(Left) A working model of how weight loss–induced changes in myocardial metabolism may reverse obesity-related left ventricular (LV) relaxation impairment (asterisks indicate study findings). Weight loss decreases myocardial fatty acid (FA) utilization and oxidation. This in turn may decrease intracellular FA metabolites, which can impair oxidative phosphorylation (Ox. phos.) and hence LV relaxation. Moreover, because FA oxidation contributes to overall myocardial mitochondrial oxygen consumption (MVO2), total MVO2 decreases. Total MVO2 also decreases with decreased uncoupling protein (UCP) or adenine nucleotide transporter (ANT) activity. A decrease in total MVO2 leads to improved LV relaxation if there is enhanced flow of energy directed toward adenosine triphosphate (ATP) production and subsequent LV relaxation rather than dissipation by uncoupling. A decrease in MVO2 may also diminish free radical production and oxidative stress (Ox. stress), which can negatively affect relaxation. (Right) A pre-gastric bypass surgery positron emission tomography–derived myocardial image (top) illustrates higher MVO2 than is seen in the post–surgery image (bottom) in the same subject. The color scale depicts $^{11}\text{C}$ activity; higher counts are represented as white and red, lower counts (and lower MVO2) in blue and green. (Images from the article by Lin et al., page 1804.)
Myocardial Oxygen Consumption Change Predicts Left Ventricular Relaxation Improvement in Obese Humans After Weight Loss

C. Huie Lin1, Suraj Kurup1, Pilar Herrero2, Kenneth B. Schechtman3, J. Christopher Eagon4, Samuel Klein5, Víctor G. Dávila-Román1, Richard I. Stein5, Gerald W. Dorn II6, Robert J. Gropler2, Alan D. Waggoner1 and Linda R. Peterson1

Obesity adversely affects myocardial metabolism, efficiency, and diastolic function. Our objective was to determine whether weight loss can ameliorate obesity-related myocardial metabolism and efficiency derangements and that these improvements directly relate to improved diastolic function in humans. We studied 30 obese (BMI >30 kg/m²) subjects with positron emission tomography (PET) (myocardial metabolism, blood flow) and echocardiography (structure, function) before and after marked weight loss from gastric bypass surgery (N = 10) or moderate weight loss from diet (N = 20). Baseline BMI, insulin resistance, hemodynamics, left ventricular (LV) mass, systolic function, myocardial oxygen consumption (MVO₂), and fatty acid (FA) metabolism were similar between the groups. MVO₂/g decreased after diet-induced weight loss (P = 0.009). Total MVO₂ decreased after dietary (P = 0.02) and surgical weight loss (P = 0.0006) and was related to decreased BMI (P = 0.006). Total myocardial FA utilization decreased (P = 0.03), and FA oxidation trended lower (P = 0.06) only after surgery. FA esterification and LV efficiency were unchanged. After surgical weight loss, LV mass decreased by 23% (Doppler-derived) E/E′ by 33%, and relaxation increased (improved) by 28%. Improved LV relaxation related significantly to decreased BMI, insulin resistance, total MVO₂, and LV mass but not FA utilization. Decreased total MVO₂ predicted LV relaxation improvement independent of BMI change (P = 0.02). Weight loss can ameliorate the obesity-related derangements in myocardial metabolism and LV structure and diastolic function. Decreased total MVO₂ independently predicted improved LV relaxation, suggesting that myocardial oxygen metabolism may be mechanistically important in determining cardiac relaxation.


INTRODUCTION

Obesity is a major risk factor for heart failure (1). Data suggest that “obesity cardiomyopathy,” is a distinct clinical entity characterized by left ventricular (LV) remodeling, reduced cardiac efficiency, and LV diastolic dysfunction, which may progress to systolic dysfunction (2–4). The mechanisms responsible for the relation between obesity and heart failure in humans are not well-understood but may, in part, involve altered myocardial substrate metabolism (4,5). Results from studies in animal models demonstrate obesity increases myocardial fatty acid (FA) metabolism and oxygen consumption (MVO₂) leading to increased oxidative stress, cardiac dysfunction, and apoptosis (6–9). Interventions that reduce FA accumulation and/or oxidative stress in cardiac myocytes prevent the development of myocardial dysfunction in these models (6). Excessive amounts of FA metabolites in skeletal muscle also adversely affect ATP generation and function (10). In humans, obesity and insulin resistance are related to similar increases in MVO₂ and myocardial FA metabolism and oxidative stress markers (4,11).

Weight loss in humans ameliorates obesity-related cardiac hypertrophy and diastolic dysfunction (12–14). Weight loss also improves the excessive myocardial FA uptake and storage.
related to obesity (15,16). However, the effects of weight loss on myocardial FA oxidation, MVO₂, and efficiency are unknown. Furthermore, it is not known whether weight loss-induced changes in myocardial metabolism predict improvement in cardiac function in humans. We hypothesized (i) weight loss would reverse the high rates of MVO₂ and FA metabolism and decrease the cardiac inefficiency associated with obesity, (ii) improvements in MVO₂ and/or FA metabolism would predict improved LV relaxation. To evaluate the relationship between metabolism and functional changes over a wide range of weight loss, two different modes of weight loss were studied, diet and gastric bypass surgery. Positron emission tomography (PET) was used to quantify MVO₂ and myocardial FA metabolism. Echocardiography with tissue Doppler imaging was used to quantify cardiac structure, systolic and diastolic function (LV relaxation (E’)) and E/E’).

METHODS AND PROCEDURES

Study subjects
Obese (BMI >30 kg/m²) subjects enrolled in this prospective, interventional study. Surgery subjects were recruited from the bariatric surgery center at Barnes–Jewish Hospital, diet subjects from the Volunteer for Health office. All subjects completed screening, including a history, physical examination, and blood testing. Individuals with suggestive histories were screened for coronary disease and sleep apnea using exercise stress echocardiography and polysomnography. Subjects were sedentary upon study entry. Exclusion criteria: weight >159 kg, age <21 or >50 years (to decrease the impact of aging) (17), insulin-requiring diabetes, heart failure, a history of coronary disease, chest pain, or untreated sleep apnea, being an active smoker, pregnant, lactating, or postmenopausal. Subjects in the surgery group and the diet groups were purposefully studied after different periods of weight loss (16 ± 5 and 8 ± 2 months, respectively) in order to maximize weight loss and weight stability (14,18), and minimize weight regain and subject drop out (14). This study was designed to recruit subjects who would undergo different weight loss interventions in order to obtain a large spectrum of weight loss, and hence, metabolic and functional changes for comparison. Both groups were screened and imaged over the same 5-year time frame by the same research team, using the same equipment. Written, informed consent was obtained before subject participation.

Gastric bypass surgery
The same surgeon (J.C.E.) performed all bypass procedures at Barnes–Jewish Hospital using standard surgical techniques. Briefly, a small (~20 ml) proximal gastric pouch was created by stapling the stomach, and a 75-cm Roux-en-Y limb constructed by transecting the jejunum distal to the ligament of Treitz and creating a jejunojejunostomy 75 cm distal to the transection.

Diet
Diet subjects participated in 20 group behavior modification sessions, led by a behaviorist, a registered dietitian, and a physical therapist. The meal plans ranged from 1,200 to 1,500 kcal/day, depending on subject sex and BMI. The plans were designed to achieve a ≤1% body weight/week. Macronutrient content of the plan followed the Expert Panel’s recommendations on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, convened by the NIH and the Dietary Guidelines for Americans (19). Subjects completed daily food records. Subjects were taught a variety of weight-management skills. The exercise approach included a balance of strength, flexibility, balance, and endurance instruction. Goals gradually increased to 30 min of exercise, 5 days/week. Two weeks before follow-up imaging studies, calorie intake was adjusted to maintain stable body weight.

Cardiac PET imaging and image analysis
The evening before the imaging study, at a standardized time, all subjects were given a standard meal containing 12 kcal/kg adjusted body weight (ideal body weight + ((actual body weight–ideal body weight) × 0.25)). After this, subjects remained fasted until their imaging studies were completed. All imaging started at 8 AM.

Imaging studies were performed with a Siemens tomograph (ECAT 962 HR+; Siemens Medical Systems, Iselin, NJ). Subjects underwent positioning and transmission scans. Myocardial blood flow (needed for myocardial FA metabolism calculation), MVO₂, and FA utilization, oxidation, and esterification were obtained using PET imaging after injections of ¹⁸O-water, ¹¹C-acetate, and ¹³C-palmitate, using well-validated kinetic models as previously described (4,17,20–22). The calculations that describe the relationship between the different measures of FA metabolism are: FA utilization/g = blood flow/g × FA uptake/g × (average plasma-free FA at the time of the ¹³C-palmitate injection); FA utilization/g = FA oxidation/g + esterification/g. The intraclass correlation coefficient for the MVO₂ image analysis is 0.96. Total MVO₂, FA utilization, and oxidation were calculated by multiplying each by LV mass. One subject did not undergo FA imaging due to technical difficulties.

Measurement of plasma insulin and substrates
Subjects underwent phlebotomy throughout the PET study. Samples were drawn before the study and after each tracer injection during the imaging that followed. Plasma insulin and substrate levels presented here are averages of those measurements. Plasma insulin levels were measured by radiomunnoassay, glucose by automated hexokinase assay. Plasma-free FA was measured using an enzymatic method (NEFA C kit, WAKO Chemicals USA, Richmond, VA). The homeostasis model assessment of insulin resistance was used to calculate insulin resistance, using the first AM, fasting glucose and insulin levels (23).

Echocardiography
Immediately following MVO₂ measurement, all subjects underwent a complete two-dimensional, M-mode, and Doppler echocardiographic study using second harmonic imaging. Two-dimensional guided M-mode measurements were obtained from the parasternal cross-sectional view for LV diameter and wall thickness measurements. Ejection fraction was calculated using the modified Simpson method. LV end-diastolic and left atrial volumes were measured using the method of discs. Left atrial volumes were indexed to body surface area. LV mass was measured using the area-length method. LV mass was also indexed to height⁷ power. Pulsed-wave Doppler-derived transmitral inflow measurements were obtained from the apical four-chamber view with the sampling gate at the mitral leaflet tips. The early diastolic (E) and late atrial (A) velocities were measured and the E/A ratio, a load-dependent measure of diastolic function was calculated. The relatively load-independent tissue Doppler-derived measures of LV systolic function and relaxation, S’ and E’, respectively, were measured at the septal and lateral annulus and averaged to obtain one S’ and one E’ for each echocardiogram (24). E/E’ (septal) ratio was also obtained (25). LV mass, E’, and E/E’ were not obtained on one, one, and five subjects, respectively. Calculations: cardiac output = time velocity integral of the LV outflow tract x its area; cardiac work = cardiac output × mean arterial pressure; efficiency = work/MVO₂ (work and MVO₂ were converted to joules/g/min as previously described) (26,27). A single investigator (A.D.W.) blinded to all clinical parameters, measured all echocardiograms. The intraobserver correlation coefficient was obtained to assess reproducibility of measurements by remeasuring 50% of the studies in a random fashion. All reported measurements represent the average of three consecutive cardiac cycles. Reproducibility measurements (intraobserver correlation coefficient and (95% confidence intervals)) for the primary outcomes of LV diastolic function and LV mass were as follows: E-wave (0.987 (0.968–0.995)), E’ (0.919 (0.726–0.952)), and LV mass (0.856 (0.620–0.929)).
**ARTICLES**

**INTERVENTION AND PREVENTION**

Table 1  Pre- and postweight loss (diet group, N = 20)

<table>
<thead>
<tr>
<th></th>
<th>Preweight loss</th>
<th>Postweight loss</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35 ± 5</td>
<td>36 ± 7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female (%)</td>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race (%white)</td>
<td>75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>39 ± 6</td>
<td>36 ± 7</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>182 ± 38</td>
<td>153 ± 35</td>
<td>0.02</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>153 ± 112</td>
<td>118 ± 73</td>
<td>0.09</td>
</tr>
<tr>
<td>HOMA</td>
<td>3.8 ± 2.0</td>
<td>2.7 ± 1.5</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Medication use

- Metformin: 0% 0%
- Sulfonylureas: 0% 0%
- ACE inhibitors: 0% 0%
- Angiotensin receptor blockers: 0% 0%
- Hydrochlorothiazide: 0% 0%
- Statins: 0% 0%

**Hemodynamics**

- Heart rate (bpm): 69 ± 11 61 ± 12 0.01
- Mean arterial pressure (mm Hg): 89 ± 9 89 ± 10 0.83

**Cardiac structure**

- LV mass (g): 186 ± 34 186 ± 32 0.95
- LV mass/height^2.7 (g/m^2.7): 44 ± 7 44 ± 8 0.9
- LV end-diastolic volume (ml): 124 ± 25 114 ± 24 0.10
- Left atrial volume (ml): 52 ± 14 48 ± 14 0.21
- Left atrial volume index (ml/m²): 24 ± 6 22 ± 6 0.43

**Systolic function**

- LV ejection fraction (%): 60 ± 5 60 ± 6 0.75
- S’ (cm/s): 8.4 ± 1.2 8.1 ± 0.9 0.28
- Cardiac minute work (mm Hg·l/min): 453 ± 99 421 ± 135 0.24

**Diastolic function**

- E’ (cm/s): 14.0 ± 2.7 14.1 ± 2.2 0.92
- E/E’: 5.9 ± 1.1 6.1 ± 1.1 0.44
- E/A ratio: 1.65 ± 0.43 1.81 ± 0.44 0.24

One subject did not have a postintervention cholesterol panel. Significant P values are in bold.

ACE, angiotensin converting enzyme; bpm, beats/min; HOMA, homeostasis model index; LV, left ventricular.

Statistical analyses

All data are expressed as mean ± s.d. SAS software (version 9.2; SAS Institute, Cary, NC) was used. Between-group comparisons used unpaired Student’s t-tests. Within-group comparisons used paired Student’s t-tests. Fisher’s exact tests were used to compare proportions between groups. Linear regression was used to evaluate the relations between continuous variables. All cardiac endpoints and independent variables were predetermined. The tissue Doppler measure of LV relaxation (E’) was the primary measure of LV relaxation because of its load-independence. A priori it was decided to use the continuous variables mean arterial pressure and homeostasis model assessment of insulin resistance were used rather than categorical variables hypertension, diabetes, or metabolic syndrome status. If more than one variable correlated with an endpoint, analysis of covariance was used to determine its independent predictor(s). To enter the multivariate analyses, an independent variable had to have a P < 0.10 in the univariate analyses. In the multivariate models, each independent variable was adjusted for all other independent variables. A P < 0.05 was considered significant.

**RESULTS**

**Subject characteristics**

There were few differences between groups at baseline (Tables 1 and 2). Most importantly, the groups’ BMI, plasma triglycerides, LV mass, hemodynamics, homeostasis model assessment of insulin resistance, and systolic function were similar. The only significant baseline differences between the group were that the surgery group was slightly older and had a higher fraction of women, diabetic (3/10), hypertensive (5/10), and treated sleep apnea (3/10) subjects than the diet group; LV end-diastolic volume was lower in the surgery group, likely because there was a higher percentage of women in this group, and women are known to have smaller LV cavity size than men.

After weight loss, the only medication change made was the two subjects in the surgery group taking oral diabetic medications discontinued their use. Tables 1 and 2 also show weight loss-induced changes. The surgery group had a greater decrease in BMI than the diet group (P < 0.0001). Surgery decreased plasma triglycerides and insulin resistance. Three subjects were diabetic pre- but not postsurgery. The diet group’s insulin resistance also decreased. Heart rate decreased in the diet group.

**Weight loss effects on MVO₂ and LV efficiency**

MVO₂ Baseline total MVO₂ or MVO₂ indexed to heart weight did not differ between groups. After weight loss total MVO₂ decreased in both groups (Figure 1). In the surgery group, this was mostly due to the decrease in LV mass because MVO₂/g did not change. In the diet group, this was mostly due to decreased MVO₂/g (P = 0.009) because LV mass did not change. Total MVO₂ change correlated strongly with the decrease in BMI (Figure 1c and Table 3). Change in MVO₂/g trended toward a correlation with a change in cardiac work (P = 0.10).

**Efficiency.** Baseline myocardial efficiency (work/MVO₂) was similar between groups and did not change in either group after intervention despite decreases in MVO₂, likely due to a trend toward a decreased cardiac work in the surgery subjects (P = 0.10).

**Weight loss effects on myocardial FA metabolism and its components**

**Plasma substrates and hormones.** Baseline plasma-free FAs (Table 4) and insulin were similar between groups (data not shown). Plasma glucose was different between the surgery and the diet groups (6.4 ± 1.8 vs. 5.0 ± 0.6 μU/ml, P = 0.004). Postsurgery, glucose decreased to 4.9 ± 0.4 μU/ml (P = 0.02); insulin decreased from 16.2 ± 10.3 to 4.2 ± 2.5 μU/ml (P = 0.004). Insulin decreased in the diet group (13.9 ± 5.9 to 10.6 ± 6.8 μU/ml, P = 0.009).

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with weight loss (Table 4). However, myocardial FA oxidation/g change correlated with MVO₂/g change (r = 0.39, P = 0.04). Baseline total myocardial FA utilization and oxidation were similar between groups. After surgery, total myocardial FA utilization decreased, mirroring the postsurgical LV mass decrease, and total myocardial FA oxidation trended lower (Figure 2a,b). Total and per gram FA esterification did not change with either intervention (Table 4). Total FA utilization change trended toward relating to BMI change (Table 3). No FA metabolism measure correlated with diastolic function change (Table 5).

**Weight loss effects on diastolic function and relation to myocardial metabolism**

**LV relaxation.** Baseline E′ was worse in the surgery group than in the diet group, but LV relaxation improved markedly after surgery (Table 2 and Figure 3a,b). Improved relaxation correlated with weight loss amount, increased insulin sensitivity, an LV mass decrease, and a total MVO₂ decrease (Table 5 and Figure 3c). In multivariate modeling, in all subjects, total MVO₂ predicted LV relaxation improvement independent of BMI change (Table 6). LV mass decrease also independently predicted LV relaxation improvement. However, because of sex-related differences in MVO₂ and LV mass (26,27) we repeated the multivariate analysis in only the women, and decreased MVO₂ was the sole independent predictor of LV relaxation. In this model, BMI change and total MVO₂ change accounted for 55% of the improvement in LV relaxation. The multivariate analysis was not repeated in the men given their limited numbers.

**E/E′.** Baseline E/E′ was worse in the surgery group than in the diet group but improved (decreased) after surgery (Tables 1 and 2). The improvement correlated robustly with weight loss amount (Table 3), insulin resistance improvement (Table 3), total MVO₂ decrease (r = 0.54, P = 0.005), LV mass decrease (r = 0.73, P < 0.0001), and end-diastolic volume change (r = 0.54, P = 0.005). Weight loss independently predicted E/E′ improvement.

**Weight loss effects on LV remodeling**

Notwithstanding the constancy in blood pressure before and after weight loss in both groups, LV mass decreased after surgery (Table 2). Weight loss amount correlated with decreased LV mass (Table 3). LV end-diastolic volume also decreased significantly after weight loss, which together with the aforementioned decrease in E/E′ suggests a decrease in preload and/or plasma volume.

**DISCUSSION**

The present study is the first to demonstrate, in men and women, that weight loss can ameliorate both the myocardial oxygen and FA oxidation derangements related to obesity and that the change in MVO₂ predicts improved LV relaxation. Even moderate, diet-induced weight loss decreased MVO₂ (total and per gram) whereas marked weight loss decreased total MVO₂. The decrease in total MVO₂ related to decreased BMI. Marked weight loss decreased total FA utilization, and

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**Table 2 Pre- and postweight loss (gastric bypass group)**

| Age (years) | 44 ± 7<sup>a</sup> | 29 ± 5 | <0.0001 |
| BMI (kg/m²) | 44 ± 7 | 29 ± 5 | <0.0001 |
| Total cholesterol (mg/dl) | 167 ± 33 | 136 ± 27 | 0.04 |
| Triglycerides (mg/dl) | 168 ± 90 | 72 ± 21 | 0.005 |
| HOMA | 5.5 ± 5.3 | 0.9 ± 4.3 | 0.02 |

**Medication use**

| Metformin | 10% | 0% |
| Sulfonylureas | 10% | 0% |
| ACE inhibitors | 20% | 20% |
| Angiotensin receptor blockers | 20% | 20% |
| Hydrochlorothiazide | 20% | 20% |
| Statins | 10% | 10% |

**Hemodynamics**

| Heart rate (bpm) | 72 ± 13 | 65 ± 17 | 0.16 |
| Mean arterial pressure (mm Hg) | 89 ± 6 | 86 ± 9 | 0.38 |

**Cardiac structure**

| LV mass (g) | 180 ± 24 | 141 ± 20 | 0.0008 |
| LV mass/height² (g/m²) | 47 ± 8 | 37 ± 7 | 0.001 |
| LV end-diastolic volume (ml) | 98 ± 23<sup>c</sup> | 69 ± 11 | 0.02 |
| Left atrial volume (ml) | 45 ± 13 | 37 ± 14 | <0.05 |
| Left atrial volume index (ml/m²) | 20 ± 6 | 20 ± 9 | 0.97 |

**Systolic function**

| LV ejection fraction (%) | 61 ± 6 | 61 ± 10 | 0.83 |
| S′ (cm/s) | 7.9 ± 0.6 | 7.9 ± 0.6 | 0.87 |
| Cardiac minute work (mm Hg*min/l/min) | 445 ± 90 | 347 ± 81 | 0.10 |

**Diastolic function**

| E′ (cm/s) | 8.2 ± 1.2<sup>d</sup> | 10.4 ± 1.8 | 0.004 |
| E/E′ | 12.5 ± 2.1<sup>d</sup> | 8.1 ± 0.9 | 0.0006 |
| E/A ratio | 1.18 ± 0.44 | 1.45 ± 0.52 | 0.2 |

Significant P values are in bold. ACE, angiotensin converting enzyme; bpm, beats/min; HOMA, homeostasis model index; LV, left ventricular.

<sup>a</sup>P < 0.0005; <sup>b</sup>P < 0.05; <sup>c</sup>P < 0.01; <sup>d</sup>P < 0.0001 for baseline differences between the diet (see Table 1) and surgery groups. One subject did not have an ejection fraction available postweight loss.

Myocardial blood flow. Baseline myocardial blood flow (ml/g/min) was higher in the surgery than the diet group and did not change in either (Table 4).

Myocardial FA metabolism. Baseline myocardial FA metabolism measures/g were similar between groups and did not change
The first novel finding of this study is that weight loss decreased MVO₂/g change with weight loss. (a) Total myocardial oxygen consumption (MVO₂) decreased after diet and surgery (*P = 0.02, †P = 0.0006). (b) Typical positron emission tomography (PET)-derived myocardial images in the horizontal long-axis. The presurgery image (left) illustrates higher MVO₂ (higher C-11 activity accumulation after 1-11C-acetate injection) than in the postsurgery image (right) in the same subject. The color scale graphically depicts C-11 activity: higher counts represented as white and red; lower counts (and lower MVO₂) represented in blue and green. (c) Relation between MVO₂ change and BMI change.

**Figure 1** MVO₂ changes with weight loss. (a) Total myocardial oxygen consumption (MVO₂) decreased after diet and surgery (*P = 0.02, †P = 0.0006). (b) Typical positron emission tomography (PET)-derived myocardial images in the horizontal long-axis. The presurgery image (left) illustrates higher MVO₂ (higher C-11 activity accumulation after 1-11C-acetate injection) than in the postsurgery image (right) in the same subject. The color scale graphically depicts C-11 activity: higher counts represented as white and red; lower counts (and lower MVO₂) represented in blue and green. (c) Relation between MVO₂ change and BMI change.

**Table 3** Correlations with cardiac endpoints in all subjects

<table>
<thead>
<tr>
<th></th>
<th>ΔBMI</th>
<th>ΔMAP</th>
<th>ΔHOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔMVO₂/g</td>
<td>r = -0.09, P = 0.63</td>
<td>r = -0.23, P = 0.22</td>
<td>r = -0.32, P = 0.09</td>
</tr>
<tr>
<td>ΔTotal MVO₂</td>
<td>r = 0.50, P = 0.006</td>
<td>r = -0.06, P = 0.77</td>
<td>r = 0.17, P = 0.39</td>
</tr>
<tr>
<td>ΔTotal myocardial FA utilization</td>
<td>r = 0.35, P = 0.07</td>
<td>r = 0.21, P = 0.29</td>
<td>r = 0.31, P = 0.39</td>
</tr>
<tr>
<td>ΔLV mass</td>
<td>r = 0.52, P = 0.004</td>
<td>r = 0.33, P = 0.08</td>
<td>r = 0.36, P = 0.12</td>
</tr>
<tr>
<td>ΔE/E’</td>
<td>r = 0.77, P &lt; 0.0001</td>
<td>r = 0.14, P = 0.51</td>
<td>r = 0.43, P = 0.03</td>
</tr>
</tbody>
</table>

Significant correlations are in bold. FA, fatty acid; HOMA, homeostasis model index; LV, left ventricular; MAP, mean arterial pressure; MVO₂, myocardial oxygen consumption.

Total FA oxidation trended lower. LV relaxation and E/E’ (an estimate of LV filling pressure) (25), both improved after surgery-induced weight loss. In all subjects, LV relaxation improvement correlated with amount of weight loss, LV mass change, insulin resistance improvement, and a decrease in total MVO₂. In multivariate analyses, total MVO₂ decrease independently predicted improved LV relaxation in all subjects and alone in women.

The first novel finding of this study is that weight loss decreased MVO₂ requirements. This is similar to the finding that whole body oxygen consumption decreases with weight loss (28). In our study, myocardial FA oxidation/g decreases contributed to MVO₂/g change, which is in agreement with studies showing that FAs are the major substrate oxidized in the postabsorptive heart (4), and that FAs "cost" relatively more oxygen to burn than glucose (29). There is also a suggestion that part, but not all, of the decrease in MVO₂/g is due to a decrease in work (P = 0.10), consistent with the fact that MVO₂ is used for both mechanical and nonmechanical processes. The absence of LV mass change in the presence of this MVO₂/g change after diet therapy suggests that metabolism changes may precede, and thus contribute to significant structural and functional remodeling, consistent with a study in animals demonstrating that metabolism changes precede trophic changes (30). The present study’s finding that total MVO₂ changes postsurgery (after an LV mass change, i.e., remodeling) and those of previous studies also demonstrate that the converse is true: that LV structural remodeling influences metabolism (31). The lack of a significant change in MVO₂/g in the surgery group may result from smaller numbers of surgery subjects, or it may be that there is a continuum of metabolic and structural changes that are not perfectly matched as weight loss progresses. E.g., MVO₂/g may change first, then after significant structural remodeling occurs and the denominator decreases, the ratio becomes similar to baseline but total MVO₂ is decreased. A study with multiple
sampling points is needed to prove this; however, subject radiation exposure and costs currently limit many repeated samplings using PET.

Another major finding of this study was the strong correlation between change in MVO$_2$ and improvement in LV relaxation, independent of weight loss amount or blood pressure or myocardial FA metabolism change. The relaxation improvement after surgery (28%) is greater than that in surgical weight loss studies with shorter-term follow-up (~18% after 3 months) (12,32). Although it may appear counterintuitive that a decrease in MVO$_2$ could increase in LV relaxation, there are possible mechanisms for this salutary link. First, MVO$_2$ as measured in our study by C-11 acetate injection and PET imaging is almost exclusively from the function of mitochondria, a known source of free radical generation (33), which contributes to cardiac dysfunction development in animal models of obesity (6,7). Thus, it is logical to propose that the decrease in MVO$_2$ found in the current study in humans may relate to decreased reactive oxygen species generation and hence, functional improvement (see proposed working model, Figure 4). Second, decreased MVO$_2$ may improve LV relaxation if there is better coupling of MVO$_2$ to ATP generation, and of ATP generation to relaxation. I.e., if less energy generated from oxidative metabolism is dissipated (by uncoupling protein and/or adenine nucleotide transporter activity) and/or if less oxygen use is “wasted” (33) by the creation of free radicals, more ATP should be available for relaxation. This is supported by a study in adipose tissue, which showed that uncoupling proteins 2 and 3 mRNA expression decreases after weight loss (34). With this improved coupling, we had expected efficiency would improve. However, the lack of a change in efficiency (cardiac minute work/MVO$_2$) may be due to the fact that this common measure of cardiac work used does not directly incorporate the work of LV sarcomeric relaxation (moving actin and myosin apart), an ATP-requiring process (as evidenced by rigor mortis rather than relaxation when metabolism stops) (35).

We also hypothesized that myocardial FA metabolism would decrease with weight loss and that this would also relate to improved LV diastolic function. We did find a decrease in total myocardial FA utilization and a trend toward a decrease in total FA oxidation but no difference in FA utilization or oxidation/g. This is partially consistent with the findings of

### Table 4 Myocardial fatty acid (FA) metabolism/g and its contributors

<table>
<thead>
<tr>
<th></th>
<th>Prediet</th>
<th>Postdiet</th>
<th>Pregastric bypass</th>
<th>Postgastric bypass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma FA (µmol/ml)</td>
<td>666 ± 143</td>
<td>644 ± 131</td>
<td>734 ± 257</td>
<td>571 ± 135</td>
</tr>
<tr>
<td>Myocardial blood flow (ml/g/min)</td>
<td>0.96 ± 0.21</td>
<td>1.03 ± 0.22</td>
<td>1.22 ± 0.24*</td>
<td>1.10 ± 0.18</td>
</tr>
<tr>
<td>FA utilization (nmol/g/min)</td>
<td>148 ± 38</td>
<td>144 ± 36</td>
<td>166 ± 48</td>
<td>148 ± 79</td>
</tr>
<tr>
<td>FA oxidation (nmol/g/min)</td>
<td>134 ± 37</td>
<td>128 ± 37</td>
<td>141 ± 47</td>
<td>127 ± 50</td>
</tr>
<tr>
<td>FA esterification (nmol/g/min)</td>
<td>14 ± 20</td>
<td>14 ± 12</td>
<td>25 ± 29</td>
<td>15 ± 17</td>
</tr>
</tbody>
</table>

FA, fatty acid.

*P < 0.01 baseline differences between groups. No postweight loss changes.

### Table 5 Correlations with left ventricular relaxation improvement ($\Delta E'$)

<table>
<thead>
<tr>
<th></th>
<th>$\Delta$BMI</th>
<th>$\Delta$MAP</th>
<th>$\Delta$HOMA</th>
<th>$\Delta$Total MVO$_2$</th>
<th>$\Delta$LV mass</th>
<th>$\Delta$Total myocardial fatty acid utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta E'$</td>
<td>$r = -0.46$</td>
<td>$r = -0.01$</td>
<td>$r = -0.41$</td>
<td>$r = 0.56$</td>
<td>$r = 0.56$</td>
<td>$r = 0.18$</td>
</tr>
<tr>
<td>P</td>
<td>P = 0.01</td>
<td>P = 0.95</td>
<td>P = 0.03</td>
<td>P = 0.002</td>
<td>P = 0.002</td>
<td>P = 0.37</td>
</tr>
</tbody>
</table>

Significant correlations are in bold.

HOMA, homeostasis model index; LV, left ventricular; MAP, mean arterial pressure; MVO$_2$, myocardial oxygen consumption.

### Figure 2

Total myocardial fatty acid metabolism changes with weight loss. (a) Total myocardial fatty acid (FA) utilization decreased after surgery (*P < 0.05). (b) Total FA oxidation change, †P = 0.06.
Viljanen et al., who found a decrease in myocardial FA uptake (µmol/100 g/min) after diet therapy (15). Differences in tracers, the sex of the study subjects, and types of weight loss may account for the differences in our results. For example, the study by Viljanen et al. was in men (15), and the present study included both men and women. Sex has a major affect on myocardial metabolism at baseline (26,27), and it may also affect myocardial responses to weight loss. The present study was not powered to evaluate the effects of sex on the heart's metabolic response to weight loss and requires future study.

The diet study by Viljanen et al. also had a marked weight loss within a much shorter period of time, and it may be that there is a continuum of myocardial FA metabolic responses depending on rapidity of weight loss and whether there is a weight stabilization period or not (15). Our study further showed that decreased myocardial FA oxidation contributes to an overall decrease in MVO₂ thereby potentially indirectly contributing to an improvement in relaxation. Our finding that LV relaxation abnormalities are reversible in obese humans, suggests that at this stage of obesity-related heart disease, mechanisms besides or in addition to FA-induced apoptosis likely contribute to diastolic dysfunction.

**Limitations**

Although this study does show the strength of the relationships between myocardial FA metabolism and MVO₂ and relaxation, it does not prove cause and effect, direction of the association, or the potential influence of unmeasured factors. More studies are needed to further test the proposed working model shown in Figure 4. Given the short-term risk of mortality and insurance issues with surgery, subjects were not randomized to treatment, and so the groups were heterogeneous. Despite this, the groups were similar in many respects. In the surgery arm, only white women enrolled because they represent ~80% of surgery patients, similar to other studies (36). The surgery group was slightly older at baseline than the diet

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**Table 6 Independent predictors of LV relaxation improvement**

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th></th>
<th></th>
<th>Women only</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R²</td>
<td>∆BMI</td>
<td>∆Total MVO₂</td>
<td>∆E’</td>
<td>R²</td>
<td>∆BMI</td>
</tr>
<tr>
<td>∆E’</td>
<td>0.34</td>
<td>P = 0.33</td>
<td>P &lt; 0.03</td>
<td>∆E’</td>
<td>0.55</td>
<td>P = 0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>∆BMI</td>
<td>LV mass change</td>
<td></td>
<td></td>
<td>∆BMI</td>
</tr>
<tr>
<td>∆E’</td>
<td>0.35</td>
<td>P = 0.32</td>
<td>P &lt; 0.03</td>
<td>∆E’</td>
<td>0.33</td>
<td>P = 0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>∆BMI</td>
<td>HOMA change</td>
<td></td>
<td></td>
<td>∆BMI</td>
</tr>
<tr>
<td>∆E’</td>
<td>0.26</td>
<td>P = 0.08</td>
<td>P = 0.19</td>
<td>∆E’</td>
<td>0.32</td>
<td>P = 0.11</td>
</tr>
</tbody>
</table>

HOMA, homeostasis model index; LV, left ventricular; MVO₂, myocardial oxygen consumption.
Because FA oxidation is a major contributor to overall mitochondrial improve adenosine triphosphate (ATP) production and hence, relaxation. This may impair oxidative phosphorylation, so their diminishment should result in decreased intracellular FA metabolites. These metabolites results in decreased myocardial FA utilization and oxidation. This may obesity-related impaired left ventricular (LV) relaxation. Weight loss in myocardial fatty acid (FA) and oxygen metabolism may reverse obesity-related LV hypertrophy, obesity-related impaired diastolic function. Thus, patients with obesity-related LV hypertrophy, decreased LV relaxation, and/or estimated increased filling pressures may reap the most cardiac benefits from surgery surgery-induced weight loss. Whether these particular changes result in a long-term decrease in cardiovascular morbidity and mortality deserves further study.

ACKNOWLEDGMENTS
We gratefully acknowledge our subjects’ participation, Kristin O’Callaghan’s editorial assistance, and Ava Ysaguirre’s assistance with manuscript preparation. This work was funded by grants RO1-HL073120, UL1 RR024992 (CTSA), 5 P60 DK020579, and DK 56341 from the National Institutes of Health, and a grant from the Barnes–Jewish Hospital Foundation, St Louis, MO.

DISCLOSURE
The authors declared no conflict of interest.

REFERENCES

Figure 4 A potential model of how weight loss-induced changes in myocardial fatty acid (FA) and oxygen metabolism may reverse obesity-related impaired left ventricular (LV) relaxation. Weight loss results in decreased myocardial FA utilization and oxidation. This may result in decreased intracellular FA metabolites. These metabolites can impair oxidative phosphorylation, so their diminishment should improve adenosine triphosphate (ATP) production and hence, relaxation. Because FA oxidation is a major contributor to overall mitochondrial oxygen consumption, total myocardial oxygen consumption (MVO₂) then decreases. Total MVO₂ may also decrease as a result of decreased uncoupling protein (UCP) or adenine nucleotide transporter (ANT) activity. A decrease in total MVO₂ should lead to improved left ventricular (LV) relaxation (an ATP-requiring process), if there is improved flow of energy directed toward ATP production and subsequent LV relaxation rather than dissipation by UCP or ANT. A decrease in MVO₂ may also lead to diminished free radical production and consequent oxidative stress (Ox. Stress), which can negatively affect relaxation. Text with an asterisk (*) indicates findings of this study.

group, however, a significant aging effect would be expected to decrease FA metabolism, which was not seen (17). The size of the groups were relatively small, which increases the possibility of a type 2 error in the analyses that did not show a difference from pre- to postintervention e.g., the surgery group’s size may have contributed to the lack of a significant change in MVO₂/g; however, the primary focus of this study was to evaluate the effects of a spectrum of weight loss on heart metabolism, structure, and function rather than to compare the effect of different methods. Measurement of local, cardiac reactive oxygen species and changes in myocardial metabolism of other substrates and energetics was not done.

Clinical implications
Our data support an association between excessive MVO₂ and diastolic dysfunction in humans, suggesting that altering MVO₂ might be a target for new therapies aimed at improving diastolic dysfunction. Our results also demonstrate that patients with significant diastolic function who lose marked amounts of weight have can have dramatic improvements in diastolic dysfunction. Thus, patients with obesity-related LV hypertrophy, LV filling pressure, decreased MVO₂, and decreased left ventricular (LV) relaxation, and/or estimated increased filling pressures may reap the most cardiac benefits from surgery surgery-induced weight loss. Whether these particular changes result in a long-term decrease in cardiovascular morbidity and mortality deserves further study.