Myocardial lipid accumulation due to high fat diet in PPAR-alpha overexpressing mouse hearts reduces endocardial 2-D principal strains

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Purpose

Evidence exists for detrimental effects of lipotoxicity following altered fatty acid metabolism in the heart, but little, if any information is known on the potential mechanical effects of intramyocardial lipid accumulation on myocardial stiffness. Thus, we examined the effects of induced increases in myocardial lipid on the transmural compliance of the left ventricular (LV) wall using a combination of localized ^{1}H spectroscopy of myocardial, mobile lipid content and 2-D principal strains on the *in vivo* mouse heart. The approach allowed further comparison of NMR detection of lipid to the specific content of triacylglyceride (TAG) in the myocardium from biochemical assay. For this study, altered myocardial lipid content and 2-D strains in the epi- and endocardium of the LV were determined, over a two week period of high fat diet, in both non-transgenic mice and a transgenic mouse model of increased myocardial lipid due to cardiac-specific overexpression of the proxisome proliferators activated nuclear receptor α (MHC-PPARα).

Method

Mice were anesthetized (1% isoflurane inhalation) and situated in a 30 mm birdcage ^{1}H resonator within a 14.1 T magnet throughout the 1 hour scanning protocol. Body temperature was continuously monitored and maintained at 37°C. Heart rate ranged 400-590 bpm.

PPARα mice (n=8) and nontransgenic littermates (NTG, n=9), at 5 months of age, were studied before and after a high fat diet (43% of calories as long chain fatty acids) provided ad libetum for a 2 week period. Measurement of positive and negative 2-D strains, E1 and E2, were performed in both epi- and endocardium from high resolution, tagged cardiac images of *in vivo* mouse hearts. At the end of the high fat diet, strain measurements were coupled with localized ^{1}H spectra of lipid content for comparison between NTG and PPARα hearts.

Following the 2nd scanning protocol, mice were sacrificed and the hearts excised and frozen in liquid nitrogen cool tongs, for assay of triacylglyceride content.

In vivo myocardial lipid content was assessed using image guided localized water suppressed MRS of the acyl chain methylene protons (Fig. 1a) and normalizing lipids signal to total signal from unsuppressed water. ^{1}H MRS was localized to LV septum at midbase (1x1x1mm voxel, Fig. 1b) to avoid signal contamination from pericardial fat. Cardiac triggering and respiratory blanked PRESS spectroscopic sequence (TE=11.5 ms, TR=2500 ms) was used with and without CHESS water saturation method.

Short axis cardiac triggered and respiratory blanked MRI was performed (FLASH-sequence, FOV=20mm, slice=1mm) with high-resolution DANTE tagging (0.3mm lines separation) at midbase to provide 2-D diastolic-systolic strain measurements of E1 (stretch) and E2 (compression) in the epi- and endocardial levels of the LV wall (1).

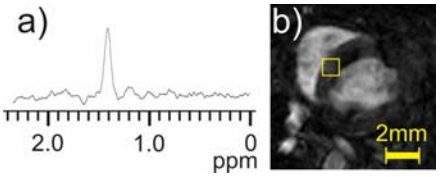

Fig. 1. ^{1}H signal from methylene protons (a) and the localization of the voxel (b).

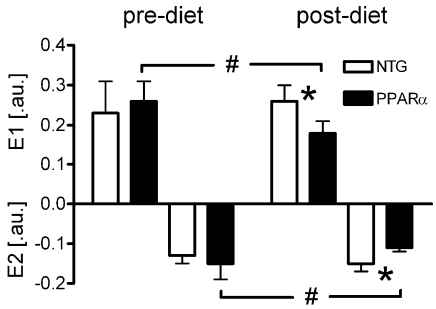

Fig. 2. Septum endocardial principal strains E1 and E2 in NTG and PPARα mice before and after high fat diet. *P<0.05. Post-diet PPARα vs. post-diet NTG; # P<0.05, pre-diet PPARα vs. post-diet PPARα.

Results

From MRS following the high fat diet, PPARα hearts showed 130% greater lipid content than NTG hearts (mean ± SD; PPARα = 3.20 ± 1.53, NTG = 1.38 ± 0.64, P<0.05). From direct assay, mean TAG content in PPARα was also elevated over NTG, but less dramatically at 73%. Lipid content in NTG hearts was similar to that of previously reported levels in C57Bl mouse hearts (1.27 ± 0.09) from Schneider et al (2). Consistent with previous studies of the myocardium, the NMR signal from lipid was exclusive to the intracellular compartment with no evidence of extracellular lipid (2). Importantly, both positive (E1) and negative (E2) 2-D strains in the endocardial layer of the studied region were reduced in PPARα hearts following the high fat diet (Fig. 2). No change in either strain occurred in NTG. A strong correlation exists between each of the endocardial values of E1 and E2 and the lipid content of all hearts (Fig. 3) (E1: Pearson r = -0.76, P<0.05, E2: Pearson r = -0.78, P<0.05). Interestingly, no correlation existed between the detected mobile lipid content measured by MRS and TAG content (Pearson r = 0.33, P>0.05).

Conclusions

These findings indicate that the reductions of principal 2-D strains, associated with both stretch and compression in the endocardium, are a consequence of elevated myocardial lipid. This endocardial stiffness may result from intracellular lipid infiltration of the cardiomyocyte. Additionally, comparison of NMR signal from lipid to TAG content indicates that the lipid resonances reflect all constituents of the detectable mobile lipid pool, and are not exclusive to triacylglyeride content alone.

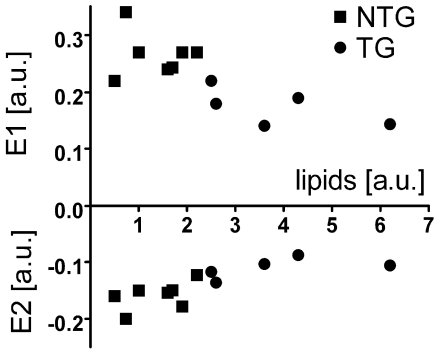

Fig.3. E1 and E2 strains versus relative lipid content (water = 100) following high fat diet.

1. Hankiewicz J. H. and Lewandowski E.D. Improved Cardiac Tagging Resolution at Ultra-High Magnetic Field Elucidates Transmural Differences in Principal Strain in the Mouse Heart and Reduced Stretch in Dilated Cardiomyopathy. J Cardiovasc Magn Reson 9: 891-898, 2007.

2. Schneider J. E., Tyler D. J, ten Hove M, Sang A. E., Cassidy P. J., Fischer A., Wallis J., Sebag-Montefiore L. M., Watkins H., Isbrandt D., Clarke K. and Neubauer S. In Vivo Cardiac ^{1}H-MRS in the Mouse. Magn Reson Med 52: 1029-1035, 2004.