Changes in atrial structure and function in diabetes and obesity

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We have examined the development of the pro-arrhythmic substrate in the atria in a novel mouse model of diet induced obesity and type 2 diabetes (T2DM) (Leiter & Reifsnyder, 2004).

Methods: NONcNZO10/LtJ (RCS10) mice (RCS10) and SWR/J (SWR) mice as diet-resistant non-obese controls were randomly allocated in two steps to groups of n=6: 1) one at 8-10 weeks of age and at 30 weeks of age and 2) according to diets, standard chow (NOM), high fat chow (10% fat) (HFD), and high fat chow with chocolate bar supplement (CHOC). Parameters measured: Hearts were removed under full anaesthesia and left atria dissected for electrophysiology study using multi-electrode array (MEA). Plasma levels of leptin, and selected biomarkers of matrix remodelling and inflammation were measured. Tissue samples were analysed histologically for cardiomyocyte hypertrophy, fibrosis and inflammatory infiltration. All values are reported in mean ± standard error unless indicated otherwise. General Linear Model (GLM) ANOVA was used to determine significant differences between strain, diet and age factors, and Tukey's post-hoc test was conducted to determine diet differences. Student t-test was used to compare inter-group differences when ANOVA was significant.

Results: At 10-weeks, RCS10:CHOC mice had elevated body weight compared to controls (33.3 ± 0.4 g *vs* 22.3 ± 0.6 g, $P < 0.001$), greater unfasted blood glucose ($P < 0.001$) and significantly elevated plasma leptin levels (2902.7 ± 515.9 *vs* 70.8 ± 61.4 pg/mL, $P < 0.001$). Atrial refractory period was increased in RCS10:HFD and RCS10:CHOC animals compared to controls (49.3 ± 2.9 *vs* 39.5 ± 3.4, $P < 0.05$; 75.7 ± 4.7 *vs* 54.2 ± 2.2 ms, $P < 0.001$ respectively). RCS10 animals fed NOM, HFD, and CHOC diets had reduced conduction velocity compared to controls (0.303 ± 0.007 *vs* 0.327 ± 0.006 m/s, $P < 0.05$; 0.269 ± 0.009 *vs* 0.309 ± 0.008 m/s, $P < 0.01$; 0.244 ± 0.007 *vs* 0.314 ± 0.006 m/s, $P < 0.001$ respectively) and increased conduction heterogeneity with increasing fat content diets with significant increase CHI in HFD and CHOC diets compared to controls (1.90 ± 0.06 *vs* 1.67 ± 0.03, $P < 0.01$; 2.30 ± 0.07 *vs* 1.75 ± 0.05, $P < 0.001$ respectively). RCS10 animals fed NOM, HFD, and CHOC diet showed increased cardiomyocyte diameter compared to controls (8.33 ± 0.23 *vs* 7.78 ± 0.17 μm, $P < 0.001$; 8.35 ± 0.14 *vs* 7.60 ± 0.16 μm, $P < 0.001$; 8.76 ± 0.22 *vs* 7.65 ± 0.20 μm, $P < 0.001$ respectively). Fibrosis was increased in 10-week old RCS10 animals fed HFD and CHOC diets compared to controls (2.80 ± 0.53 *vs* 0.81 ± 0.08 %, $P < 0.05$; 3.31 ± 0.81 *vs* 0.70 ± 0.05 %, $P < 0.05$ respectively). All of these changes were either similar or exacerbated in 30 week old animals.

RCS10 mice fed NOM, HFD and CHOC demonstrated greater inflammatory cell infiltrates compared to controls (4.89 ± 0.32 *vs* 4.01 ± 0.25, $P=0.06$; 5.12 ± 0.30 *vs* 3.94 ± 0.14, $P < 0.01$; 5.57 ± 0.43 *vs* 4.11 ± 0.28, $P < 0.05$ respectively). Matrix remodelling: MMP-2 levels were significantly elevated in RCS10 mice compared to controls (70.1 ± 4.5 *vs* 56.4 ± 4.1 ng/mL, $P < 0.05$) with no significant effect with increasing fat content diets ($P=0.14$). TIMP-1 was significantly decreased in RCS10 animals compared to controls (138.4 ± 32.2 *vs* 361.9 ± 40.3 pg/ml, $P < 0.001$). TGFβ1 was significantly increased in RCS10 mice compared to controls (704.2 ± 131.5 *vs* 39.1 ± 22.4 pg/mL, $P < 0.001$). Biomarkers of Inflammation: Plasma levels of TNFα were significantly elevated in RCS10 mice compared to controls (246.6 ± 17.0 *vs* 117.8 ± 23.0 pg/mL, $P < 0.001$), regardless of diets fed ($P=0.321$). Overall concentration of ICAM-1 was significantly elevated in RCS10 mice compared to controls (223.2 ± 24.6 *vs* 148.2 ± 15.4 pg/mL, $P < 0.05$), regardless of diet ($P=0.145$). VCAM-1 was significantly increased in RCS10 mice compared to controls (12.4 ± 0.3 *vs* 10.9 ± 0.2 ng/mL, $P < 0.001$). RCS10 mice fed CHOC diet demonstrated significantly greater VCAM-1 levels compared to NOM diet.

Conclusions: This study has identified key pathological changes in both structural and electrophysiological remodelling of the atria in response to high-fat feeding of mice with polygenic diabesity. These changes are consistent with the development of a pro-arrhythmic substrate. Additionally, biomarkers of extracellular matrix remodelling and inflammation are altered in the diabesity mouse.

Leiter EH, Reifsnyder PC. (2004) Differential levels of diabetogenic stress in two new mouse models of obesity and type 2 diabetes. *Diabetes* **53:** S4-S11.