Assessment of cardiac remodelling after myocardial infarction in diabetic mice using self-gated MRI

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Background: Type II diabetic patients suffer from an increased prevalence, severity and prognosis of cardiovascular disease. Indeed, diabetes mellitus increases the frequency of myocardial infarction (MI) and diabetic patients have a higher risk of developing heart failure (HF) following an ischemic event. However, little is known about the physiological mechanisms involved in the myocardial response to ischemia in diabetic patients. The leptin receptor-deficient *db/db* mouse is a well-established model of type II diabetes which presents inability to regulate metabolism, resulting in a diabetic phenotype at an early age. Enhanced sensitivity to MI suggests that the diabetic mouse is an excellent animal model for studying the mechanisms behind post MI-induced HF (1). In this setting, the self-gated MRI technique could be particularly advantageous and provide refined gating accuracy. Overcoming the decreased ECG sensitivity, the use of this approach will improve the image acquisition and support studies on animals with cardiovascular disease. The aim of the present study is to evaluate left ventricular structure and function in the diabetic mouse heart as it changes post MI.

Materials and methods: Non-diabetic controls and diabetic mice were subjected to chronic MI by ligation of the left anterior descending coronary artery or sham surgery at 6 weeks of age. *In vivo* MRI was performed at 7, 10 and 14 weeks at a 7T Bruker Biospec Avance 70/20 (Bruker Biospin, Germany) with a water cooled BGA-12 (400 mT/m) gradient system. A 72 mm volume coil was used for transmission and an actively decoupled quadrature rat head surface coil (Rapid Biomedical GmbH, Germany) for receive only. Cine movies were obtained of the complete cardiac cycle using a self-gated fast low-angle shot (FLASH) gradient echo sequence with an oblique saturation slice navigator scan. Scan parameters were FA/TE/TR = 10°/2.2ms/6.9ms, FOV 40×40 mm² with a 128x128 matrix. The sequence was repeated 300 times per slice and the images were reconstructed to 10 frames/cycle. The whole left ventricle was covered by acquiring 6-8 contiguous short axis slices, with thickness of 1mm, from apex to base. Using in-house built semi-automatic software (2), endocardial volumes were obtained adding up the luminal areas from each slice. End-diastolic (EDV) and end-systolic volumes (ESV) were extracted. As a common measure of contractility, ejection fraction (EF) was estimated. Only animals that completed imaging at all time points were included in the analysis: non-diabetic sham, n=6; non-diabetic MI, n=8; diabetic sham, n=6; diabetic MI, n=7. Statistical analysis was performed using SPSS 16.0 (SPSS Inc., USA). Non-parametric Mann-Whitney tests were used for comparisons between groups. All values are reported as mean ± SEM.

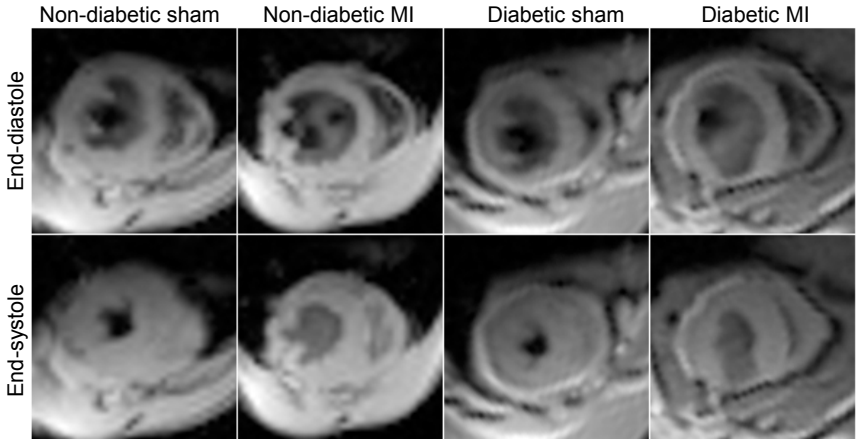

Figure 1: Images from mid-ventricular short-axis view at 14 wks age from each group. MI is visible as distinct akinetic areas and/or scarring of the wall resulting in reduced contractility compared to shams.

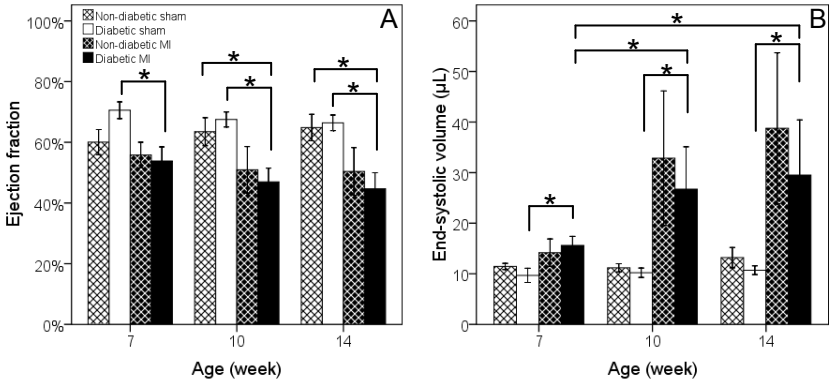

Figure 2: Ejection fraction (A) and end-systolic volume (B) at 7, 10 and 14 wks. Error bars display SEM; * denotes significant difference, p<0.05, between groups.

Results and discussion: Using the self-gated MRI technique, high-quality images with accurate gating was obtained, with sufficient quality to be assessed with volumetric analysis (Figure 1).

The diabetic MI group displayed increased mortality rate (15%) compared to all other groups (0%). EF was reduced in diabetic MI mice compared to both diabetic and non-diabetic sham mice at 10 and 14 wks of age (Figure 2A). This reduced contractility may be partly explained by an increase in ESV (Figure 2B) compared to diabetic sham (Figure 2B) (7 wks: 15.6 ± 1.6µL vs. 9.7 ± 2.7µL, p=0.05; 10 wks: 26.7 ± 7.7µL vs. 10.2 ± 0.9µL, p=0.04; 14 wks: 29.5 ± 9.8µL vs. 10.7 ± 0.9µL, p=0.001). Results also indicated an increased ESV in the diabetic MI mice group compared to non-diabetic sham (p=0.07 at all time-points).

In contrast, non-diabetic MI mice did not differ significantly from non-diabetic sham with regard to either EF or ESV. However, non-diabetic MI mice showed an increased EDV compared to non-diabetic sham at 10 wks (55.5 ± 12.5µL vs. 32.5 ± 3.5µL, p=0.02) and 14 wks of age (64.6 ± 13.4µL vs. 36.9 ± 1.8µL, p=0.01). These data suggest that the diabetic myocardium experiences altered mechanisms behind cardiac remodelling after MI compared to the non-diabetic heart. While diabetic MI mice display a rapid onset of increased ESV resulting in a reduction in cardiac contractility, non-diabetic MI show an increase in EDV with preserved EF for the duration of this study.

Conclusion: We have demonstrated that imaging of the infarcted diabetic mouse heart is achievable using a self-gated FLASH. Segmenting slices from the whole heart reveals volumes that can be used in functional analysis and the results are accurate enough to detect differences between genotypes and interventions. Using this method, we have shown that diabetic mice may have different mechanisms of cardiac remodelling after MI, compared to non-diabetic mice.

References:

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