Impacts of experimental type-1 diabetes on cardiac function are not the same in male and female STZ-treated mice

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There is strong clinical evidence for increased myocardial jeopardy for women with diabetes, however the processes underlying this vulnerability remain largely undefined, as we highlighted recently (Reichelt *et al*., 2013). Significant progress has been made in understanding the consequences of modulating specific sex-steroids on the progression of diabetic cardiopathology in males and females. However, less is understood about how the milieu of male and female sex hormones (with variable actions in males and females) culminates in increased diabetic cardiopathology in females. The aim of this study was to evaluate the differential impacts of streptozotocin induced diabetes on cardiac function in C57BL/6 female and male mice.

Type 1 diabetes (T1D) was induced in male and female C57Bl/6 mice aged 15 weeks by injecting 55mg/kg streptozotocin (STZ) for 5 consecutive days (with citric acid vehicle) (n = 6-7/group). T1D was allowed to progress without treatment for 10 weeks. Blood glucose was assessed at the end of the protocol (tail vein sample), before mice were injected with sodium pentobarbital. Once anesthetised, hearts were extracted and perfused on a Langendorff isolated heart perfusion system. Hearts were allowed to equilibrate for 15 minutes before hearts were electrically paced at 420 beats per minute for a further 15 minutes.

STZ induced significant hyperglycaemia in male mice (male Veh 16 ± 0.8; male STZ 30.89 ± 3.1 mmol/L, $P < 0.05$), but the increased BGL in females did not reach statistical significance (female Veh 14 ± 1; female STZ 20 ± 3 mmol/L). Bodyweight was lower in females (23 ± 0.9) than males (31 ± 0.6), but not affected by STZ. Conversely, in relation to function, left ventricular developed pressure (DevP) was significantly decreased in STZ females (Veh 88 ± 7 mmHg; STZ 67 ± 6 mmHg, $P < 0.05$) but modestly (and not significantly) reduced in STZ-treated males (Veh 103 ± 5 mmHg; STZ 91 ± 4 mmHg).

Taken together, these data suggest that despite milder hyperglycaemia in STZ-treated females, they displayed worsened cardiac systolic dysfunction. Thus, these data are consistent with clinical indications that females are more vulnerable to diabetic cardiopathology. Future studies will evaluate oral glucose tolerance test in female as an additional measurement of glucose intolerance, and determine insulin levels in all STZ-treated animals. In conclusion, these data suggest that even when females do not display overt hyperglycaemia, cardiopathology contributing to contractile dysfunction may be progressing.

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