Effects of Short-Term High-Fat, High-Energy Diet on Hepatic and Myocardial Triglyceride Content in Healthy Men

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Context: An association has been suggested between elevated plasma nonesterified fatty acid (NEFA) levels, myocardial triglyceride (TG) accumulation, and myocardial function.

Objective: Our objective was to investigate the effects of an elevation of plasma NEFA by a high-fat, high-energy (HFHE) diet on hepatic and myocardial TG accumulation, and on myocardial function.

Design: There were 15 healthy males (mean ± SD age: 25.0 ± 6.6 yr) subjected to a 3-d HFHE diet consisting of their regular diet, supplemented with 800 ml cream (280 g fat) every day.

Methods: ^{1}H-magnetic resonance spectroscopy was performed for assessing hepatic and myocardial TGs. Furthermore, left ventricular function was assessed using magnetic resonance imaging.

Results: The HFHE diet increased hepatic TGs compared with baseline (from 2.01 ± 1.79 to 4.26 ± 2.78%; $P = 0.001$) in parallel to plasma TGs and NEFA. Myocardial TGs did not change (0.38 ± 0.18 *vs.* 0.40 ± 0.12%; $P = 0.7$). The HFHE diet did not change myocardial systolic function. Diastolic function, assessed by dividing the maximum flow across the mitral valve of the early diastolic filling phase by the maximum flow of the atrial contraction (E/A ratio), decreased compared with baseline (from 2.11 ± 0.39 to 1.89 ± 0.33; $P = 0.031$). This difference was no longer significant after adjustment for heart rate ($P = 0.12$).

Conclusions: Short-term HFHE diet in healthy males results in major increases in plasma TG and NEFA concentrations and hepatic TGs, whereas it does not influence myocardial TGs or myocardial function. These observations indicate differential, tissue-specific partitioning of TGs and/or fatty acids among nonadipose organs during HFHE diet. **(*J Clin Endocrinol Metab* 93: 2702–2708, 2008)**

Dietary triglycerides (TGs) are absorbed for more than 95% by the gut. After absorption, these TGs can either be oxidized or stored in adipose tissue. A minimal part of these dietary TGs may be stored in nonadipose tissue, such as the pancreas, liver, and myocardium. Storage of TGs in nonadipose tissues is very tightly regulated, and disruption of this regulation is associated with functional and structural changes. In humans, high-fat (HF) diets rapidly increase plasma TG and nonesterified fatty acid (NEFA) levels, increase hepatic TG content, and cause insulin resistance (1). Short-term HF diets also increase intramyocellular TG content in skeletal muscle accompanied by molecular adaptations that favor fat storage in muscle rather than oxidation (2).

In some conditions, the myocardium can also accumulate TGs. This increase in myocardial TG content may be of pathophysiological relevance. Patients suffering from type 2 diabetes mellitus show increased myocardial TG content (3), and healthy volunteers, who were fed a very low calorie diet for 3 d, showed

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Abbreviations: A, Atrial contraction; bpm, beats per minute; CRP, C-reactive protein; E, early filling phase; ECG, electrocardiogram; HEP, high-energy phosphate; HF, high-fat; HFHE, high-fat, high-energy; LV, left ventricular; MR, magnetic resonance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NEFA, nonesterified fatty acid; PCr, phosphocreatine; ppm, parts per million; RPP, rate pressure product; TE, echo time; TG, triglyceride; TR, repetition time.

increased plasma NEFA levels and accumulated myocardial TGs. The increase in myocardial TGs was associated with alterations in myocardial function (4). In addition, in an animal model, a HF diet for 7 wk causes cardiac steatosis and myocardial dysfunction (5).

Increased plasma NEFA levels are also associated with abnormal myocardial energy metabolism. In patients with type 2 diabetes mellitus, myocardial high-energy phosphate (HEP) metabolism was significantly impaired (6). Furthermore, obese men with preserved systolic and diastolic function showed abnormal myocardial HEP metabolism, which was associated with insulin resistance (7).

Proton (^{1}H)-magnetic resonance spectroscopy (MRS), phosphorus (^{31}P)-MRS, and magnetic resonance imaging (MRI) are imaging tools, perfectly capable of assessing hepatic and myocardial TG content, myocardial HEP metabolism, and myocardial function noninvasively (8–11).

In humans, a single HF containing meal had no influence on myocardial TG content and on hepatic TG content (12, 13). This one-meal intervention might have been too subtle to initiate myocardial and hepatic TG accumulation. The effect of a prolonged disturbance of plasma lipids on myocardial TG accumulation remains to be investigated.

Therefore, the goal of the present study was to investigate the effect of a 3-d HF, high-energy diet on hepatic and myocardial TG accumulation, myocardial HEP metabolism, and on myocardial function in healthy subjects using MRS and MRI.

Subjects and Methods

Subjects

There were 15 healthy men who volunteered to participate in this study that was approved by the local ethics committee. Only males were included because the hormonal status or use of contraceptives may affect lipid metabolism in women. Given the well-documented effects of estrogens on lipid metabolism (including plasma lipid levels, adipose tissue) and the gender differences in expression of certain cell-surface receptors/transporters of fatty acids, (14, 15) we decided to exclude women at this stage to avoid the possible confounding influences of potential fluctuation in lipid metabolism in women on hepatic and myocardial TG accumulation. All volunteers signed written informed consent. Subjects were included if they met the following criteria: 1) age older than 18 yr; and 2) no known acute or chronic disease based on history, physical examination, and standard laboratory tests [blood counts, serum creatine, alanine aminotransferase, aspartate aminotransferase, and electrocardiogram (ECG)].

Exclusion criteria included treatment with drugs, smoking, substance abuse, hypertension, or impaired glucose tolerance (experienced with a 2-h oral glucose tolerance test) (16). All subjects performed exercise (walking, running, biking) regularly (range 3–5 h weekly), but none of the subjects engaged in high-performance sports.

Study design

Subjects underwent magnetic resonance (MR) scanning in the afternoon at two different occasions. Before both visits, they were instructed to follow different dietary regimes for 3 d before the measurements. The use of alcohol was not allowed during the 3-d diets. In the first regime, each subject used his normal diet. Mean intake was approximately 2100 kcal/d. The calories were approximately divided as follows: carbohydrates 40%, fat 35%, and protein 25%.

This reference diet was used for the collection of baseline data. The last meal was consumed 4 h before venous blood samples and data collection. During the second regime, the subjects were placed on a 3-d hypercaloric diet characterized by high-fat, high-energy (HFHE) content. The HFHE diet consisted of the same intake as the reference diet, complemented with 800 ml cream every day. The cream added 2632 kcal/d (carbohydrates 3.5%, fat 94%, and protein 2.5%). Therefore, during the HFHE diet, total energy intake was approximately 4732 kcal/d with the calories divided as: carbohydrates 20%, fat 69%, and protein 11%.

The last 200 ml cream was taken 4 h before data collection. The HFHE content was used to induce an elevation of plasma NEFA and TG levels. At each visit, after venous blood collection, MRI and MRS of the heart and liver were performed.

Proton MRS

All MRI/MRS studies were performed using a 1.5-T whole-body MR scanner (Gyroscan ACS/NT15; Philips, Best, The Netherlands) with subjects in the supine position at rest.

Cardiac ^{1}H-MR spectra were obtained from the interventricular septum as described before (9). The body coil was used for radio frequency (RF) transmission, and a 17-cm diameter circular surface coil was used for signal reception.

A point-resolved spectroscopy sequence was used to acquire single voxel MR spectroscopic data from an 8-ml voxel, located in the interventricular septum (Fig. 1). Spectra were acquired at end systole, with an echo time (TE) of 26 msec and a repetition time (TR) of at least 3000 msec. A total of 1024 data points was collected using a 1000-Hz spectral width and averaged over 128 acquisitions. The spectroscopic data acquisition was ECG triggered, and respiratory gating based on navigator echoes was applied to minimize breathing influences (9). Without changing any parameter, spectra without water suppression with a TR of 10 sec and four averages were obtained, to be used as an internal standard.

^{1}H-MRS of the liver was performed with an 8-ml voxel positioned in the liver, avoiding gross vascular structures and adipose tissue depots. The 12th thoracic vertebra was used as a landmark to ensure the same position of the voxel during both visits. Spectra were obtained without respiratory motion compensation using the same parameters as described previously. Only 64 averages were collected with water suppression.

All ^{1}H-MR spectroscopic data were fitted using Java-based MR user interface software (jMRUI version 2.2; developed by A. van den Boo-

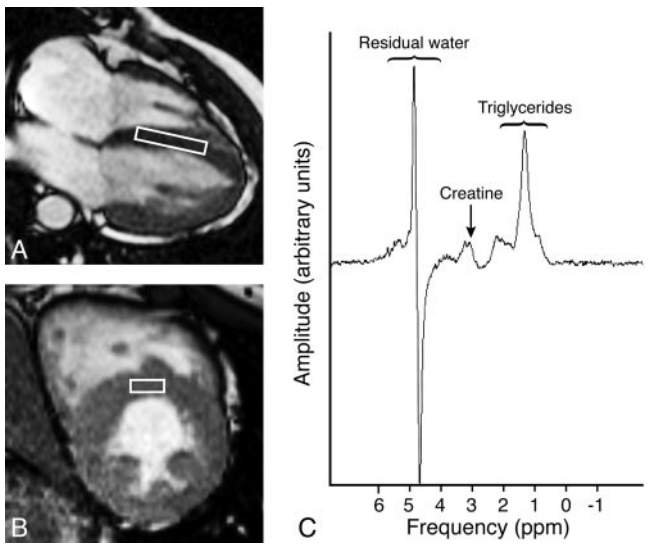

FIG. 1. Myocardial voxel localization for ^{1}H-MRS. Voxel position in four-chamber (A) and short-axis (B) views. An 8-ml voxel was positioned in the interventricular septum in end systole. C, A typical water-suppressed spectrum is demonstrated.

gaart, Katholieke Universiteit Leuven, Leuven, Belgium) (17) as described before (9). Resonance frequency estimates for intramyocardial lipids were described with the assumption of gaussian line shapes at 0.9, 1.3, and 2.1 parts per million (ppm) [only data from the peaks at 0.9 and 1.3 ppm were summated and used on statistical analysis (18)]. Prior knowledge was incorporated into the fitting algorithm using previously published criteria (19–21). The water signal from spectra without water suppression obtained from the same voxel was used as an internal reference for relative quantification of lipid resonances. The water signal peak at 4.7 ppm was quantified using a Lorentzian line shape and analyzed using the Advanced Magnetic Resonance fitting algorithm. The percentage of myocardial and hepatic TG signals relative to the water signal was calculated as: (signal amplitude of TGs)/(signal amplitude of water) × 100 (percent TGs uncorrected for T2 decay times of the studied metabolites).

Phosphorus MRS

A 10-cm diameter surface coil was used to acquire ECG-triggered ^{31}P-MR spectra of the left ventricular (LV) anterior wall with subjects in the supine position. Volumes of interest were selected by image-guided spectroscopy with three-dimensional image selected *in vivo* spectroscopy. Shimming was performed automatically, and tuning and matching of the ^{31}P-surface coil were performed manually. Technical details of data acquisition and spectral quantification were similar as described before (11). Shortly, spectroscopic volume size was typically 7 × 7 × 7 cm. Acquisitions were based on 192 averaged free induction decays, and total acquisition time was 10 min. ^{31}P-MR spectra were quantified automatically in the time domain using prior spectroscopic knowledge, and were corrected for partial saturation effects and for the ATP contribution from blood in the cardiac chambers. The phosphocreatine (PCr)/ATP ratios of the spectra were calculated and used as a parameter representing myocardial HEP metabolism (22).

MRI

The entire heart was imaged in short-axis orientation using ECG-gated breath holds with a sensitivity encoding balanced turbo field echo sequence. Imaging parameters included the following: TE = 1.67 msec, TR = 3.3 msec, flip angle = 35°, slice thickness = 10 mm with a gap of 0 mm, field of view = 400 mm^2, and reconstructed matrix size = 256 × 256. The temporal resolution was 25–39 msec. All images were analyzed quantitatively using dedicated software (MASS; Medis, Leiden, The Netherlands). LV ejection fractions were assessed as measures of LV systolic function. Furthermore, an ECG-gated gradient-echo sequence with velocity encoding was performed to measure blood flow across the mitral valve for the determination of LV diastolic function. Imaging parameters included the following: TE = 4.8 msec, TR = 14 msec, flip angle = 20°, slice thickness = 8 mm, field of view = 350 mm^2, matrix size = 256 × 256, Velocity encoding gradient = 100 cm/sec, and scan percentage = 80%. Analysis was performed using dedicated software (FLOW; Medis). The early filling phase (E) and the atrial contraction (A) were analyzed, and the ratio of the maximal flow rate of E and the maximal flow rate of A (E/A) were calculated. In addition, the peak deceleration gradient of E was assessed. Furthermore, LV filling pressures (E/Ea) were estimated (23). During MRI, blood pressure and heart rate were measured.

Assays

Plasma glucose and TGs were measured by a fully automated P800 analyzer (Roche, Almere, The Netherlands) and insulin using an Immulite 2500 random access analyzer with a chemoluminescence immunoassay (Diagnostic Products Corp., Los Angeles, CA). Coefficients of variation were less than 2% for glucose and TGs, and less than 5% for insulin. The homeostasis model of assessment index was calculated as (glucose × insulin)/22.5. Plasma NEFAs were measured using a commercial kit (NEFA-C; Wako Chemicals, Neuss, Germany). C-reactive protein (CRP) was determined with a us-CRP ELISA (Diagnostic Systems Laboratories, Inc., Webster, TX). The sensitivity was 1.6 μg/liter, and the interassay coefficients of variation ranged from 3–5%.

Statistical analysis

Statistical analysis was performed with SPSS for windows version 12.0 (SPSS, Inc., Chicago, IL). Data are expressed as mean ± SD. The two study conditions were compared by the two-tailed paired *t* test. The linear mixed model was used for correcting within-subject differences when necessary. Significance was assumed when $P < 0.05$.

Results

Clinical and biochemical characteristics

All participants completed the protocol uneventfully. The mean age of the studied subjects was 25.0 ± 6.6 yr. Characteristics of the studied subjects at baseline and after the HFHE diet are shown in Table 1.

After the HFHE diet, postprandial plasma insulin levels increased significantly (from 9.1 ± 4.6 to 21.4 ± 8.8 mU/liter; $P = 0.001$), as did plasma TGs (from 1.3 ± 0.4 to 2.9 ± 1.1 mmol/liter; $P < 0.001$) and plasma NEFAs (from 0.54 ± 0.29 to 0.92 ± 0.33 mmol/liter; $P = 0.002$) levels (Fig. 2). Plasma glucose levels remained unchanged (4.9 ± 0.3 *vs.* 5.0 ± 0.4 mmol/liter).

MRS

After the HFHE diet, ^{1}H-MRS revealed a significant increase in hepatic TG content compared with baseline (4.26 ± 2.78% *vs.* 2.01 ± 1.79%; $P = 0.001$; Fig. 2). Typical hepatic ^{1}H-MR spectra of one volunteer before and after the HFHE diet are shown

TABLE 1. Clinical and biochemical characteristics

	Baseline	HFHE diet	*P* value
Body mass index (kg/m^2)	23.4 ± 2.5	23.6 ± 2.5	0.098
Systolic blood pressure (mm Hg)	123 ± 13	125 ± 13	0.673
Diastolic blood pressure (mm Hg)	67 ± 8	64 ± 8	0.179
Heart rate (beats/min)	60 ± 9	69 ± 11	0.008
Plasma glucose (mmol/liter)	4.9 ± 0.3	5.0 ± 0.4	0.356
Plasma insulin (mU/liter)	9.1 ± 4.6	21.4 ± 8.8	<0.001
HOMA index	2.0 ± 1.2	4.9 ± 2.3	0.001
Plasma TGs (mmol/liter)	1.3 ± 0.4	2.9 ± 1.1	<0.001
Plasma NEFAs (mmol/liter)	0.54 ± 0.29	0.92 ± 0.33	0.002
Plasma alanine aminotransferase (mmol/liter)	25 ± 16	28 ± 13	0.769
Plasma aspartate aminotransferase (mmol/liter)	33 ± 10	33 ± 7	0.250
γ-glutamyl transferase (mmol/liter)	20 ± 8	20 ± 6	0.849

Values are mean ± SD. *P* values were calculated using two-tailed paired-samples *t* tests.

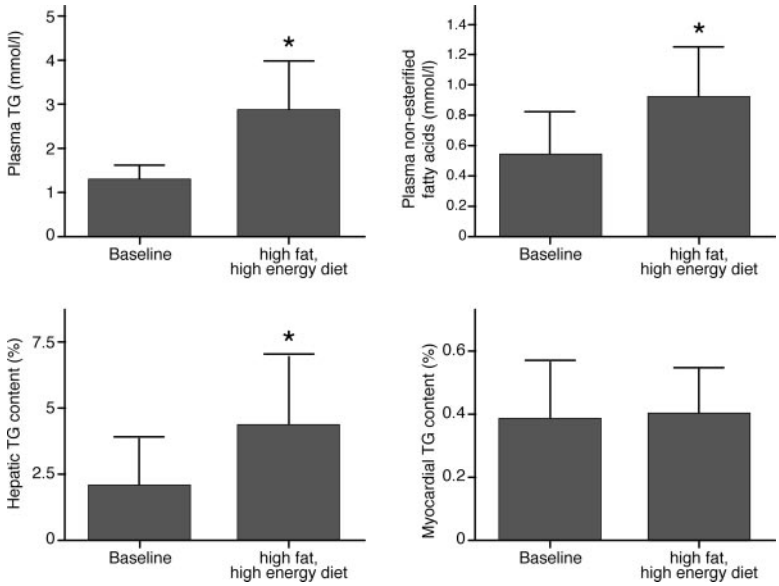

FIG. 2. Lipid response to the HFHE diet. *Bars* represent mean + SD. Hepatic and myocardial TG content is relative to the myocardial and hepatic water signals. *, $P < 0.05$.

in Fig. 3. No significant difference in myocardial TG content was detected after the HFHE diet compared with baseline (0.40 ± 0.12% *vs.* 0.38 ± 0.18%; $P = 0.7$; Fig. 2).

In eight subjects, ^{31}P-MRS was successfully completed on both study occasions. In the other seven subjects, ^{31}P-MRS data at baseline or after the HFHE diet could not successfully be completed due to technical problems or insufficient spectral quality [relative Cramer-Rao SD > 20% (11)]. After the HFHE diet, the myocardial PCr/ATP ratio remained unchanged (2.37 ± 0.51 *vs.* 2.35 ± 0.46; $P = 0.95$).

Myocardial function by MRI

The parameters of myocardial function are shown in Table 2. The HFHE diet did not affect LV systolic function. Myocardial workload, represented by the rate pressure product (RPP) (RPP = heart rate × systolic blood pressure) was significantly increased after the HFHE diet compared with baseline [from 7312 ± 1354 to 8563 ± 1867 mm Hg × beats per minute (bpm); $P = 0.02$]. The HFHE diet decreased the E/A ratio, a measure of diastolic function, significantly compared with baseline (from 2.11 ± 0.39 to 1.89 ± 0.33; $P = 0.031$) and increased heart rate significantly from 60 ± 9 to 69 ± 11 bpm ($P = 0.008$). After adjustment for heart rate, there were no significant differences in E/A ratios between the two diets ($P = 0.12$).

Discussion

This study shows that in males, a short-term intervention with a hypercaloric, HF diet increases postprandial plasma NEFA and TG concentrations considerably, which is associated with a more than 2-fold increase in hepatic TG content. In contrast, this HFHE diet has no acute effects on myocardial TG content, myocardial HEP metabolism, or myocardial function, despite the increased supply of NEFAs and TGs to the heart. These observations stress the short-term physiological and tissue-specific flexibility of ectopic TG pools.

Increased plasma NEFA and TG levels after the 3-d hypercaloric HF diet, indicating good dietary compliance of the volunteers, were associated with a more than 2-fold increase in hepatic TG content. Westerbacka *et al.* (24) previously reported similar findings on the effects of dietary interventions on hepatic TG content in women. The liver acts as a buffer for excessive postprandial flux of NEFAs and TGs (25). The current observation indicates that these hepatic TG stores already expand during very short-term HFHE diets. Based on the unchanged plasma levels of liver enzymes and CRP, short-term hepatic TG accumulation did not contribute to overt indications for hepatic cellular damage or steatohepatitis. Previously published data showed that hepatic liver steatosis is associated with insulin resistance (26). Our study supports these findings. However, because our study only involves a short-term exposure to an unphysiologically HFHE diet, we cannot simply extrapolate the findings of our study to the longer term.

The HFHE diet was also associated with increased plasma insulin levels. Insulin promotes the synthesis and storage of TGs in the liver, and inhibits the release of very low-density lipoprotein-TGs into the circulation (27). In addition, insulin increases the expression or activity of enzymes that catalyze lipid synthesis, whereas insulin inhibits the activity or expression of those that catalyze degradation. Many of these processes require an insulin-induced increase of the transcription factor sterol-regulatory-element-binding protein-1c (28), which, in the liver, is increased by a HF diet (29).

In contrast to the accumulation of hepatic TGs, myocardial TG content remained unchanged after the HFHE diet. Apparently, increased plasma NEFA and TG levels after short-term consumption of a HFHE diet do not change the interrelationship between myocardial NEFA/TG uptake and oxidation in the healthy human heart. This absence of effects of a HFHE diet on myocardial TG content is also in contrast to the response of skeletal muscles, which have accumulated TGs under HF feeding conditions (1, 2). We expected a similar response of the myocardium to a HFHE diet based on these reports. Apparently, increased plasma NEFA and TG levels are not a determinant of excessive myocardial fatty acid uptake, in excess of fatty acid oxidation during short-term HFHE diets in healthy male volunteers. This might be explained by the increased RPP in our study after the HFHE diet. Because plasma glucose concentrations were constant, and plasma NEFA and TG levels increased, the increased cardiac workload probably led to an increase in cardiac lipid oxidation rates (30, 31) that compensated for the increased lipid availability resulting in no net change in myocardial TG content. In the conditions of our study, carbohydrate intake was not changed. It has been suggested (32) that in healthy, nondiabetic human subjects, dietary induced intramyocellular TG accumulation and NEFA oxidation in healthy humans may be influenced by dietary carbohydrate intake, plasma glucose

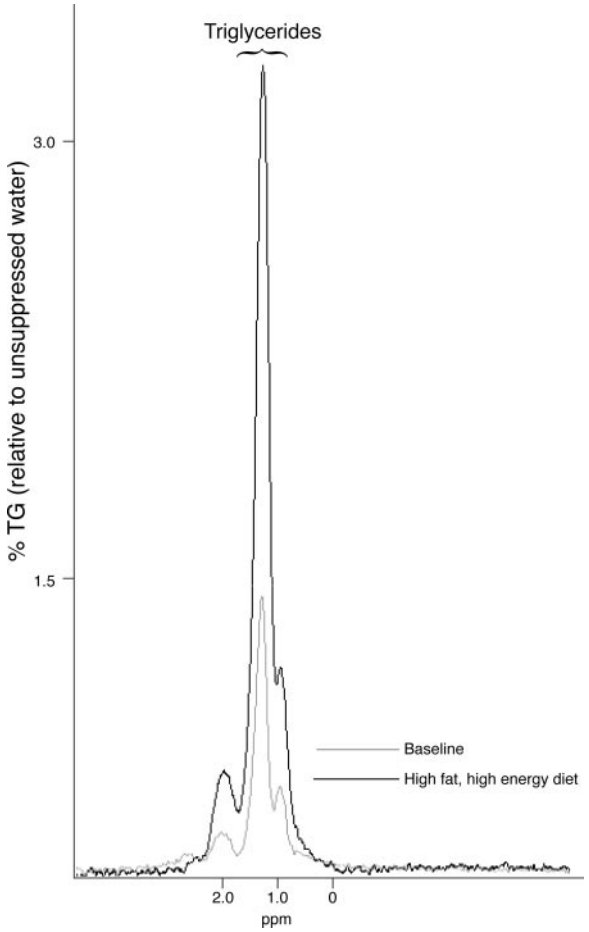

FIG. 3. Typical ^{1}H-MRS of the liver of one subject before and after the HFHE diet. Only the TG region is displayed. Note the marked increase in hepatic TGs after the HFHE diet. % TG, Amount of TGs relative to water × 100.

availability (33), and muscular glycogen stores (34). We cannot exclude the possibility that HF diets with decreased carbohydrate content may have resulted in changed myocardial TG content.

Chronically elevated plasma NEFA levels in patients with type 2 diabetes mellitus are associated with altered myocardial HEP metabolism (6). Increased fatty acid availability in these patients results in increased NEFA uptake in the mitochondria, which decreases the amount of ATP produced per molecule of oxygen consumed in the mitochondrial electron transport chain (35). In the present study, the short-term HFHE diet and the associated increase in plasma NEFA levels did not affect myocardial HEP metabolism. In our opinion these findings are in line with the unchanged myocardial TG content that may indicate no dysregulation of mitochondrial substrate handling.

We used MRI to study the impact of a HFHE diet-induced increase of plasma NEFA levels on LV function. Chronically elevated levels of plasma NEFA have been associated with decreased diastolic function in obesity (36). In the present study, short-term elevated plasma NEFA levels as a consequence of a HFHE diet did not affect myocardial systolic and diastolic function. Although there was a slight decrease in the diastolic E/A ratio after the HFHE diet, mainly caused by an increase in A peak flow rate, this change in the E/A ratio was accompanied by an increased heart rate, which is a well-known postprandial alteration, especially during HF feeding (37–39). An elevated heart rate accounts for an increased preload of the left ventricle, which influences LV filling velocities. Adjusted for heart rate, the E/A ratios before and after the HFHE diet were not significantly different, indicating no change in LV diastolic function.

Caloric restriction also increases plasma NEFA levels, which is accompanied by decreased plasma glucose and unchanged plasma insulin levels. This leads to myocardial TG accumulation, associated with decreased myocardial function (4). Increased plasma NEFA levels after the HFHE diet were accompanied by unchanged plasma glucose and increased plasma insulin levels. After a HFHE diet, there are no changes in myocardial TG content or myocardial function. Apparently, increased plasma NEFA levels after caloric restriction or HFHE diets are associated with different metabolic states, and, therefore, influence myocardial TGs and function differently. These findings are in line with the hypothesis that there might be an association between myocardial TG accumulation and diastolic function. Most likely, myocardial TG stores themselves are inert but, rather, are a reflection of increased intracellular concentrations of fatty acid intermediates that alter myocellular structure and function by complex molecular mechanisms (40). Further studies need to be conducted to unravel this hypothesis.

Some potential limitations of this study should be addressed.

TABLE 2. The effects of HFHE diet on metabolic and LV functional parameters

	Baseline	HFHE diet	*P* value
TG content liver (%)	2.01 ± 1.79	4.26 ± 2.78	0.001
TG content heart (%)	0.38 ± 0.18	0.40 ± 0.12	0.696
PCr/ATP	2.37 ± 0.51	2.35 ± 0.46	0.945
Ejection fraction (%)	60 ± 4	62 ± 5	0.100
RPP (mm Hg × bpm)	7312 ± 1354	8563 ± 1867	0.023
E peak deceleration (ml/sec^2 × 10^{-3})	5.0 ± 1.0	5.1 ± 1.2	0.668
E/Ea	8.8 ± 2.0	9.1 ± 4.0	0.659
E (ml/sec)	614 ± 89	630 ± 125	0.529
A (ml/sec)	299 ± 64	340 ± 75	0.024
E/A	2.11 ± 0.39	1.89 ± 0.33[a]	0.031[a]

Values are mean ± SD. *P* values were calculated using two-tailed paired-samples *t* tests. E/A, Maximum flow across the mitral valve of the early diastolic filling phase divided by the maximum flow of the atrial contraction; E/Ea, estimation of left ventricular filling pressures.

[a] Adjusted for heart rate, there was no significant difference in E/A ratio between the two diets.

First, excluding women from the study and the narrow age range used in this study limit the generalizability of the present study. Further studies need to be initiated to extend the present finding to subjects from both genders and different ages.

Second, data on myocardial lipid uptake and oxidation rates would extend our findings. However, to approximate myocardial lipid uptake and oxidation rates, positron emission tomography using palmitate tracers should be performed, which is a complicated technique. Finally, only half the volunteers completed ^{31}P-MRS measurements, and, therefore, sample size for this parameter is limited and should be interpreted with caution.

Conclusions

Short-term HFHE diet in healthy males results in major increases in plasma TG and NEFA concentrations and hepatic fat content, whereas it does not influence myocardial TG content or myocardial function. These observations indicate differential, tissue-specific partitioning of TGs and/or fatty acids among nonadipose organs during a HFHE diet.

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