Early Impairment of Transmural Principal Strains in the Left Ventricular Wall After Short-Term, High-Fat Feeding of Mice Predisposed to Cardiac Steatosis

Janusz H. Hankiewicz, PhD; Natasha H. Banke, PhD; Mariam Farjah, PhD; E. Douglas Lewandowski, PhD

Background—Myocardial lipid accumulation precedes some cardiomyopathies, but little is known of concurrent effects on ventricular mechanics. We tested the hypothesis that intramyocardial lipid accumulation during a short-term, high-fat diet (HFD) affects 2-dimensional strains in the heart. We examined the hearts of nontransgenic (NTG) mice and of transgenic mice predisposed to elevated triacylglyceride (TAG) storage linked to low-level overexpression of peroxisome proliferator activated receptor (PPAR-α).

Methods and Results—Myocardial lipid and transmural principal strains E1 and E2 were determined in vivo with 1H magnetic resonance spectroscopy/imaging before and after 2 weeks of an HFD in both PPAR-α and NTG littermate mice. Baseline lipid was elevated in PPAR-α compared with NTG mice. An HFD increased mobile lipid by 174% in NTG mice (P<0.05) and by 79% in PPAR-α mice (P<0.05). After an HFD, lipid and TAG were higher in PPAR-α versus NTG mice by 63% and 81%, respectively. However, TAG in PPAR-α mice after an HFD was similar to TAG in PPAR-α mice fed a regular diet, suggesting that the magnetic resonance spectroscopy signal from lipid is not exclusive to TAG. Only at the highest lipid contents, achieved in PPAR-α mice, were strains affected. Endocardial strain was most compromised, with a negative correlation to lipid (P<0.05).

Conclusions—A short-term HFD elevated myocardial lipid measures as determined by magnetic resonance spectroscopy, which became dissociated from TAG content in hearts predisposed to cardiac steatosis. The increased lipid was associated with concurrent, transmural reductions in E1 and E2 strains across the left ventricular wall. Strains were attenuated at the highest levels of lipid accumulation, suggesting a threshold response. Thus, 2-dimensional strains are impaired early and without left ventricular diastolic dysfunction, owing to cardiac steatosis. (Circ Cardiovasc Imaging. 2010;3:710-717.)

Key Words: cardiomyopathy ■ lipids ■ MRI ■ spectroscopy
resolution, cardiac MRI tagging grids of 0.33 mm in our laboratory has enabled different responses of 2D strains in endocardial and epicardial layers to be distinguished. In studying the link between cardiac lipid content and 2D strain, we examined the responses of both normal mice and a transgenic mouse model of elevated myocardial triacylglycerol (TAG) due to chronic, low-level, cardiac-specific overexpression of the peroxisome proliferator activated receptor-α (PPAR-α). Previous studies of hearts from this novel, transgenic model have shown global indices of LV dysfunction after more prolonged exposure to an HFD than was applied in the current in vivo study of 2D strains across the LV wall. The current approach tested the hypothesis that intramyocardial lipid accumulation, caused by a short-term HFD, induces early transmural changes in positive and negative 2D strains in the LV wall before evidence of altered diastolic function is apparent. In addition, the protocol enabled distinction between changes in the mobile lipid pool, as detected by 1H MRS, and the TAG pool, from assays of tissue samples. The findings provide new insights into the LV wall mechanics of hearts exposed to HFDS with potential for lipid accumulation and suggest a stepwise effect, or threshold, in myocardial lipid levels in contributing to contractile dysfunction.

Methods

Animal Model

Experiments were performed on 5-month-old mice with low-level, cardiac-specific overexpression of PPAR-α in the heart, driven by the α-myosin heavy-chain promoter (MHC-PPAR-α line 404-4) and age-matched, nontransgenic (NTG) littermates (NTG n=8, MHC-PPAR-α n=8). Separate groups of mice (NTG n=4, MHC-PPAR-α n=4) were euthanized to determine baseline myocardial TAG content before the protocols. Additional NTG (n=3) and MHC-PPAR-α (n=3) mice were studied before and after 2 weeks of a regular chow diet as additional controls. No sex differences in the measured parameters occurred among either transgenic or NTG mice at any point in the protocols. This cardiac-specific, low-overexpressing line of MHC-PPAR-α mice, line 404-4, has been described earlier. Mice were housed under controlled temperature, humidity, and light conditions and were allowed ad libitum access to normal chow (diet 7012 Teklad LM-485: 17% fat, 58% carbohydrate, and 25% protein; Harlan-Teklad, Madison, Wis) and water. For HFD studies, prediet analyses were performed and the regular chow was replaced with high-fat chow (diet TD 97268: 43% fat, 19% carbohydrate, and 19% protein; Harlan-Teklad, Madison, Wis) and water. For HFD studies, prediet analyses were performed and the regular chow was replaced with high-fat chow (diet TD 97268: 43% fat, 19% carbohydrate, and 19% protein; Harlan-Teklad, Madison, Wis) and water.

MRI/MRS Acquisition

Imaging and localized spectroscopy were performed on a 600-MHz Bruker Avance console (Bruker Biospin, Billerica, Mass) equipped with an actively shielded 14.1-T, 89-mm-bore vertical magnet and a 1000 mT/m, 110-μs rise-time microimaging gradient system. ParaVision 4.0 and corresponding Topspin 1.5 control programs were used to conduct MRI and MRS experiments. The restrained mouse with cradle was placed in an upright position in a linearly polarized 600-MHz birdcage resonator (inner diameter = 26 mm and active length = 52 mm). To avoid motion artifacts and ensure reproducible volume localization for spectroscopy, all acquired images and spectra were cardiac triggered and blanked during inspiration. The experimental protocol consisted of heart localization, cardiac tagging, and localized spectroscopy. After the mouse was positioned in the magnet, the heart was localized with a group of orthogonal and oblique images by using a fast gradient echo sequence, fast low-angle shot (FLASH). Depending on the heart and respiration rates, total experimental time was ~2 hours.

Cardiac Tagging

For 2D principal strain measurements, true, short-axis, tagged images were acquired with a high-resolution grid (0.33×0.33-mm in-plane dimension and <0.1-mm line thickness) according to the modified DANTE sequence described previously. The sequence saturates 1H nuclei in 2 orthogonal planes, suppressing the nuclear MR signal during imaging. This suppression generates a visible dark square grid on images perpendicular to the suppressed planes taken after tagging. The tagging grid decay is determined by the tissue spin-lattice T1 relaxation time and can be used to track tissue motion during myocardial contraction and expansion. After tagging-grid generation, at least 8 tagged images (echo time = 1.9 ms, repetition time [TR] >300 ms, field of view = 20 mm, slice thickness = 1 mm, number of acquisitions [NA] = 4, and acquisition matrix = 256×256) were acquired from end diastole through end systole up to rapid filling of the left ventricle with a temporal resolution of 8 ms.

Localized Cardiac MRS

Localized 1H MRS was performed with a modified cardiac triggering and respiratory blanked point-resolved spectroscopy sequence. To avoid contamination from pericardial fat, very small volumes of interest (1×1×1 mm; 1 μL) were selected within the septum at the midventricle from the axial and sagittal scout images (Figure 1A). To match the MRS volume, location measurements of E1 and E2 were performed on the midventricular septum in both epi- and endocardial layers. Manual shimming was conducted with a point-resolved spectroscopy sequence without water suppression on a larger volume of interest (3×3×2 mm) covering the midventricular septum (TR >250 ms). Line width (half height) of the unsuppressed 1H signal of the water peak ranged from 50 to 90 Hz.

For MRS, the ECG R-wave triggered a chemical shift—selective, water-suppression train of 3 saturation, narrow-band hermit pulses (length = 21.6 ms, bandwidth = 250 Hz). Each saturation pulse was followed by gradients to destroy water transverse magnetization. Entire suppression time was 90 ms and was shorter than the shortest recorded R-R period (95 ms). The next R peak in the ECG triggered the execution of a voxel-selective, stimulated echo sequence with 1-ms hermit pulses (bandwidth ~5400 Hz) to excite protons in a selected volume of interest at the end of diastole. Spoiling gradients followed excitation pulses to suppress unwanted signal components and determined an echo time of 11.5 ms.

The proton signal from water was determined from a brief unsuppressed point-resolved spectroscopy experiment (TR >500 ms, NA = 64). The carrier frequency was centered between the water and methylene peaks. Water-suppressed (NA = 512) and unsuppressed (NA = 128) spectra were acquired from the same volume for quantitative comparison of lipid with a reproducibility of 7%. Complex data points (1024) were acquired at an 8-kHz receiver spectral width and a TR >2500 ms. Figure 1B shows representative in vivo spectra acquired from the midventricular septum of PPAR-α and NTG mice before and after an HFD.
TAG Assay
After the postdiet protocol, mice were anesthetized (80 mg/kg ketamine and 12 mg/kg xylazine IP), and hearts were excised and frozen in LN2. Lipid extracts were obtained and TAGs were quantified by colorimetric assay (Wako Pure Chemical Industries, Osaka, Japan) as previously described.18

MRI/MRS Data Analysis
Tagged images were zero-filled to 512/H11003/512 at 0.039 mm/pixel and processed with Matlab (MathWorks, Natick, Mass).19 For homogeneous strain calculations, the reference frame was the image taken at end diastole. Figure 2A and 2B shows representative tagged images at end diastole and end systole obtained with a 0.33-mm tagging resolution with 3 grids resolved across the LV wall. Motion of the tagging grid required manual tracking. Deformed tagging square-like elements were divided into 2 adjacent triangles, and the position of the centroids was calculated.20 Strains were calculated from relative displacement of coupled centroids of the epicardial and endocardial elements and endocardial, excluding midwall, elements (Figure 2C and 2D). Maximum strain values were assigned as diastolic−systolic strain. Epicardial and endocardial contours of tagged images were used to determine percentage of wall thickening (%WT) in 4 segments of the mid-LV wall (septal, lateral, anterior, and posterior) and LV internal diameter at diastole.

Time-domain MRS signals were zero-filled to 16K, exponentially filtered, and after Fourier transformation, phase-corrected. Chemical shifts were assigned relative to water at 4.7 ppm. For comparison of lipids, acyl-chain methylene signals were integrated and normalized to the signal from unsuppressed water.

Statistical Analysis
All statistical analyses were performed with GraphPad Prism version 5.02 for Windows (GraphPad Software, San Diego, Calif). Mean values between MHC-PPAR-α mice and wild-type NTG mice were compared with the unpaired Student’s t test. Intergroup comparison of means was performed with ANOVA and a Bonferroni post test. Intragroup comparisons of means were performed with a Student’s paired t test. The Person r was used for bivariate correlation analysis between lipid accumulation and strain and between lipid accumulation and TAG content. All data are presented as mean±SD, with statistical significance set at P<0.05.

Results
Animal Model
Heart rates in the anesthetized mice situated in the imaging probe were similar to those previously reported, with physiologic rates ranging from 400 to 634 beats/min.21−23 Body weight of NTG mice was unaffected by the 2-week HFD (prediet=28.7±4.2 g, postdiet=28.8±4.0 g), whereas mean body weight of MHC-PPAR-α mice increased by 5% (prediet=24.9±2.5 g, postdiet=26.3±2.9 g; P<0.05).

Lipids and TAG Content
Two lipid resonances were detected on in vivo spectra acquired from the midventricular septum, as shown in Figure 1B. The prominent peak at 1.41 ppm was assigned to the methylene group, and the weaker peak at 0.98 ppm was assigned to the terminal methyl group.24,25 Consistent with previous studies of mouse hearts, the nuclear MR signal from...
lipids was exclusive to the intracellular compartment, with no evidence of extracellular lipids. Lipid content in hearts of MHC-PPAR-α and NTG mice increased after an HFD. +P<0.05, prediet MHC-PPAR-α vs prediet NTG; #P<0.05, prediet MHC-PPAR-α vs postdiet MHC-PPAR-α; and $P<0.05, prediet NTG vs postdiet NTG.

Figure 3 displays lipid levels determined by MRS. Mobile lipid content of MHC-PPAR-α hearts was greater than in NTG hearts, and the HFD increased lipid content in both groups. The 4 experimental groups of pre- and postdiet NTG and MHC-PPAR-α mice displayed 3 different levels of mobile lipid content in the heart. However, only at the highest of the 3 lipid contents did principal strains change, as discussed in the next section. Lipid content did not change during the 2 weeks of the regular chow diet in either MHC-PPAR-α or NTG hearts. Consistent with the $^1$H MRS of lipid, TAG content in separate groups of hearts harvested for assay was also elevated in PPAR-α hearts at baseline versus NTG (Figure 4). Whereas mobile lipids were elevated in both groups after the HFD, TAG content in MHC-PPAR-α hearts harvested immediately after the post-HFD MRS/MRI study remained similar to TAG levels of the MHC-PPAR-α hearts harvested from mice not fed the HFD. Thus, despite increasing lipid content during 2 weeks of the HFD, MHC-PPAR-α hearts contained TAG levels similar to those of MHC-PPAR-α hearts from mice not fed the HFD. These data suggest that the increased lipid content of MHC-PPAR-α hearts after 2 weeks of the HFD was represented by changes in lipid species other than TAG and that this $^1$H MRS signal from lipid was neither solely attributable nor exclusive to myocardial TAG content alone.

**2D Strains**

Figure 5 displays 2D principal E1 and E2 strains from both experimental groups before and after HFD in epicardium and endocardium. Strains did not change after 2 weeks of a regular chow diet. There were no differences in epicardium and endocardium E1 and E2 between NTG and MHC-PPAR-α mice before the HFD. After the HFD, the biggest changes in both E1 and E2 strains appeared in the endocardial layer of MHC-PPAR-α hearts, whereas no significant change in either strain occurred in NTG hearts. After the HFD, endocardial E1 and E2 strains in MHC-PPAR-α hearts dropped by 30% and 25%, respectively (P<0.05). Endocardial E1 and E2 in postdiet MHC-PPAR-α hearts were 35% and 33% lower, respectively, than corresponding values in the postdiet NTG hearts (P<0.05). Although epicardial strains were reduced after the HFD, only E1 dropped significantly (20% change, P<0.05). Epicardial E2 strains in postdiet MHC-PPAR-α hearts were 12% lower than in postdiet NTG hearts (P<0.05).

Interestingly, E1 and E2 both remained at control levels in the prediet groups, despite elevated lipid content in the MHC-PPAR-α hearts, whereas the increased lipid resulting from the HFD did not affect strain in NTG hearts. Not until lipid was elevated to values >2.0 in the MHC-PPAR-α hearts did strain values become affected by the diet (Figures 3 and 5). These data suggest that short-term intramyocardial lipid accumulation does not impact 2D myocardial strains until a critical lipid content is established, as seen in the MHC-PPAR-α hearts after 2 weeks of an HFD. As shown in Figure 6, a significant negative correlation exists between the endocardial values of E1 and lipid content for all hearts (before and after the HFD), as revealed by bivariate correlations (Pearson r = -0.63, P<0.05), but such correlation did not exist for E2 values.

These changes in principal 2D strain mirror the response of more macroscopic changes in LV function, as indicated by the %WT in the left ventricle. Figure 7 displays % WT values for both the septal region (Figure 7A) and averaged %WT for the whole LV wall (Figure 7B), which are consistent with previous MRI data for the in vivo mouse heart. Notably, the data indicate a significant drop in %WT in the hearts of PPAR-α mice after only 2 weeks of an HFD. Previously
published echocardiographic measurements only indicate changes in fractional shortening in this low-overexpressing strain after 4 weeks of an HFD.14 Another study reported no impairment of contractile performance in isolated perfused hearts after 2 weeks of an HFD for either MHC-PPAR-α/H9251 or NTG27 mice.

Discussion
This study provides the first demonstration of coincident changes in LV wall mechanics and intramyocardial lipid content in response to short-term exposure to an HFD. Although previous studies in both humans and animals have associated the eventual development of cardiomyopathy in hearts with alterations in fatty acid metabolism that produce increases in myocardial TAG, the current findings demonstrate that the 2D strain values in the LV wall are compromised during the same time course of the elevated lipid content. Whereas previous investigations have shown that lipid accumulation in the myocardium predates global changes in LV function and the eventual development of cardiomyopathy, we present here the first data showing early changes in LV wall mechanics that coincide with initial increases in myocardial lipid in hearts that are susceptible to steatosis.

In contrast, normal hearts showed elevated lipid content after the brief HFD, but at levels significantly lower than in PPAR-α hearts, yet retained normal LV wall function. The increase in myocardial mobile lipids and TAG in NTG mice demonstrates that even a relatively short-term exposure to an HFD induces cardiac lipid accumulation. Although the modest elevation of lipid in both the PPAR-α hearts at baseline and the NTG hearts after the HFD did not affect 2D strains, the heightened postdiet lipid content induced in the PPAR-α mice was associated with impaired 2D strains in the epicardial layer (Figure 5). Importantly, these results suggest an acute, stepwise response of 2D strain reduction to increasing lipid levels, below which no changes in LV wall mechanics were displayed.

As indicated in Figure 3, the HFD protocol produced 3 levels of myocardial lipid content among the experimental groups: the lowest lipid level occurred in the prediet NTG hearts, elevated lipid content was similarly detected in postdiet NTG hearts and prediet PPAR-α hearts, and the highest lipid content was induced in the postdiet PPAR-α hearts. Although the low and elevated lipid levels in both NTG and PPAR-α hearts were not associated with any contractile dysfunction, the highest lipid content, as observed in PPAR-α hearts after the HFD, was associated with significant reductions in both principal strains E1 and E2 (Figure 5). The implication of this distinction among strain values of the experimental groups is that a critical level of intramyocardial lipid was reached in the postdiet hearts that produced changes in LV wall mechanics.
The predisposition of the low-overexpressing PPAR-\(\alpha\)/H9251 mouse heart for increased TAG content in response to high dietary fat is known to result in eventual contractile dysfunction, as shown by indices of LV function in the in vivo and ex vivo mouse heart after 4 weeks of an HFD. Importantly, the authors also reported no evidence of fibrosis or apoptosis in the MHC-PPAR-\(\alpha\)/H9251 hearts after as much as 8 weeks of an HFD. However, evidence of LV diastolic dysfunction and reduced fractional shortening was observed in this 404-4 line after 4 weeks of an HFD. Recently published data from isolated, perfused hearts of the same 404-4 line showed no evidence of contractile dysfunction after 2 weeks of an HFD.

In the current study, we observed no evidence of diastolic dysfunction after only 2 weeks of an HFD (Figure 7C), despite reductions in 2D strain (Figure 5) and in %WT of the left ventricle (Figures 7A and 7B). The more pronounced response of 2D strains in the endocardial layer than in the epicardium is consistent with the compromised mechanics of the LV wall in diseased hearts. The present study does not distinguish whether the primary mechanism of reduced strain is either the direct action of lipotoxic intermediates or the purely mechanical influence of lipid droplet infiltration of the myocardium. However, the general effect of increased lipid content on transmural changes in principal strains in LV wall function can be interpreted as reduced tissue compliance due to reductions in stretch and compression. These reduced changes may contribute to compromised LV WT.

Interestingly, a recent MRS/MRI study in healthy humans on the effects of a short-term HFD did not demonstrate changes in lipid content or impaired function and is thus consistent with our current observations of the cardiac response to a short-term HFD in NTG mice. Evidence of compromised LV wall function only occurred at the highest lipid level, which was induced in the hearts of the MHC-PPAR-\(\alpha\) mice (Figures 3 and 5). Therefore, the use of principal 2D strain measurements and the specificity of the strain changes in the endocardial layer may provide a more sensitive index for early changes in LV wall dynamics at elevated lipid levels.

After the HFD, lipid content in the septum was not correlated with LV TAG content (Figure 8). Indeed, whereas both TAG and the MRS-documented lipid content increased in NTG hearts after the HFD, the response of TAG and lipid values to the HFD diverged in PPAR-\(\alpha\) hearts. This divergence suggests that the elevation of lipid content in hearts predisposed to steatosis is not restricted solely to TAG. Therefore, we propose that the intramyocardial lipid signals detected by \(^1\)H MRS in this particular study originated from a larger pool of mobile lipid and not exclusively from TAG. Nonetheless, the key finding of this report remains that in response to a short-term HFD of 2 weeks, both of the 2D strains did not change with significant increases in the myocardial content of either total mobile lipid or TAG until a critical level of lipid content had been reached.
Methodological Considerations and Study Limitations

Systolic strains represent the measure of myocardial deformation and thus represent an index of contractility within the chamber wall. The strain tensor, as an index of myocardial deformation, is induced by internal stress from active contractile elements and passive components owing to material properties.

Image-guided, or localized, MRS is currently the only noninvasive modality that provides direct in vivo measurements of cardiac metabolites without exogenous tracers. Several in vivo human MRS studies have examined the impact of diet and health on myocardial lipid accumulation. Szczepaniak et al reported that MRS can detect cardiac triglyceride in a 6-cm³ volume of myocardium in lean individuals and provides valid and reproducible results with correlation to LV volume, septal wall shortening, and the individual’s weight. In healthy persons, myocardial lipid levels have been positively correlated to body mass index, and individuals and provides valid and reproducible results with correlation to LV volume, septal wall shortening, and the individual’s weight. In healthy persons, myocardial lipid levels have been positively correlated to body mass index, and myocardial triglyceride response was related with body mass index after a 48-hour fast. Work by McGavock et al showed that lipid overstorage in human cardiac myocytes occurs early in impaired glucose tolerance and type 2 diabetes mellitus patients. However, in the present study, comparison of mobile lipid content, by MRS, to TAG content from biochemical assays of myocardium indicates that the MRS signal from lipid is not exclusively attributable to TAG alone.

Applying tagging grids of 0.33 mm enabled the current evaluation of transmural changes in 2D principal strains in response to elevated myocardial lipid. Thus, the combination of ultrahigh-field MRI and MRS offers a unique combination of high sensitivity and high spectral and spatial resolution for longitudinal in vivo murine studies of cardiac function and metabolism.

Conclusions

This study examined the influence of moderate lipid accumulation in the myocardium on principal E1 and E2 strains in the LV wall. Myocardial lipid and TAG levels were increased in hearts of normal and transgenic MHC-PPAR-α mice that exhibited low overexpression of PPAR-α. However, the elevated cardiac lipid content in MHC-PPAR-α mice after an HFD was not associated with further increases in TAG content.

This short-term HFD induced cardiac lipid accumulation without immediate evidence of contractile dysfunction. However, at a critical level of elevated myocardial lipid, as displayed in MHC-PPAR-α mice fed the HFD, E1 and E2 strains were attenuated, with the most pronounced reductions in the endocardial layer. The negative consequences of a short-term HFD on 2D strains were apparent in the MHC-PPAR-α hearts only, suggesting an underlying pathophysiological or genetic requirement for cardiac steatosis in the development of LV dysfunction.

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Disclosures

None.

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Elevated Cardiac Lipid Reduces 2D Strains

Previous MRS data of elevated myocardial lipids in human subjects with impaired glucose tolerance or type-2 diabetes suggest lipid overstorage is an early manifestation of type 2 diabetes, preceding heart failure. This study explored the link between short-term dietary, high fat intake and early changes in left ventricular (LV) wall mechanics in normal and diseased hearts. The approach, in studying transgenic mice, is the first to combine localized MRS of cardiac lipid with transmural resolution of 2-dimensional strains in the LV wall using cardiac tagged MRI at ultra-high magnetic field (14.1 T). Our earlier work showed these strains to change prior to global impairment of LV function in myopathic hearts. The responses of endocardial and epicardial mechanics, of the in vivo mouse heart, to a two week, high fat diet (HFD) link overstorage of lipid (steatosis) to early impairment in LV wall contractility. We report on normal mice and transgenic mice overstorage of lipid (steatosis) to early impairment in LV wall contractility. We report on normal mice and transgenic mice between short-term dietary, high fat intake and early changes in left ventricular (LV) wall mechanics in normal and diseased hearts. The approach, in studying transgenic mice, is the first to combine localized MRS of cardiac lipid with transmural resolution of 2-dimensional strains in the LV wall using cardiac tagged MRI at ultra-high magnetic field (14.1 T). Our earlier work showed these strains to change prior to global impairment of LV function in myopathic hearts. The responses of endocardial and epicardial mechanics, of the in vivo mouse heart, to a two week, high fat diet (HFD) link overstorage of lipid (steatosis) to early impairment in LV wall contractility. We report on normal mice and transgenic mice overstorage of lipid (steatosis) to early impairment in LV wall contractility. We report on normal mice and transgenic mice.

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