally impaired than hearts of male glut4-KD mice relative to WT. Pyruvate supplementation significantly improved developed pressure in female and male glut4-KD & glut4-KO hearts. Interestingly, female glut4-KO hearts were most responsive to pyruvate supplementation.

Developed Pressure	**Genotype**	**Basal (mmHg)[#]**	**With 5 mM pyruvate (mmHg)[#]**
Female	WT	137.9 ± 12.9	126.5 ± 11.6
	KD	106.2 ± 13.1 *	139.7 ± 13.3
	KO	108.4 ± 5.7 *	182.7 ± 7.6
Male	WT	151.2 ± 13.3	147.2 ± 6.7
	KD	145.8 ± 6.2 †	175.9 ± 6.3
	KO	91.7 ± 10.4 *	157.4 ± 18.9
[#] $p<0.05$ sex × genotype * $p<0.05$ *vs* WT, †$p<0.05$ *vs* KO			

The acute improvement in isolated function of glut4-deficient hearts after pyruvate supplementation suggests that substrate limitation is a major cause of contractile dysfunction. The responsiveness of glut4-deficient hearts to pyruvate indicates that adaptive metabolic remodelling may have occurred early in development to preserve metabolic 'flexibility'. This adaptation may be accentuated in insulin resistant hearts of females.

Sowers, J.R. (1998) *Archives of Internal Medicine* **158**, 617-321.
Taegtmeyer, H., McNulty, P. & Young M. (2002) *Circulation* **105**, 1727-1733.