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Myocardial Triglyceride Content and Epicardial Fat Mass in Human Obesity: Relationship to Left Ventricular Function and Serum Free Fatty Acid Levels

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Context and Objective: Ectopic fat accumulation within and around the myocardial wall has been implicated in the pathogenesis of heart disease in obesity. We evaluated myocardial and epicardial fat, left ventricular (LV) function, and metabolic risk factors in nine (five lean, four moderately obese) men.

Methods: Myocardial fat percent was quantified in the septum by proton magnetic resonance spectroscopy. Reproducibility was assessed by triplicate systolic and diastolic measurements. LV parameters and epicardial fat were determined by magnetic resonance imaging. Waist-to-hip ratio and liver enzymes (alanine transaminase) were used as surrogate markers of visceral and liver fat contents.

Results: Myocardial fat (2.1 ± 0.5 *vs.* 0.8 ± 0.1, $P = 0.03$) and epicardial fat (120 ± 33 *vs.* 55 ± 12 g, $P = 0.08$) were higher in obese than lean subjects. Individuals with above-median alanine transaminase values had a 4-fold elevation in myocardial fat. The coefficient of variation of repeated myocardial fat percent determinations was 17 ± 3 and 23 ± 3% in systole and diastole, respectively. Myocardial fat was correlated with free fatty acid (FFA) levels ($r = 0.76$; $P = 0.017$), epicardial fat ($r = 0.69$; $P = 0.042$), and waist-to-hip ratio ($r = 0.70$; $P = 0.035$), and it showed a tendency to associate positively with LV work. Epicardial fat was associated with peripheral vascular resistance (positively) and the cardiac index (negatively). FFA levels were significantly correlated with LV mass ($r = 0.72$; $P = 0.030$) and forward work ($r = 0.74$; $P = 0.023$).

Conclusions/Interpretation: The accumulation of triglyceride in and around the myocardium of moderately obese individuals is significant, and it is related to FFA exposure, generalized ectopic fat excess, and peripheral vascular resistance. These changes precede LV overload and hypertrophy. **(*J Clin Endocrinol Metab* 91: 4689–4695, 2006)**

THE ACCUMULATION OF fat in nonadipose tissues and around visceral organs has been implicated in the relationship between metabolic and cardiovascular disease (1–6). The bulk of evidence on the adverse consequences of ectopic fat deposition stems from studies relating metabolic risk and fat content in the liver, skeletal muscle, and abdominal cavity. The accumulation of triglycerides within and around the heart is the focus of increasing attention as a more direct mechanism underlying these associations (7–9).

Animal studies have provided consistent evidence that excess accumulation of triglycerides in cardiomyocytes impairs left ventricular (LV) function and promotes cardiac fibrosis and apoptosis in obese rats (7) and in high-fat-fed rabbits (10). Studies in humans are few. The use of magnetic proton spectroscopy (^{1}H-MRS) for the evaluation of myocardial fat content in end systole *in vivo* has been recently introduced and validated (11–13), showing the same level of accuracy as compared with direct biochemical measurements in lean and obese Zucker rats and short-term reproducibility of approximately 17% in the human myocardial septum (11). By using this technique in humans, it has been recently shown that septal myocardial fat percent is unaffected by a single high-fat meal, whereas it was increased by 3-fold after a prolonged (48-h) fasting period (14). Because starvation up-regulates free fatty acid (FFA) release from adipose tissue stores, the consequent elevation in FFA supply, as triglyceride substrate, may explain the above finding, but FFA levels were not reported in this study. Along with FFA from the circulation, the heart receives direct drainage of fatty acids from epicardial fat surrounding the cardiac muscle. Epicardial fat in humans (9) and myocardial fat in animals (7) were individually found to be positively associated with the mass of the left ventricle, implicating these fat depots in heart hypertrophy in obesity. So far, the modulation of myocardial fat in humans remains to be elucidated, and it is not known whether myocardial steatosis is associated with a larger epicardial fat depot surrounding the organ.

The present study was conducted to evaluate the effect of obesity on myocardial fat, epicardial fat mass, and circulating FFA levels and the association between myocardial fat and recognized indicators of ectopic fat deposition, including waist-to-hip ratio and liver enzymes, as surrogate markers of

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Abbreviations: CV, Coefficient of variation; EDV, end-diastolic volume; ESV, end-systolic volume; FFA, free fatty acids; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; ^{1}H-MRS, magnetic proton spectroscopy; LDL, low-density lipoprotein; LV, left ventricular; RPP, rate-pressure product; SV, stroke volume; TE, echo time; TR, repetition time; VOI, volume of interest; WHR, waist-to-hip ratio.

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visceral and liver fat contents, respectively. The study was performed in human subjects with normal LV function to determine the reproducibility of systolic and diastolic ^{1}H-MRS measurements of septal myocardial fat percent at our laboratory.

Subjects and Methods

Study design

Nine subjects with normal LV function, including five lean [body mass index (BMI), 22 ± 1 kg/m^2; range, 19–24) and four obese individuals (BMI, 30 ± 1 kg/m^2; range 28–33 kg/m^2; $P = 0.0005$ between groups), were studied by ^{1}H-MRS, each on six consecutive occasions during the same study day. Magnetic resonance imaging (Philips Gyroscan Intera 1.5 T Nova Dual MR scanner; Philips Medical Systems, Best, The Netherlands) was performed to quantify epicardial fat and to determine LV mass, function, and dimensions [end-diastolic volume (EDV) and end-systolic volume (ESV)]. Subjects were healthy as judged by history, physical examination, and routine blood testing. None had a history of diabetes or cardiovascular disease or was taking any medication. The protocol was approved by the Ethical Committee of Turku University Hospital, and all subjects gave their written informed consent before taking part in the study.

Metabolic characterization

Metabolic characterization, as shown in Table 1, included 1) anthropometric measurements (weight, height, and waist and hip circumferences), 2) assessment of systolic and diastolic blood pressure and heart rate, 3) lipid profile [FFA, triglycerides, total cholesterol, low-density lipoprotein (LDL)-cholesterol, and high-density lipoprotein (HDL)-cholesterol], glucose profile [fasting plasma glucose, glycosylated hemoglobin (HbA_{1c}), and C-peptide], and liver function measurements [alanine transaminase (ALT) and γ-glutamyl-transpeptidase]. Blood pressure was measured in the sitting position after 5 min of rest (Omron-5M automatic device). Systolic blood pressure was multiplied by heart rate to obtain the rate-pressure product (RPP) indicative of LV work. Weight and height were measured in light clothing without shoes. BMI was calculated by dividing the weight (in kilograms) by the square of height (in meters). The waist-to-hip ratio (WHR) was determined by measuring the waist circumference at the narrowest part of the torso and the hip circumference in a horizontal plane at the level of the maximal extension of the buttocks.

LV function and dimensions

LV mass, EDV, ESV, and ejection fraction were measured from continuous short axis slices by using the balanced turbo field echo sequence. Imaging parameters included repetition time (TR) of 3.8 msec, echo time (TE) of 1.9 msec, and matrix of 256 × 256. Slice thickness was 8 mm with no gap between slices. Thirteen to 16 slices were required to cover the left and right ventricles completely from apex to atrium. Image analysis was performed by using Philips post-processing software (ViewForum R4.1; Philips Medical Systems). Cine loops were reviewed to identify end-diastolic and end-systolic frames. Epicardial and endocardial contours were outlined manually. Papillary muscles were included in the LV cavity volume to gain better reproducibility (15). Cardiac output and stroke volume (SV) were computed from ESV, EDV, and heart rate. Forward LV work was calculated as the product of systolic blood pressure, SV, and heart rate, and forward LV work per gram of tissue was calculated as forward LV work/LV mass. The cardiac index was calculated as the ratio between cardiac output and body surface area. Peripheral vascular resistance was calculated as the ratio of mean blood pressure (mm Hg) to cardiac output (ml/min).

Epicardial fat mass

The mediastinum was imaged using a body coil. Epicardial fat was measured on an axial T1-weighted sequence with TR of 2.1 msec, TE of 0.8 msec, field of view of 44.8 × 44.8 cm, matrix of 256 × 256, and slice thickness of 10 mm. Epicardial fat measurements were obtained by using Philips post-processing software (ViewForum R4.1, Philips Medical Systems). Regions of interest were manually drawn along the borders of fat surrounding the heart from the apex to the pulmonary trunk. All the analyses were evaluated by an experienced radiologist. Epicardial fat areas were multiplied by slice thickness and converted in grams by using fat density of 0.9196 g/ml (16).

LV ^{1}H-MRS

Each subject underwent six series of signal acquisition, each including 10 spectra. Subjects remained positioned in the scanner during the entire series, with no time interval between consecutive measurements. A Philips Gyroscan Intera 1.5 T scanner with a SENSE flex-L-coil was used. After location of the heart, the left ventricle was imaged in two distinct orientations to detect the spectroscopic volume of interest (VOI). VOIs (10 × 15 × 15 mm) were placed on LV short-axis images, and attention was paid to include only myocardium. Single-voxel proton spectroscopy, with PRESS sequence, was used to determine the molecular contents of lipids and water. TE of 30 msec and TR of 3000 msec were used. Considering the T_1 constants of lipids and water (17), the maximum error due to the TR is approximately 1%; because lipid and water T_2 values are close to TE, T_2 correction was required. Cardiac triggering was used with breath-hold to ensure stable location of the VOI throughout the study. The magnet was shimmed during the first breath-hold, and the quality of shimming was shown by the width of the water peak; the peak width obtained was sufficiently narrow to avoid separate gradient tuning; fine tuning with B(0)-map was sufficiently rapid to be performed during each breath-hold. Each spectrum was measured separately to minimize the effect of unequal phase errors, and spectra were summed afterward. Spectra were collected in two cardiac phases, namely end

TABLE 1. Characteristics of the study population

	All subjects (n = 9)		Lean subjects (n = 5)	Obese subjects (n = 4)
	Mean ± SEM	Range		
Age (yr)	37 ± 5	22–59	29 ± 4	46 ± 7
BMI (kg/m^2)	26 ± 2	19–33	22 ± 1	30 ± 1[a]
WHR (cm/cm)	0.92 ± 0.03	0.81–1.02	0.87 ± 0.04	0.98 ± 0.02[b]
Plasma glucose (mmol/liter)	5.2 ± 0.2	4.3–5.8	5.1 ± 0.3	5.2 ± 0.2
HbA_{1c} (%)	5.4 ± 0.1	5.1–6.0	5.4 ± 0.2	5.5 ± 0.1
C-peptide (nmol/liter)	0.55 ± 0.07	0.32–0.90	0.63 ± 0.11	0.45 ± 0.03
ALT (U/liter)	31 ± 5	15–63	30 ± 9	32 ± 4
γ-GT (U/liter)	27 ± 6	10–57	28 ± 8	26 ± 10
FFA (mmol/liter)	0.51 ± 0.07	0.23–0.80	0.36 ± 0.04	0.70 ± 0.06[a]
Total cholesterol (mmol/liter)	3.9 ± 0.3	2.4–5.8	4.5 ± 0.3	3.2 ± 0.3[b]
HDL-cholesterol (mmol/liter)	1.4 ± 0.1	0.8–1.7	1.4 ± 0.1	1.4 ± 0.2
LDL-cholesterol (mmol/liter)	2.1 ± 0.2	1.2–3.7	2.4 ± 0.3	1.6 ± 0.2
Triglyceride (mmol/liter)	1.0 ± 0.2	0.4–2.3	1.4 ± 0.3	0.6 ± 0.1[b]

Data are given as mean ± SEM. γ-GT, γ-Glutamyl-transpeptidase.
[a] $P \leq 0.001$; [b] $P < 0.05$ between lean and obese subjects.

systole and end diastole, corresponding to cardiac triggering delay times of 300–350 msec and 600–800 msec, respectively, depending on heart rate. In either phase, 10 spectra were collected, each one during breath hold, and subsequently summed. The series was repeated three times in each cardiac cycle phase for the measurement of intra-individual reproducibility, and triplicate end-systolic and end-diastolic measurements were averaged for the determination of inter-individual variability, for group comparison, and for the evaluation of associations.

Calculation of myocardial fat percent

In myocardial proton spectra, water molecules and lipid methylene and methyl groups generate the higher signals. The number of contributing protons in the frequency region of fatty acids was determined and multiplied by the molecular mass and relative appearance of different triglycerides (18) to obtain fat distribution, S_f as:

$$S_f = \frac{1}{3} A_f \sum_{i=1}^{n} \frac{b_i}{p_i} m_i\,(tot)$$

where 1/3 accounts for the 1:3 triglyceride to fatty acid ratio, A refers to the area of the peak, b_i accounts for the proportions of most common fatty acids (18), p_i is the number of protons in the corresponding peak range, and m_i is the molecular mass of triglyceride. A similar parameter was derived for water (S_w, $b = 1$, m = molecular mass of water). The areas of the spectra were calculated after phase correction with no filtering and fitting by covering the frequency range of the CH_3, $(CH_2)_{n-2}$, βCH_2, αCH_2, and CH_2 groups next to double-bonded CH groups (18). Filtering and Lorentzian fitting were made to confirm the quality of the spectra (data not shown). The full width at half-maximum value was 13–15 Hz, corresponding to 0.20–0.23 ppm at 1.5-T field strength.

Then fat content was calculated according to a previously reported formula (17) and adapted to the content of water in the myocardium (19):

$$F_{\%} = \frac{S_f}{S_w/0,78}$$

Biochemical analysis

All laboratory specimens were drawn after a 12-h fasting period. Fasting plasma glucose was determined using the glucose oxidase method (Analox Glucose analyzer, GM9). HbA_{1c} was measured by the Variant II HbA_{1c} analyzer based on chromatographic separation on a cation-exchange cartridge (Bio-Rad Laboratories, Hercules, CA). Plasma C-peptide and insulin were measured using electrochemiluminescence immunoassay (Roche Modular E170 analyzer; Roche Diagnostics GmbH, Mannheim, Germany). Total cholesterol, HDL-cholesterol, and triglyceride concentrations were measured in plasma by standard enzymatic methods using Roche Diagnostics reagents with an automated analyzer (Roche Modular P800). LDL-cholesterol was calculated by using Friedewald's equation (20). Serum FFA were measured enzymatically (Wako Nefa C kit; Wako Chemicals GmbH, Germany).

Statistical analysis

Results are expressed as mean ± SEM. ANOVA was used in group comparisons. Regression analyses were carried out according to standardized methods. Coefficients of variation (CV) of triplicate measurements were calculated to determine the reproducibility of the technique, as CV percent = (within-subject SD)/(within-subject mean of three myocardial fat percent measurements) × 100.

Results

The hemodynamic and cardiac parameters (Table 2) documented normal LV function and volumes, but a higher LV mass, forward work, and cardiac index in obese *vs.* lean subjects (the latter falling short of statistical significance).

The location of the VOI in the myocardial wall in a typical study is shown in Fig. 1. The septal wall thickness allowed VOI location well within the myocardial tissue, thus avoiding blood contamination in all subjects, especially during systole. Within-subject reproducibility over repeated ^{1}H-MRS measurements showed a CV of 17 ± 3 and 23 ± 3% in systole and diastole, respectively ($P = 0.11$), with no difference between obese and lean subjects. Between-subject variability was 21 and 52% during systole and 40 and 44% during diastole in lean and obese subjects, respectively.

TABLE 2. Hemodynamic and LV parameters in the study groups

	Lean subjects	Obese subjects	*P* value
SBP (mm Hg)	143 ± 5	152 ± 6	0.28
DBP (mm Hg)	87 ± 5	91 ± 2	0.48
HR (bpm)	72 ± 3	74 ± 4	0.77
LV EF (%)	57 ± 2	57 ± 3	0.86
LV mass (g)	109 ± 6	120 ± 4	0.18
LV CO (liters/min)	6.5 ± 0.11	7.3 ± 0.72	0.26
LV ESV (ml)	76 ± 3	87 ± 11	0.32
LV EDV (ml)	175 ± 3	202 ± 21	0.20
LV SV (ml)	99 ± 3	115 ± 14	0.24
RPP (mm Hg × bpm)	10395 ± 848	11310 ± 943	0.49
LV FW (RPP·SV)	1021 ± 54	1291 ± 170	0.13
LV FWm (FW/g)	9.4 ± 0.5	10.7 ± 1.2	0.33
Cardiac index (liters/min·m^2)	934 ± 45	1103 ± 106	0.16

CO, Cardiac output; DBP, diastolic blood pressure; EF, ejection fraction; FW, forward work; m, LV mass; SBP, systolic blood pressure.

Differences in ectopic fat depots and in circulating FFA are shown in Figs. 2 and 3. A 3-fold elevation in myocardial fat was observed in obese individuals, whether expressed as percentage in the septal heart region (2.1 ± 0.5 *vs.* 0.8 ± 0.1%; $P = 0.032$; Fig. 3) or as mass per gram of LV (21 ± 5 *vs.* 8 ± 1 mg/g; $P = 0.032$) and in the entire LV wall (2.46 ± 0.55 *vs.* 0.89 ± 0.11 g; $P = 0.016$). The comparison of individual measurements provided similar results ($P = 0.03$, 0.10, and 0.006 in the three repeated systolic evaluations). Epicardial fat and circulating fatty acids were twice as high in obese *vs.* lean individuals, and a significant WHR ($P = 0.039$) and waist difference was observed between the two groups (Fig. 3). Because age was a significant correlate of myocardial fat ($r = 0.75$; $P = 0.021$), epicardial fat ($r = 0.97$; $P < 0.0001$), and WHR ($r = 0.73$; $P = 0.024$), age-adjusted comparisons were also made, with minor effects on the statistical significance. To investigate the relationship between tissue fat accumulation in the heart and in the liver, we used ALT levels as a surrogate marker of hepatic steatosis (21); subjects were divided according to the ALT median value, showing that the group in the higher ALT range had a 4-fold elevation in myocardial fat (Fig. 4); the correlation between these variables did not achieve statistical significance because of one outlier ($r = 0.90$; $P = 0.002$; $n = 8$).

Associations

Septal myocardial fat percent was associated with FFA levels ($r = 0.67$; $P = 0.049$) (Fig. 5) and epicardial fat ($r = 0.66$; $P = 0.056$) but not with blood pressure, cholesterol, triglycerides, glucose, or HbA_{1c} levels. LV myocardial fat was associated with FFA ($r = 0.76$; $P = 0.017$), epicardial fat ($r = 0.69$; $P = 0.042$), and WHR ($r = 0.70$; $P = 0.035$) and, more weakly, with the BMI ($P = 0.06$). Myocardial fat percent showed a trend to associate positively with RPP ($P = 0.07$) and forward LV work ($P = 0.10$), whereas epicardial fat was

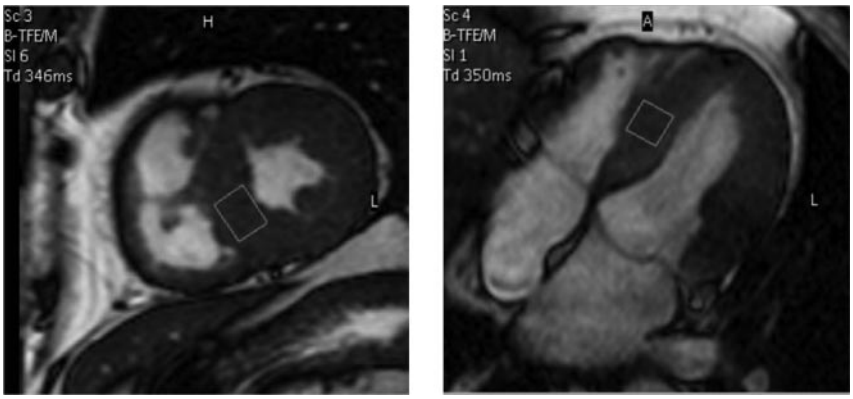

FIG. 1. VOI location in the septal wall, as confirmed in short-axis (*left*) and four-chamber orientations (*right*).

inversely associated with the cardiac index (r = 0.74; P = 0.022) (Fig. 5) and positively related to peripheral vascular resistance (P = 0.0057, BMI-adjusted), and FFA levels were significantly correlated with LV mass (r = 0.72; P = 0.030) (Fig. 5) and forward LV work (r = 0.74; P = 0.023).

Discussion

The present data demonstrate that epicardial and myocardial fat depots are both expanded in moderately obese men, thereby indicating that myocardial steatosis coexists with a more generalized abnormality in fat tissue topography including intraabdominal obesity and fatty liver. To the best of our knowledge, the present findings are the first to document a concurrent 3-fold and 2-fold elevation in myocardial and epicardial fat, respectively, in moderately obese *vs.* lean men. Although the study group was relatively small, because of the complexity and duration of the reproducibility MR sessions, the results were consistent and the differences were pronounced. A within-subject reproducibility of approximately 20% was observed for myocardial fat measurements, in line with previous findings of 17% CV in humans (11). A slight difference in VOI location between consecutive evaluations and the prolonged duration of the whole session, possibly inducing slight body or respiratory motion, may have affected the reproducibility; respiratory gating might to some extent improve it but was not available here. However, notably the current CV is less than one tenth of the difference observed between obese and lean men.

A borderline correlation between BMI and myocardial fat percent has been reported in humans (11), and epicardial fat has been an increasing focus of investigation in human obesity (8, 9, 22). This study extends previous findings by providing conclusive evidence of a remarkably consensual effect of obesity on epicardial and myocardial fat. By using the PRESS sequence, which controls for out-of-volume effects and by limiting direct measurements to the myocardial septum, lipid contamination from epicardial to myocardial fat was minimized (11); postmortem studies have documented that myocardial triglycerides are located within the cytosol and that the infiltration of epicardial fat between myocardial fibers, especially in the right ventricular wall, occurs only in morbid obesity (23). Consistent with previous evidence (14), we could not find any association between circulating triglyceride and myocardial fat. In addition, neither epicardial nor myocardial fat was associated with the plasma glucose or cholesterol profile in the current series. In a previous study, a 48-h fasting period was associated with a 3-fold elevation in myocardial fat percent, suggesting that fasting-

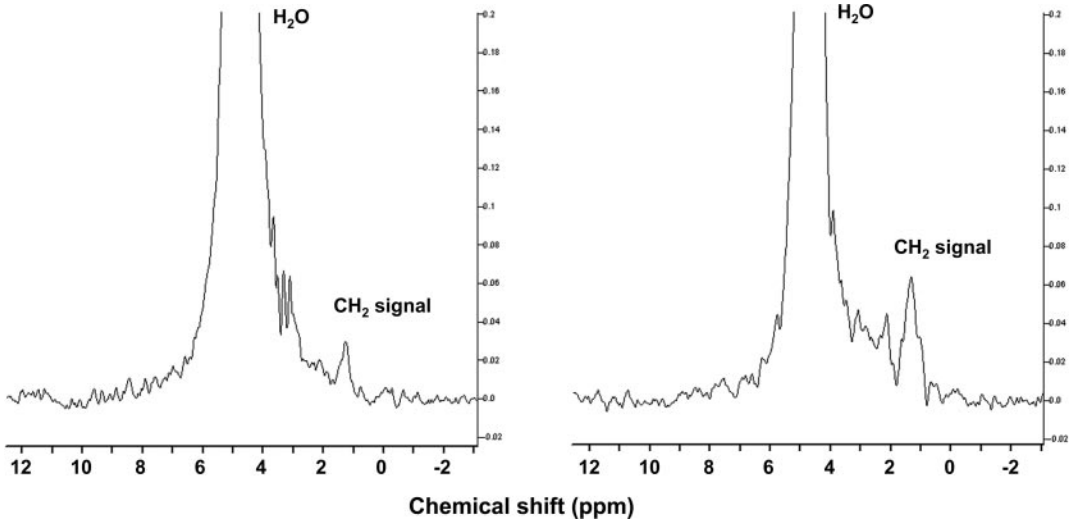

FIG. 2. Examples of spectra in one lean and one obese study subject. Filtering of the signal was carried out with the 5-Hz line-broadening exponential function. The main methylene peak is visible at 1.3 ppm. Amplitude is expressed in arbitrary units.

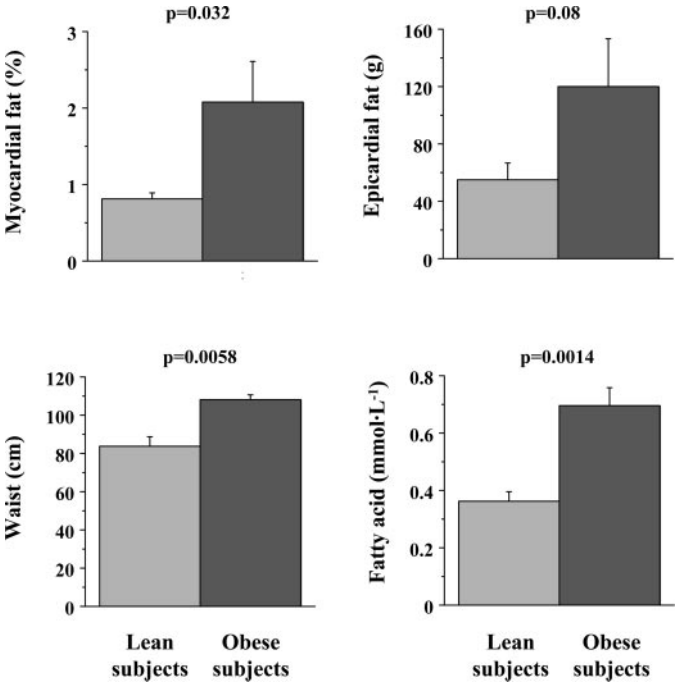

FIG. 3. Consensual increase in ectopic fat and circulating FFA levels in patients with obesity. Age-adjusted *P* values are 0.039 (myocardial fat percent), 0.001 (epicardial fat), 0.002 (waist), and 0.006 (FFA).

induced enhancement of FFA release from adipose tissue may be a strong drive of cardiac lipid content. The significant relationship between myocardial fat and FFA reported here supports this line of reasoning.

Epicardial and myocardial fat receive the same coronary blood supply; similar to other visceral adipose depots, epicardial fat is characterized by a high rate of FFA release (24), which encounters no physical barrier or fascia in its transit toward cardiomyocytes (25). Thus, the heart muscle receives a dual direct fatty acid supply from epicardial fat and from circulation. In the current dataset, FFA levels were a significant predictor of LV mass, whereas myocardial and epicardial fat were more strongly related to LV work and mechanical load. Peripheral vascular resistance, which is regarded as an early determinant of LV hypertrophy in obesity (26), was significantly related to epicardial fat. In humans (27), obesity and insulin resistance are associated with an increased myocardial uptake and oxidation of fatty acids, partly because of an enhanced availability of substrate, leading to increased oxygen requirements and decreased cardiac efficiency. In obese animals (7), the resulting mismatch between FFA uptake and oxidation eventually shifts the fate of the substrate into the production of fatty acid intermediates, free radicals, and excess storage in myocardial triglycerides, causing cardiomyocyte apoptosis, increased oxidative stress, and impairment in cardiac function. Similar to our figures, myocardial triglyceride content was three times higher in 14-wk Zucker fa/fa rats compared with control animals (7); the rise in myocardial fat was progressive during growth and preceded the formation of toxic products and the occurrence of heart dysfunction. Taken together, the current and previous evidence (11, 14, 27) is consistent in suggesting that the mechanisms delineated in animal models of obesity are operative also in humans: increased availability of circulating fatty acids, as observed in obesity and during prolonged fasting (14), promotes substrate extraction and storage by the myocardium. Notably, these alterations were associated with normal LV function in this and previous human investigations, indicating that they may represent early events. In our data, LV hypertrophy and overload can be surmised from the association of epicardial fat and peripheral vascular resistance (a main determinant of LV hypertrophy) as well as the incipient rise in LV mass and workload observed in obese individuals (Table 2).

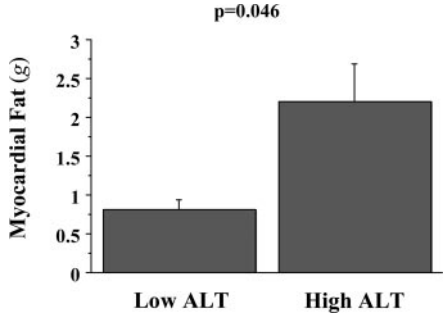

FIG. 4. Myocardial fat in subjects with higher *vs.* lower alanine transaminase (ALT).

We have previously shown that among inflammatory and metabolic factors, liver steatosis was the strongest predictor of myocardial insulin sensitivity and perfusion in patients with type 2 diabetes (6), and we postulated that hepatic fat content may be an indicator of a generalized condition of ectopic triglyceride deposition, involving the cardiac wall; in turn, lipids in the heart wall would be directly responsible for myocardial insulin resistance. The current work is supportive of this hypothesis. Myocardial fat was more strongly associated with visceral obesity (as reflected in epicardial fat mass and WHR) than with the degree of overweight itself (as the BMI). Notably, the relationship observed between myocardial fat and ALT, a recognized surrogate marker of steatosis (21), was independent of obesity because ALT was not different between lean and obese individuals ($P = 0.87$). Direct and indirect mechanisms may explain the association. The liver is most important in controlling the amount of triglyceride and FFA reaching circulation. Additionally, liver and heart share the peculiarity of first-pass organs into which FFA drain from a visceral fat depot , *i.e.* intraabdominal and epicardial adipose tissue, respectively. Epicardial and intraabdominal fat masses are correlated in size (8) and show similar biochemical properties, including a higher lipolytic rate than their sc counterparts (24). In addition, like the liver, the heart is uniquely capable of disposing of FFA because of its energy requirements and has a suggested role in packaging and secreting fatty acids as lipoproteins (28). Finally, besides FFA, hypoadiponectinemia, which was not available in this study, could link myocardial and liver steatosis in obesity, given the strong inverse relationship between hepatic fat content and plasma adiponectin levels (29), together with the recent demonstration that adiponectin inhibits hypertrophic signaling in the myocardium through activation of AMP-activated protein kinase signaling (30).

In conclusion, the accumulation of triglyceride in the myo-

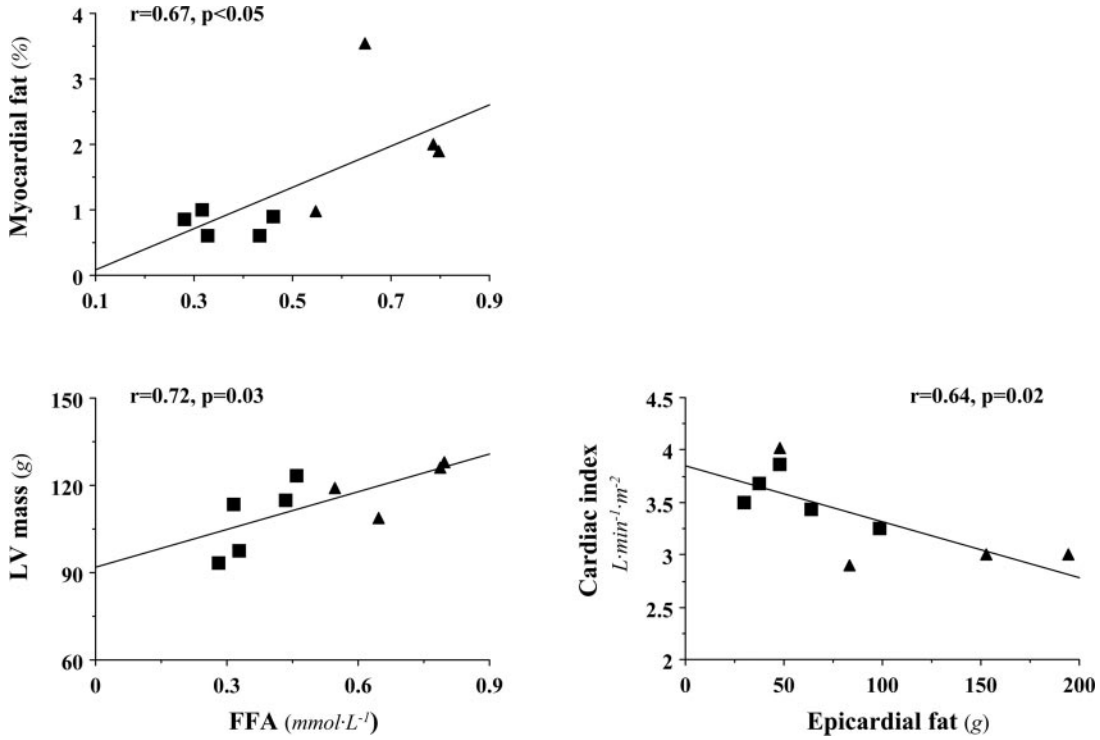

FIG. 5. Regression analysis showing significant associations of FFA with myocardial fat and LV mass, or between epicardial fat and the cardiac index in obese (▲) and lean (■) men.

cardium of moderately obese men is significant and may result from fatty acid overflow to the heart because of a generalized condition of ectopic fat excess, correlating with the severity of peripheral vascular resistance. These features precede, and likely contribute to, LV overload and hypertrophy.

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