

Effect of maternal exposure to high fat feeding on cardiac metabolism and function in offspring

Petronella A. van Ewijk^{1,2}, Sabina Paglialunga¹, Anne Gemmink³, Jos M.G.M. Slenter², Joachim E. Wildberger², Jan F. Glatz⁴, Joris Hoeks¹, Matthijs K.C. Hesselink³, Patrick Schrauwen¹, Vera B. Schrauwen-Hinderling^{1,2}, and Marianne Eline Kooi²

¹Human Biology, Maastricht University Medical Centre, Maastricht, Limburg, Netherlands, ²Radiology, Maastricht University Medical Centre, Maastricht, Limburg, Netherlands, ³Human Movement Sciences, Maastricht University Medical Centre, Maastricht, Limburg, Netherlands, ⁴Molecular Genetics, Maastricht University Medical Centre, Maastricht, Limburg, Netherlands

Purpose: The prevalence of obesity is increasing, also in women of child-bearing age. Research in humans has shown that a mother's BMI in early pregnancy positively correlates with the percentage of body fat in the child [1]. Furthermore, fatty acid overload leads to fat storage in so-called "ectopic" tissues (liver, skeletal muscle, heart). Ectopic lipid accumulation is associated with insulin resistance and diminished organ function. Exposure of mice to a high fat (HF) diet during early development increased the susceptibility to HF diet induced hepatic steatosis and decreased markers of hepatic mitochondrial function [2]. Here, we aimed to investigate whether maternal exposure to a HF diet during gestation and lactation also increases the susceptibility for cardiac fat storage compromised mitochondrial function in the heart, and for concomitant decline in cardiac function in offspring.

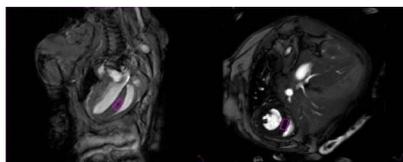


Figure 1: Four-chamber view (left) and short-axis view (right) from the heart. Localized proton spectra were acquired from a 4 µl voxel positioned at the interventricular septum (indicated in pink) using a PRESS sequence (TE:9.2 msec, TR:2 sec, NSA:512).

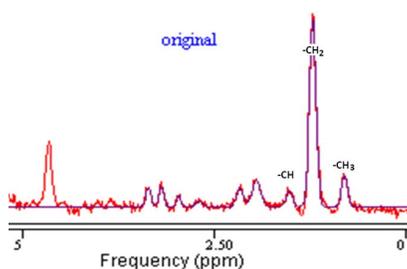


Figure 2: Spectral analysis was performed in jMRUI using the AMARES fitting algorithm.

Methods: Male and female C57BL6 mice were either fed a HF diet (45% kcal fat) starting at least 6 weeks before conception of offspring or continued their standard chow diet (9% kcal fat, LF). The two diets were continued during gestation and lactation. From weaning onwards, all offspring were fed the HF diet, resulting in two experimental groups: HF/HF and LF/HF of which the male offspring was used for measurements. At 12 and 28 weeks of age cardiac mitochondrial respiration on pyruvate (+malate) and on palmitoyl-CoA + carnitine was determined using high resolution respirometry (OROBOROS Instruments). Cardiac systolic function and cardiac fat content were measured at 15, 21 and 27 weeks of age using Magnetic Resonance Imaging and Spectroscopy, respectively, on a 7 Tesla MR System (Bruker Biospin GmbH, Ettlingen, Germany). Cinematographic MR images were acquired as previously described [3], analyzed in MRICro and ejection fraction was calculated. Localized proton spectra were acquired (n=19: LF/HF=9, HF/HF=10) from the interventricular septum (Figure 1). Spectral analysis was performed in jMRUI (Figure 2). Results are presented as mean ± standard error. Repeated measures ANOVA was used to evaluate the effect of time, diet and the interaction between time and diet. Bonferroni post-test was performed in case ANOVA showed significance.

Results: At 12 weeks of age, the HF/HF mice showed a tendency (p=0.08) for higher body weight compared to the LF/HF group. For cardiac lipid content, a significant time effect and time*diet interaction effect was found. As shown in figure 3, cardiac lipid content was higher in the HF/HF group compared to the LF/HF group at 15 weeks (p=0.01), however it was decreasing in time in the HF/HF group, while cardiac lipid content was increasing in time in the LF/HF group. This resulted in a tendency for lower cardiac lipid content at 27 weeks in the HF/HF group (p=0.07).

This was accompanied by a trend for lower mitochondrial respiration on palmitoyl-CoA + carnitine in the HF/HF group (p=0.06) at 28 weeks of age (data not shown). No differences occurred in ejection fraction (LF/HF: 64.82 ± 2.60 %; 65.82 ± 1.44 %; 64.34 ± 2.18 %, HF/HF: 65.30 ± 1.73 %; 65.71 ± 1.73 %; 68.44 ± 1.07 %, at 15, 21 and 28 weeks respectively).

Discussion / Conclusion: We found that mice that are exposed to HF feeding in utero and during lactation are more susceptible to increased cardiac lipid content on a HF diet at 15 weeks of age. On the longer term, however, cardiac lipid content showed a trend to be lower in the mice subjected to early exposure to high-fat feeding compared to the LF/HF mice, which was accompanied by a tendency for lower mitochondrial respiration on a fatty acid substrate in the HF/HF group. The data may indicate that early exposure to HF initially leads to elevated cardiac lipid content. However, compensatory mechanisms may protect the heart from excessive lipid accumulation later in life. Furthermore, early exposure to HF diet may elicit negative effects on mitochondrial function.

References: [1] Reynolds, R.M., et al., JCEM, 2010. 95(12): p. 5365-9. [2] Bruce, K.D., et al., Hepatology, 2009. 50(6): p. 1796-808. [3] van de Weijer, T., et al., Am J Physiol Heart Circ Physiol, 2012. 302(3): p. H709-15.

Acknowledgment: This research was supported by the Center for Translational Molecular Medicine (CTMM) and the Dutch Heart Foundation, Dutch Diabetes Research Foundation and Dutch Kidney Foundation (PREdicT).

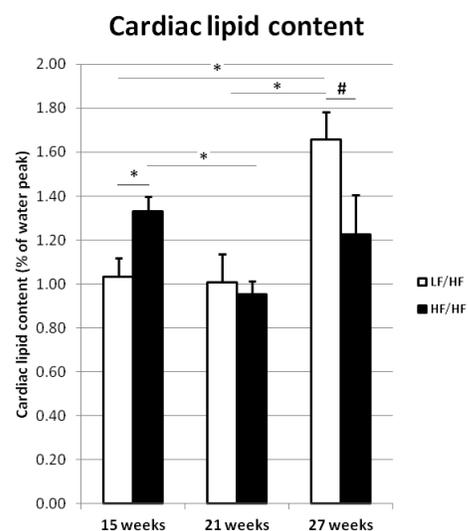


Figure 3: Cardiac lipid content was increased at 15 weeks of age in the HF/HF group (1.03±0.08 vs. 1.33±0.07, p=0.01), while no difference between the groups was observed at 21 weeks of age. At 27 weeks of age the LF/HF group showed a tendency for higher cardiac lipid content (1.66±0.13 vs. 1.23±0.18, p=0.07). Cardiac lipid content decreased from 15 to 21 weeks in the HF/HF group (p=0.02) and increased from 15 and 21 to 27 weeks in the LF/HF group (p=0.003 and p=0.01, respectively).