



Published in final edited form as:

*Obesity (Silver Spring)*. 2018 February ; 26(2): 284–290. doi:10.1002/oby.22038.

## Bariatric Surgery-induced Cardiac and Lipidomic Changes in Obesity-related Heart Failure with Preserved Ejection Fraction

Deana Mikhalkova<sup>1,\*</sup>, Sujata R. Holman<sup>1,\*</sup>, Hui Jiang<sup>2</sup>, Mohammed Saghir<sup>1</sup>, Eric Novak<sup>1</sup>, Andrew R. Coggan<sup>3</sup>, Robert O'Connor<sup>3</sup>, Adil Bashir<sup>3</sup>, Ali Jamal<sup>3</sup>, Daniel S. Ory<sup>2</sup>, Jean E. Schaffer<sup>2</sup>, J. Christopher Eagon, MD<sup>4</sup>, and Linda R. Peterson, MD<sup>1</sup>

<sup>1</sup>Cardiovascular Division and the, University Medical School, St. Louis, Missouri, USA

<sup>2</sup>Diabetic Cardiovascular Disease Center in the Department of Medicine, University Medical School, St. Louis, Missouri, USA

<sup>3</sup>The Mallinckrodt Institute of Radiology Department of Medicine, University Medical School, St. Louis, Missouri, USA

<sup>4</sup>The Department of Surgery, University Medical School, St. Louis, Missouri, USA

<sup>5</sup>Cardiovascular Medicine Division, Department of Medicine, University of Texas-Houston, USA

### Abstract

**Objective**—To determine the effects of gastric bypass on myocardial lipid deposition and function and the plasma lipidome in women with obesity and heart failure with preserved ejection fraction (HFpEF).

**Methods**—A primary cohort (N=12) with HFpEF and obesity underwent echocardiography, magnetic resonance spectroscopy before, and 3- and 6-mos after bariatric surgery. Plasma lipidomics were performed on pre- and 3-mo post-surgery in the primary cohort and confirmed in a validation cohort (N=22).

**Results**—After surgery-induced weight loss, Minnesota Living with Heart Failure questionnaire scores, cardiac mass, and liver fat decreased ( $P < 0.02$ ,  $< 0.001$ ,  $= 0.007$ ); echo-derived  $e'$  increased ( $P = 0.03$ ), but cardiac fat was unchanged. Although weight loss was associated with decreases in many plasma ceramide and sphingolipid species, plasma lipid and cardiac function changes did not correlate.

**Conclusions**—Surgery-induced weight loss in women with HFpEF and obesity is associated with improved symptoms, reverse cardiac remodeling and improved relaxation. While weight loss

Users may view, print, copy, and download text and data-mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use: [http://www.nature.com/authors/editorial\\_policies/license.html#terms](http://www.nature.com/authors/editorial_policies/license.html#terms)

Corresponding Author Linda R. Peterson, MD, FACC, Washington U. School of Medicine, Campus Box 8086, 660 S. Euclid Ave., St. Louis, MO 63110, Phone 314-362-4577, Facsimile 314-362-9982, [lpeterso@wustl.edu](mailto:lpeterso@wustl.edu).

\*Drs Mikhalkova and Holman are co-first authors

**ClinicalTrials.gov** number NCT01372397 entitled, 'Reversal of obesity cardiomyopathy' <https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S0002VB9&selectaction=Edit&uid=U0000EWQ&ts=3&cx=-ub41dr>

**Disclosure:** No author has financial interests directly pertinent to this submitted work. L.R.P. has a stock interest in Medtronic, which is broadly relevant to cardiology in general.

A patent application for use of the ceramide biomarkers is pending (J.E.S., D.S.O., L.R.P.).

associated with plasma sphingolipidome changes, cardiac function improvement was not associated with lipidomic or myocardial triglyceride changes. Our study results suggest that gastric bypass ameliorates obesity-related HFpEF and that cardiac fat deposition and lipidomic changes may not be critical to its pathogenesis.

## Keywords

Gastric bypass; lipids; heart failure; obesity; cardiac dysfunction

## Introduction

Obesity is a major risk factor for developing heart failure (HF), especially ‘heart failure with preserved ejection fraction’ (HFpEF) (1). Women are particularly at risk of developing HFpEF(1). Unlike HF with reduced ejection fraction (HFrEF), obesity-related HFpEF is increasing in prevalence in the United States. Because the pathophysiology of HFpEF and HFrEF may be different, these diseases may require distinct therapeutic approaches. Currently, no therapies improve survival in HFpEF (1).

Studies in animal models of obesity show that dysfunction of organs, such as the heart and liver, is pathophysiologically linked to excessive fat uptake and storage, and specific waxy lipids such as ‘ceramides,’ via a process known as “lipotoxicity”(2). Although there are likely multiple mechanisms underlying obesity-related HFpEF, myocardial total ceramides and toxic lipid species may play a role (3). Obesity in humans, *without HF*, is associated with cardiac dysfunction, and elevated plasma ceramide levels, myocardial fat uptake and storage (4–6). In contrast, weight loss in patients *without HF* is associated with decreased plasma triglyceride and ceramide levels (6), decreased myocardial fat utilization (7) and storage,(8) left ventricular (LV) mass, and improved cardiac function (7). Furthermore, gastric bypass-induced weight loss is associated with decreased cardiovascular death rates (9). However, in HF patients, obesity has been purported to have a protective effect because obese patients live longer than lean patients (10, 11). Thus, it is not clear whether patients with obesity-related HFpEF should, in fact, lose weight. Recent data show that in animals with obesity *and HF*, myocardial triglyceride and LV mass are increased and diastolic function is impaired and these abnormalities improve with weight loss, suggesting a benefit of weight loss even in presence of heart failure (12). Whether the same is true in humans with HFpEF is not clear. It is also not clear if weight loss in patients with HFpEF decreases plasma ceramide levels and sphingolipids.

The aim of this study was to determine the effect of gastric bypass-induced weight loss on HF symptoms, myocardial fat deposition, and on the plasma lipidomic profile in women with obesity. We also analyzed plasma lipidomic changes in a validation cohort that underwent gastric bypass surgery. To this end, we prospectively studied women with HFpEF before and 3 mo and 6 mo after gastric bypass surgery using HF questionnaires, magnetic resonance spectroscopy, echocardiography, and mass spectrometry. We hypothesized that weight loss in women with obesity and HFpEF would improve HF symptoms, diastolic function, decrease myocardial fat deposition, and alter plasma levels of ceramides and sphingolipids.

## Methods

### Subjects – Primary Cohort

The study was approved by the Washington University School of Medicine Human Research Protection Office. All patients gave written, informed consent before participating. The *primary cohort* was recruited from the bariatric surgery center at Washington U. School of Medicine. Inclusion criteria: women, between 35–65 years of age, BMI >35 kg/m<sup>2</sup>, a diagnosis of HFpEF (as determined by two physicians using the patient's medical history, physical exam, echocardiography, and in accordance with diagnostic criteria outlined by Eggebeen et al. based on the ACC/AHA guidelines)(13). Exclusion criteria: current tobacco use, not ambulatory/able to lie flat for procedures, pregnancy or lactation, cardiac conditions that interfered with assessment of diastolic function (e.g., constrictive pericarditis or atrial fibrillation/flutter), contraindication to magnetic resonance spectroscopy, other major systemic disease except than type 2 diabetes, ejection fraction <50%, uncontrolled hypertension, significant pulmonary hypertension by history and/or echocardiography, and/or evidence of ischemia on screening stress echocardiogram.

Twenty-four patients were in the primary cohort. Eleven dropped out or were screen failures: 9 for personal or financial reasons, 1 due to Crohn's disease activation, and 1 due to a positive stress test. Of the remaining 13 patients, one was not used in the final analysis due to uninterpretable echocardiographic data.

### Experimental Procedures

Primary cohort patients were extensively screened and phenotyped before surgery for evaluation of HF symptoms and signs and determination of New York Heart Association (NYHA) HF class. Patients underwent phlebotomy while fasting for a comprehensive metabolic panel, complete blood count, cholesterol profiles, glucose, and sphingolipid and ceramide measurement pre-surgery and 3 and 6 mo after surgery. All subjects were in energy balance when their pre-surgery measurements were made. A Minnesota Living with HF (MNLHF) Questionnaire was administered to assess symptomatic limitations from HF. The MNLHF 100-point scale questionnaire is a well-validated tool used in many HF clinical trials (14). A higher score indicates worse HF symptoms and a score of '0' indicates no symptoms. As a reference, prior validating studies have correlated HFpEF patients with scores to 15–48 to NYHA class II and scores of 32–67 to NYHA class III (14, 15). All patients underwent dual-energy X-ray absorptiometry (Lunar iDXA, General Electric, Fairfield Connecticut) for fat mass and fat-free mass measurement. All subjects underwent a rest and stress echocardiogram.

### Echocardiography

Resting echocardiograms pre-surgery were used to evaluate cardiac structure and function. LV mass was measured using the area-length method. Relative wall thickness was calculated as (2\*posterior wall thickness)/LV end-diastolic diameter. LV ejection fraction was calculated using the modified Simpson's method. Mitral valve inflow E wave was measured using spectral Doppler, and tissue Doppler was used to quantify early relaxation  $e'$  at both

the septal and lateral mitral valve annulus. These were averaged to obtain an  $e'$  average.  $E/e'$ , a measure of left atrial pressure was calculated. Echocardiography was repeated at 3 mo and 6 mo after surgery. (The U. of Texas cohort also had  $E$  and  $e'$  average measured at baseline.)

### **$^1\text{H}$ -Magnetic Resonance Spectroscopy**

The validation and reproducibility of  $^1\text{H}$ -magnetic resonance spectroscopy technique have been published previously by our group and others (5, 16). Magnetic resonance spectroscopy was used to measure myocardial and hepatic tissue lipid as described previously by our research group (17). Cardiac spectra were acquired from the interventricular septum at end-systole and at end-respiration. Liver spectra were obtained from a region of interest in the right lobe of the liver that did not include visible vasculature. The spectra were analyzed using AMARES fitting programs and jMRUI software.  $^1\text{H}$ -magnetic resonance spectroscopy was performed before, and 3 mo and 6 mo after surgery in the primary cohort. The regions of interest in subsequent scans were placed as close to the original regions as possible.

### **Roux-en-Y Gastric Bypass Surgery**

The same surgeon (JCE) performed all of the gastric bypass surgeries for the primary cohort. In brief, stapling across the stomach created a small gastric pouch. A Roux-en-Y limb was then constructed by cutting across the jejunum distal to the ligament of Treitz and creating a jejunojejunostomy distal to the transection.

### **Lipidomics**

Liquid chromatography-tandem mass spectrometry was used to analyze pre-surgery and 3 mo post-surgery plasma samples for long-chain and very-long-chain ceramides and sphingomyelins at the Washington University Metabolomics Facility. The reagents, sample preparation, instrumentation, internal standards, and quantification methods were previously described in detail in Fan et al. (18) and are shown in Table S1 (supplemental). Analyses were carried out blinded to subject treatment phase on samples from the initial Washington University cohort and on samples from a validation cohort of women undergoing gastric bypass at the University of Texas-Houston. Eight subjects in the primary cohort and 22 in the validation cohort had plasma samples at the pre- and 3 mo post-surgery timepoints. The validation cohort was added because the primary cohort was relatively small, and this is one of the first studies of lipidomic effects of weight loss. The validation cohort had significant obesity but they were not evaluated for signs and symptoms of HFpEF pre-operatively. Validation analysis focused on lipid species that were significantly different after weight loss in the St. Louis cohort and had a coefficient of variation less than 10%.

### **Statistical analysis**

Data were analyzed using SAS v9.3 (SAS Institute Inc., Cary, NC). Data are presented as mean  $\pm$  SE. A repeated measures analysis based on a mixed model approach was conducted to examine change in patient characteristics and heart function measures over time (pre, 3- and 6-mo after gastric bypass surgery). Mean estimates were obtained from the model results. All pair-wise comparisons were made and a Bonferroni adjustment was applied

when reporting *P* values. The Houston data contained 2 measurements per subject per time-point. A repeated measures analysis based on a mixed model approach was used to account for correlated data within subject at each time point and across time points (pre-surgery and 3 mo post). Mean estimates and comparisons between time-points were obtained from model results. Pearson correlations were created to describe the linear relationship between the change in heart function and change in lipidomic species. Comparisons of the baseline characteristics of both cohorts were done with unpaired t-tests. Statistical significance was set at  $P < 0.05$ .

## Results

### Baseline characteristics

The primary cohort data are shown in Table 1. The average age of the women was 47 years, all had at least class II obesity, and on average ~44% of their body mass was fat mass. Patients scored relatively poorly on the Minnesota Living with HF score (MLWHF) quality of life questionnaire ( $27 \pm 6$ ), which objectifies symptoms of HF (Figure 1). Eight subjects had type 2 diabetes and most were taking insulin or hypoglycemic agents (Table 2). Similarly, although the subjects' hemodynamics were in the normal range, most were taking at least one vasoactive and/or diuretic medication.

There were several echocardiographic abnormalities at baseline. Although all subjects had normal ejection fractions, their LV mass was severely increased (Figure 2) (19–21). (The normal range of LV mass in women is 66–150g with severe hypertrophy  $> 193$ g). This, in combination with increased relative wall thickness, is consistent with concentric LV hypertrophy (LVH) (19, 21). The subjects' average early cardiac relaxation, (average septal and lateral  $e'$  of  $9.5 \pm 0.6$ ) was abnormal for women in their 40s (normal  $14.2 \pm 2.3$ ) (20), though  $E/e'$  was borderline normal ( $8.2 \pm 0.5$ , normal being  $< 8$ ; see Table 1).

### Weight Loss and Metabolism, Hemodynamics, and Medications

Three and six months after gastric bypass surgery, there was progressive weight loss accompanied by significant improvements in resting heart rate (Table 1) despite fewer subjects taking beta-blocker medications (Table 2). Although there was no significant difference in plasma glucose or blood pressure, fewer subjects took antihypertensive and glucose-lowering medications after weight loss. The validation cohort also experienced metabolic improvements (Table 3), namely, lower total cholesterol, fasting glucose and insulin levels. High-density lipoprotein levels also decreased.

### Weight Loss and HF symptoms

Patients also experienced fewer HF symptoms as evidenced by the decrease in the MNLHF score (Figure 1) and NYHA class (Figure 3), suggesting that they were able to perform more activities with fewer HF symptoms.

### Weight Loss and LV Structure/Function

LV mass regressed significantly, although it was still above normal six months after surgery (Figure 2). Relative wall thickness also decreased (Table 1). The abnormally low LV

relaxation, ( $e'$ ), improved with weight loss (Table 1). The borderline normal baseline left atrial filling pressure ( $E/e'$ ) trended toward an improvement (Table 1).

### Weight Loss and Steatosis

Patients in this study had high baseline hepatic fat content,  $18.97 \pm 3.37\%$  — well above the upper limit of normal ( $5.56\%$ ) (Table 1) (5, 22, 23). Hepatic fat decreased with weight loss (Table 1). Six months after surgery, hepatic fat was within *normal levels*. In contrast, cardiac fat content was much lower than hepatic fat at baseline and did not change after the surgery.

### Weight Loss and Lipidomic Results

Four ceramides and 12 sphingomyelins in the primary cohort decreased after 3 mo of weight loss. Four Sphingomyelins and one ceramide (18:0) increased after 3 mo. All species that changed significantly in both cohorts and which had the prerequisite coefficient of variation less than 10% are shown in Table 4. (Other ceramides and sphingolipids are listed in Supplementary Table 1). The Houston cohort had a higher baseline BMI  $50.4 \pm 9.7 \text{ kg/m}^2$  ( $P=0.02$ ) but was not different in age, sex, blood pressure, or fasting glucose. Ejection fraction,  $e'$  and  $E/e'$  were also not different at baseline from the primary cohort (data not shown). The Houston cohort's metabolic profile improved 3 mo after surgery, like the primary cohort (Table 3). Again, most of the ceramide and sphingolipids species tested decreased after 3 mo of weight loss. Three of the four sphingomyelins that increased in the primary cohort (SM18:0, SM24:1, SM24:2) also increased in the validation cohort. The only lipid species that did not change in the same direction in the validation cohort and the primary cohort was the odd-chain, SM23:1, which decreased in the primary cohort and increased in the validation cohort. None of these lipidomic changes correlated with improvement in diastolic function as assessed by  $e'$ .

## Discussion

In this study we showed that gastric bypass-induced weight loss ameliorated symptoms of obesity-related HFpEF, reversed adverse LV remodeling, improved diastolic function, and was associated with alterations in the plasma lipidome in women. Surgery-induced weight loss also improved symptoms and quality of life as assessed by the MNLWHF and NYHA scores. Weight loss improved cardiac structure, specifically, LV mass and relative wall thickness, and LV relaxation as assessed by  $e'$ . Moreover, weight loss decreased liver fat and plasma levels of several sphingolipids, which have generally been implicated in lipotoxicity in animal models (2,24). The changes in plasma sphingolipids were largely replicated in a validation cohort. However, the lipidomic changes in the primary cohort did not correlate with the diastolic function improvements. Weight loss did not alter cardiac but did decrease hepatic triglyceride content. Thus, it appears that triglyceride deposition may not be critical to the pathogenesis of human, obesity-related HFpEF.

Currently few therapies have been shown to improve symptoms for HFpEF (26), which is why the results after gastric bypass-induced weight loss shown in our study are so striking. The baseline MHLHF score was  $27 \pm 6$ , which decreased to  $7 \pm 6$  after weight loss, and weight loss improved the average NYHA class. Our results are also in line with a recent finding of



reduced emergency room visits and HF hospitalizations after bariatric surgery in patients with obesity-related HFpEF (25). Importantly, gastric bypass-induced weight loss improves symptoms and quality of life *without* increasing heart rate or other cardiac markers of increased mortality, unlike other treatments of HF, such as adrenergic agonists.

Our study showed improved hemodynamics, LV structure and function after weight loss in patients with obesity-related HFpEF. It is already well-known that these parameters improve with weight loss in obesity *without* HFpEF (6). Decreased resting heart rate is an especially important finding because high resting heart rate is a well-known marker of poor outcomes (27) and because the decrease in heart rate occurred despite fewer patients taking beta-blockers after weight loss. In addition, subjects needed less antihypertensive medication to maintain a normal pressure (Table 2). Recent data from a study in obese animals with HF show that weight loss improved LVH and diastolic function (12). Our data in humans is similar, showing that there was significant reduction in LV mass and relative wall thickness. However, though mean relative wall thickness normalized, LV mass did not. A longer follow up and greater weight loss may be required for both parameters to normalize. Reduction in LVH is an especially important endpoint in women because it has been linked to higher risk of cardiovascular fatal outcomes when compared to men (28). LVH regression is also linked with reduced HF hospitalizations, and improved diastolic function (29, 30). Active relaxation ( $e'$ ) in diastole also improved (Table 1). This is a notoriously difficult parameter to influence with any therapy. For example, in the VALIDDD study, aggressive blood pressure control with valsartan resulted in only a 0.6cm/s change from baseline but was not different from the placebo-treated group (31). Interestingly, the improved LV relaxation and decrease in heart size in patients with HFpEF occurred without a change in blood pressure and in spite of fewer patients taking antihypertensive medications after weight loss. The improvements in markers of poor prognosis (increased LV mass and resting heart rate) after weight loss appear to contradict the complex, and likely multifactorial, 'obesity paradox,' in which subjects with HF and obesity have a better prognosis than those without obesity. However, our findings of the beneficial effect of weight loss on survival rates are supported by 2 large studies ( $N > 13,000$ ) of gastric bypass (9, 32).

Despite the change in LV mass, as well as marked weight loss and marked decreases of hepatic lipid (Table 1) the amount of myocardial lipid did not change. In our study, baseline cardiac lipid was ~1.18 %, which was higher than reported values in normal subjects  $\sim 0.4 \pm 0.2\%$  (16). This is in contrast to several studies in animal models of obesity that suggest excessive fat deposition is a key element in the development of toxic lipid species (such as some ceramides), lipotoxicity, and cardiac dysfunction (2). This is also in contrast to a study of diet-induced weight loss in patients with type 2 diabetes, which showed a decrease in myocardial lipid content, although this decrease did not correlate with the improvement in diastolic function (7). Our findings suggest that while myocardial triglyceride stores reflect the altered metabolic environment of obesity, the triglyceride itself may not be a major mediator of cardiac dysfunction, a notion that has been supported by findings in cultured cells (33) and rodent models of lipotoxic cardiomyopathy (34). The precise nature of lipotoxic species in the obese heart remain to be determined but changes in the plasma sphingolipids suggest these could include some ceramides and sphingomyelins. Decrease in hepatic triglyceride, but not cardiac triglyceride, 6 months following bariatric

surgery may reflect a more dynamic pool of lipid in the liver. The liver also moves less than the heart, and so is easier to image than the heart. It is also likely to be easier to detect a difference in the liver fat of our subjects after weight loss given that liver fat content was 18-fold higher than cardiac fat at baseline. Thus, it appears that myocardial oxidation (6) and/or processing of fatty acids, which can yield reactive oxygen species (24) and/or toxic lipid species – such as some ceramides (2, 3)—may play a more important role in obesity-related cardiac dysfunction than lipid deposition.

In the current study, we found that the plasma ceramides and sphingolipids levels change after gastric bypass-induced weight loss in HFpEF patients. The majority of sphingolipids and ceramides decreased, but a few increased after 3 mo. Our findings were replicated in a validation cohort of patients from UT-Houston, who also underwent gastric bypass. We did not find a correlation between the plasma lipidomic changes and the improvements in LV mass or function. A few other studies evaluated specific lipid changes after bariatric surgery, though none in HFpEF patients, and no studies evaluated their possible relationship with cardiac indices (35, 36). Generally, a decrease was found in ceramides after gastric bypass surgery (36), although changes in specific ceramide species vary somewhat among the studies. E.g., in the study by Huang, ceramides 14:0, 16:0, 20:0, and 24:0 were decreased at 3 and 6 mo post-op (35) whereas we found decreases in ceramides 22:0, 23:0, 24:0, and 25:0. There are some indications that certain ceramides, and possibly sphingomyelins, may be associated with favorable outcomes and others may be associated with adverse outcomes in patients referred for cardiac catheterization (37). However, more long-term research on the prognostic role of ceramides/sphingomyelins in patients with obesity, HFpEF, after weight loss, and in population studies is required. The lipidome during short-term weight loss may also be different than after weight stabilization for years.

## Limitations

Our study is limited by small numbers and by the relatively short duration of follow-up. Although the UT-Houston cohort was similar to the primary cohort in several baseline characteristics and had very similar lipidomic changes, the former was not rigorously evaluated for signs and symptoms of HFpEF. Thus the comparison of the 2 groups is not perfect. The results of our study cannot automatically be extended to men or other subjects who do not fit our entry criteria. We limited our study to women because they make up the vast majority of subjects who undergo gastric bypass surgery and because of the known myocardial metabolic differences between men and women who are obese (38). MR spectroscopy evaluation of steatosis is generally validated for measuring triglyceride accumulation and does not yield information regarding other lipid species deposition, such as ceramides.

## Conclusion

Gastric bypass surgery-induced weight loss in women with obesity-related HFpEF results in improvement of HF symptoms and diastolic function. Surgery-induced weight loss also decreases LV mass and resting heart rate, which are associated with increased mortality. These data suggest that gastric bypass may alleviate HFpEF in patients who are obese.



Moreover, there are intriguing alterations in the plasma lipidome in HFpEF after gastric bypass surgery. Future studies are needed to clarify the pathogenesis of these changes and whether they have potential to serve as biomarkers of cardiac and whole body function or whether they may impact function themselves.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

**Funding:** This study was funded by grants from the Diabetes Research Center (DRC) at Washington University School of Medicine, St. Louis, Missouri and the NIH (P20 HL113444; P30 DK 020579; P30 DK 056341; UL1 TR000448).

The authors thank all of the research subjects for volunteering and for the cooperation of St. Alexius New Start bariatric surgery program. The authors also thank Truong N. Lam, M.D. and Heinrich Taegtmeier, M.D., D. Phil. for their contributions to this work and Kristin O'Callaghan for her editorial assistance.

## References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006; 355:251–259. [PubMed: 16855265]
2. Unger RH, Orci L. Diseases of liporegulation: new perspective and related disorders. *FASEB*. 2001; 15:312–321.
3. Chokshi A, Drosatos K, Cheema FH, et al. Ventricular assist device implantation corrects myocardial lipotoxicity, reverses insulin resistance and normalizes cardiac metabolism in patients with advanced heart failure. *Circulation*. 2012; 125:2844–2853. [PubMed: 22586279]
4. Peterson LR, Herrero P, Schechtman KB, et al. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. *Circulation*. 2004; 109:2191–2196. [PubMed: 15123530]
5. Szczepaniak LS, Dobbins RL, Metzger GJ, et al. Myocardial triglycerides and systolic function in humans: in vivo evaluation by localized proton spectroscopy and cardiac imaging. *Magn Reson Med*. 2003; 49:417–423. [PubMed: 12594743]
6. Huang H, Kasumov T, Gatmaitan P, et al. Gastric bypass surgery reduces plasma ceramide subspecies and improves insulin sensitivity in severely obese patients. *Obesity (Silver Spring)*. 2011; 19:2235–2240. [PubMed: 21546935]
7. Lin CH, Kurup S, Herrero P, et al. Myocardial oxygen consumption change predicts left ventricular relaxation improvement in obese humans after weight loss. *Obesity (Silver Spring)*. 2011; 19:1804–1812. [PubMed: 21738241]
8. Hammer S, Snel M, Lamb HJ, et al. Prolonged caloric restriction in obese patients with type 2 diabetes mellitus decreases myocardial triglyceride content and improves myocardial function. *J Am Coll Cardiol*. 2008; 52:1006–1012. [PubMed: 18786482]
9. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med*. 2007; 357:753–761. [PubMed: 17715409]
10. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail*. 2013; 1:93–102. [PubMed: 24621833]
11. Peterson LR. To Lose Weight or Not to Lose Weight, That Is the Big Question--in Obesity-Related Heart Failure. *Diabetes*. 2015; 64:1509–1510. [PubMed: 25908877]
12. Sankaralingam S, Abo Alrob O, Zhang L, et al. Lowering body weight in obese mice with diastolic heart failure improves cardiac insulin sensitivity and function: implications for the obesity paradox. *Diabetes*. 2015; 64:1643–1657. [PubMed: 25524917]

13. Eggebeen J, Kim-Shapiro DB, Haykowsky M, et al. One week of daily dosing with beetroot juice improves submaximal endurance and blood pressure in older patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol HF*. 2016; 4:428–437.
14. Rector TS, Carson PE, Anand IS, et al. Assessment of long-term effects of irbesartan on heart failure with preserved ejection fraction as measured by the minnesota living with heart failure questionnaire in the irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial. *Circ Heart Fail*. 2012; 5:217–225. [PubMed: 22267751]
15. Lewis EF, Lamas GA, O'Meara E, et al. Characterization of health-related quality of life in heart failure patients with preserved versus low ejection fraction in CHARM. *Eur J Heart Fail*. 2007; 9:83–91. [PubMed: 17188020]
16. O'Connor RD, Xu J, Ewald GA, et al. Intramyocardial triglyceride quantification by magnetic resonance spectroscopy: In vivo and ex vivo correlation in human subjects. *Magn Reson Med*. 2011; 65:1234–1238. [PubMed: 21500254]
17. Airhart S, Cade WT, Jiang H, et al. A Diet Rich in Medium-Chain Fatty Acids Improves Systolic Function and Alters the Lipidomic Profile in Patients With Type 2 Diabetes: A Pilot Study. *J Clin Endocrinol Metab*. 2016; 101:504–512. [PubMed: 26652763]
18. Fan M, Sidhu R, Fujiwara H, et al. Identification of Niemann-Pick C1 disease biomarkers through sphingolipid profiling. *J Lipid Res*. 2013; 54:2800–2814. [PubMed: 23881911]
19. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015; 16:233–270. [PubMed: 25712077]
20. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016; 29:277–314. [PubMed: 27037982]
21. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009; 10:165–193.
22. Reeder SB, Cruite I, Hamilton G, Sirlin CB. Quantitative Assessment of Liver Fat with Magnetic Resonance Imaging and Spectroscopy. *J Magn Reson Imaging*. 2011; 34 spcone.
23. Szczepaniak LS, Nurenberg P, Leonard D, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. *Am J Physiol Endocrinol Metab*. 2005; 288:E462–468. [PubMed: 15339742]
24. Listenberger LL, Ory DS, Schaffer JE. Palmitate-induced apoptosis can occur through a ceramide-independent pathway. *J Biol Chem*. 2001; 276:14890–14895. [PubMed: 11278654]
25. Shimada YJ, Tsubawa Y, Brown DF, Hasegawa K. Bariatric Surgery and Emergency Department Visits and Hospitalizations for Heart Failure Exacerbation: Population-Based, Self-Controlled Series. *J Am Coll Cardiol*. 2016; 67:895–903. [PubMed: 26916477]
26. Li J, Becher PM, Blankenberg S, Westermann D. Current treatment of heart failure with preserved ejection fraction: should we add life to the remaining years or add years to the remaining life? *Cardiol Res Pract*. 2013; 2013:130724. [PubMed: 24251065]
27. Fox K, Borer JS, Camm AJ, et al. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol*. 2007; 50:823–830. [PubMed: 17719466]
28. Liao Y, Cooper RS, Mensah GA, McGee DL. Left ventricular hypertrophy has a greater impact on survival in women than in men. *Circulation*. 1995; 92:805–810. [PubMed: 7641360]
29. Okin PM, Devereux RB, Harris KE, et al. Regression of electrocardiographic left ventricular hypertrophy is associated with less hospitalization for heart failure in hypertensive patients. *Ann Intern Med*. 2007; 147:311–319. [PubMed: 17785486]
30. Katholi RE, Couri DM. Left ventricular hypertrophy: major risk factor in patients with hypertension: update and practical clinical applications. *Int J Hypertens*. 2011; 2011:495349. [PubMed: 21755036]
31. Solomon SD, Janardhanan R, Verma A, et al. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. *Lancet*. 2007; 369:2079–2087. [PubMed: 17586303]

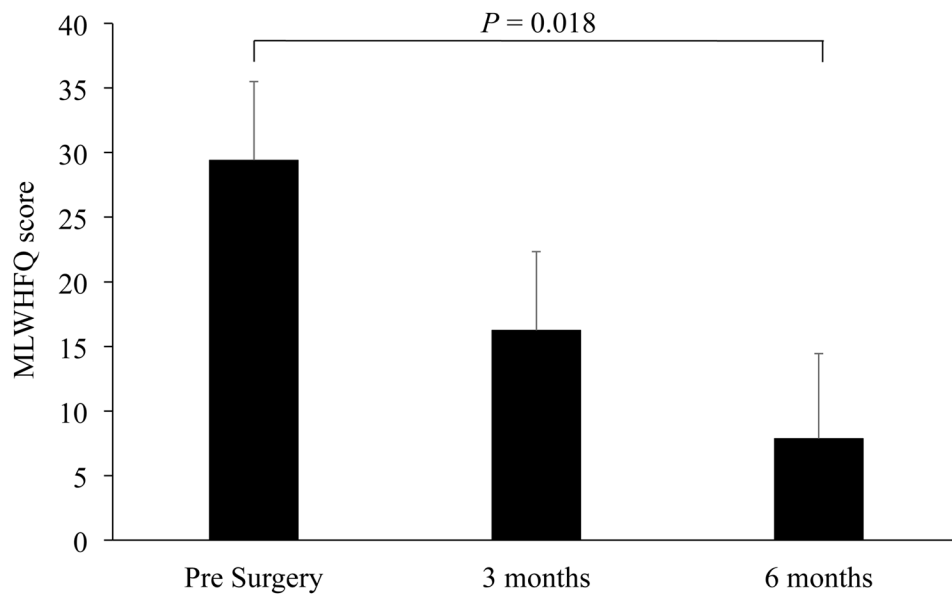
32. Sjostrom L, Narbro K, Sjostrom CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med*. 2007; 357:741–752. [PubMed: 17715408]
33. Listenberger LL, Han X, Lewis SE, et al. Triglyceride accumulation protects against fatty acid-induced lipotoxicity. *Proc Natl Acad Sci U S A*. 2003; 100:3077–3082. [PubMed: 12629214]
34. Liu L, Shi X, Bharadwaj KG, et al. DGAT1 expression increases heart triglyceride content but ameliorates lipotoxicity. *J Biol Chem*. 2009; 284:36312–36323. [PubMed: 19778901]
35. Ban RH, Kamvissi V, Schulte KM, Bornstein SR, Rubino F, Graessler J. Lipidomic profiling at the interface of metabolic surgery and cardiovascular disease. *Curr Atheroscler Rep*. 2014; 16:455. [PubMed: 25236775]
36. Sigruener A, Kleber ME, Heimerl S, Liebisch G, Schmitz G, Maerz W. Glycerophospholipid and sphingolipid species and mortality: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. *PLoS One*. 2014; 9:e85724. [PubMed: 24465667]
37. Peterson LR, Soto PF, Herrero P, et al. Impact of gender on the myocardial metabolic response to obesity. *JACC Cardiovasc Imaging*. 2008; 1:424–433. [PubMed: 19356462]
38. Zhong L, Lau YH, Sim LL, et al. Concentric Left Ventricular Hypertrophy As Independent Predictors of 1-Year Rehospitalization and Mortality in Patients Hospitalized for Acute Heart Failure and Preserved Ejection Fraction. 59:E854–E854.

**What is already known about this subject?**

- Studies in animal models of obesity show that excessive fat deposition and specifically certain lipid species (including ceramides), in the myocardium is highly correlated with cardiac dysfunction.
- Total ceramides are increased in the myocardium of patients with heart failure and decreased after left ventricular (LV) assist device therapy.
- Obesity in humans is associated with elevated plasma ceramide levels and an increased risk of cardiac dysfunction and heart failure — particularly heart failure with preserved ejection fraction (HFpEF).

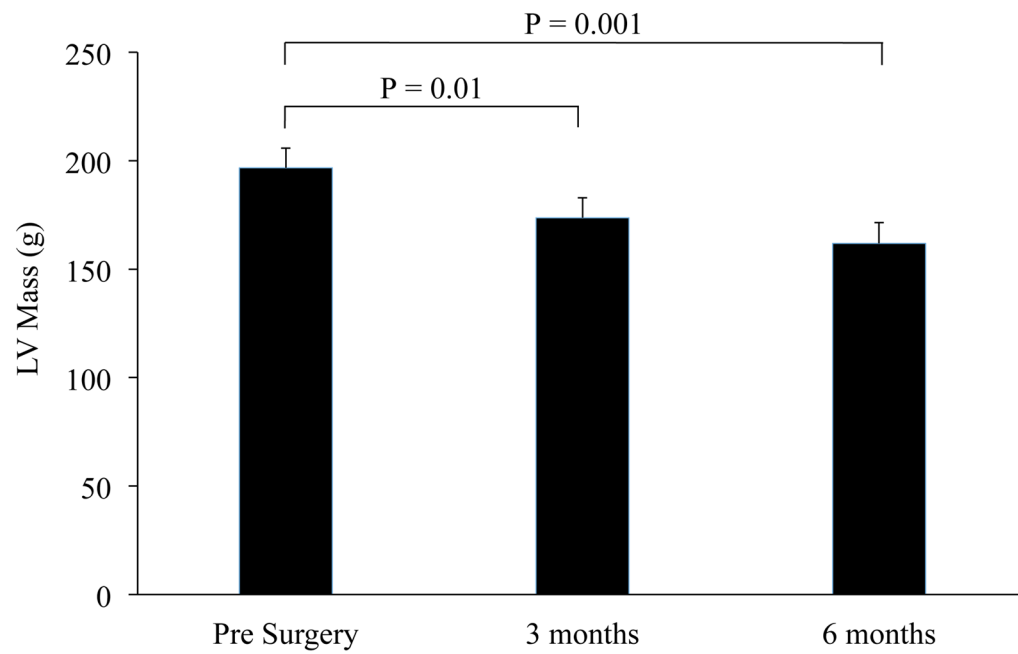
**What does our study add?**

- Our study shows for the first time that gastric bypass-induced weight loss improves symptoms of heart failure as well as diastolic function and other prognostically important measures (LV mass and resting heart rate) in patients with obesity-related HFpEF.
- This improvement in obesity-related HFpEF is associated with changes in specific plasma ceramide levels but no change in myocardial triglyceride content.



**Figure 1.**

Minnesota Living with Heart Failure (MNLWHF) score changes with weight loss. MLWHF scores (mean  $\pm$  SE) decreased significantly from pre-surgery, to the post-surgery for the St. Louis cohort (overall trend  $P=0.02$ ). Lower MNLWHF scores are indicative of fewer heart failure symptoms.

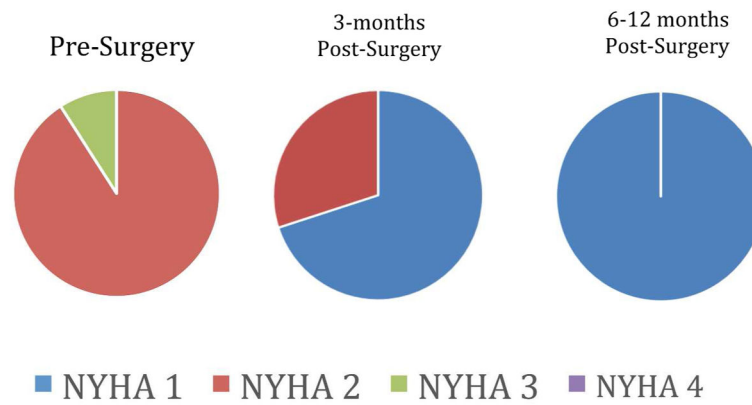


**Figure 2.**

LV mass changes from Pre Surgery to 3 and 6 months after bariatric surgery.

LV mass decreased after weight loss at 3 mo and 6 mo after surgery. Data shown are mean  $\pm$  SE.





**Figure 3.**

New York Heart Association (NYHA) Classification changes for the St. Louis cohort after surgery.

NYHA classification pre-surgery and 3- and 6-mo post-surgery. A lower NYHA classification number indicates improved functional capacity.

**Table 1**

Whole body and cardiac parameters before and after surgery (primary cohort).

	Baseline	3 mo after surgery	P value 3 mo vs baseline	6 mo after surgery	P value 6 mo vs baseline	P value Time Effect
Number	12	12		10		
<b>Weight Parameters</b>						
Weight (kg)	120 ± 4	96 ± 4	<0.001	83 ± 4	<0.001	<0.001
Body mass index (kg/m <sup>2</sup> )	43.9 ± 1.2	35.3 ± 1.2	<0.001	30.7 ± 1.3	<0.001	<0.001
Fat mass (kg)	53 ± 3	39 ± 3	<0.001	29 ± 3	<0.001	<0.001
Fat-free mass (kg)	62 ± 2	55 ± 2	<0.001	54 ± 2	<0.001	<0.001
<b>Hemodynamic Parameters</b>						
Heart rate (bpm)	81 ± 3	68 ± 3	0.01	69 ± 3	0.04	0.009
SBP (mmHg)	127 ± 4	120 ± 4	0.53	122 ± 4	0.97	0.37
DBP (mmHg)	72 ± 3	75 ± 3	1.000	77 ± 3	0.88	0.56
<b>Echocardiography</b>						
Ejection fraction (%)	63 ± 2	62 ± 2	1.000	61 ± 2	1.000	0.63
e' (cm/s)	9.5 ± 0.6	10.8 ± 0.6	0.03	10.5 ± 0.6	0.19	0.03
E/e'	8.2 ± 0.5	7.6 ± 0.5	0.73	7.0 ± 0.5	0.13	0.12
Relative wall thickness	0.44 ± 0.02	0.40 ± 0.02	0.21	0.39 ± 0.02	0.046	0.04
<b><sup>1</sup>H-Magnetic Resonance Spectroscopy – (fat/water %)</b>						
Hepatic Fat (%)	18.97 ± 3.37	7.02 ± 3.37	0.05	2.85 ± 3.70	0.009	0.007
Cardiac Fat (%)	1.18 ± 0.16	1.29 ± 0.18	1.000	1.06 ± 0.18	1.000	0.49
<b>Metabolic Parameters</b>						
Fasting Glucose (mg/dL)	120 ± 12	103 ± 12	0.88	94 ± 13	0.42	0.31
Total Cholesterol (mg/dL)	169 ± 10	154 ± 10	0.32	150 ± 11	0.18	0.11
HDL (mg/dL)	46 ± 5	45 ± 5	1.00	55 ± 5	0.08	0.04
LDL (mg/dL)	90 ± 8	87 ± 8	1.00	76 ± 9	0.44	0.32

Data are shown as mean ± SE. SBP = systolic blood pressure; DBP = diastolic blood pressure; MR = magnetic resonance. Repeated measures analyses were done using a mixed model approach. All pairwise comparisons were made using a Bonferroni adjustment. Text in **bold** font indicates a significant *P* value.

**Table 2**

Vasoactive, diabetes, and lipid medications before and after gastric bypass surgery in the primary cohort.  
(Values are expressed as number taking a medication/total patients)

Medication	Baseline	3 months post surgery	6 months post surgery
<b><i>Vasoactive/Diuretic Medication</i></b>			
ACE-Inhibitors/ARBs	7/12	3/10	2/10
Beta-Blockers	3/12	3/10	1/10
Loop/Thiazide diuretic	4/12	1/10	1/10
<b><i>Diabetic Medication</i></b>			
Oral hypoglycemic	6/12	1/10	0/10
Insulin	3/12	1/10	0/10
<b><i>Lipid Management</i></b>			
Statins	5/12	4/10	1/10
Other lipid Rx	1/12	1/10	3/10

ACE = angiotensin converting enzyme inhibitor; ARBs = angiotensin receptor blockers; Rx = medication

**Table 3**

Metabolic Profile of the UT-Houston patients at baseline and after 3 mo of weight loss

	<b>Pre-surgery</b>	<b>3 mo after surgery</b>	<b>P value</b>
Total Cholesterol (mg/dL)	176 ± 6	150 ± 6	<b>&lt;0.001</b>
High Density Lipoprotein (mg/dL)	41 ± 2	37 ± 2	<b>&lt;0.001</b>
Triglycerides	155 ± 45	98 ± 9	0.22
Free fatty acids (mmol/L)	0.90 ± 0.05	0.93 ± 0.06	0.67
Fasting glucose (mg/dL)	105.1 ± 9.9	79.4 ± 2.2	<b>0.02</b>
Fasting insulin (IU/L)	20.63 ± 3.85	9.93 ± 0.90	<b>0.01</b>

Data shown as mean ± SE. N = 19; Text in **bold** font indicates significant *P* values.

**Table 4**

The Sphingomyelins and Ceramides that Changed Significantly at 3 mo post-surgery in the Primary and Validation Cohorts Presented as a Fold-change (3 mo – baseline/baseline) from Pre- Surgery Values.

	Primary Cohort (WUSM)	Validation (UTHouston) Cohort	<i>P</i> Value
Ceramide 23:0	$-0.48 \pm 0.09$	$-0.28 \pm 0.07$	0.13
Ceramide 24:0	$-0.39 \pm 0.11$	$-0.22 \pm 0.07$	0.24
Sphingomyelin 14:1	$-0.39 \pm 0.09$	$-0.24 \pm 0.04$	0.08
Sphingomyelin 14:0	$-0.27 \pm 0.09$	$-0.20 \pm 0.04$	0.46
Sphingomyelin 18:0	$0.22 \pm 0.05$	$0.26 \pm 0.07$	0.74
Sphingomyelin 20:0	$-0.23 \pm 0.09$	$-0.12 \pm 0.05$	0.32
Sphingomyelin 22:1	$-0.17 \pm 0.09$	$-0.09 \pm 0.06$	0.48
Sphingomyelin 24:2	$0.29 \pm 0.09$	$0.34 \pm 0.09$	0.72
Sphingomyelin 23:1	$-0.15 \pm 0.08$	$0.25 \pm 0.07$	<b>0.003</b>
Sphingomyelin 21:0	$-0.41 \pm 0.07$	$-0.26 \pm 0.07$	0.27
Sphingomyelin 24:1	$0.30 \pm 0.13$	$0.36 \pm 0.08$	0.74
Sphingomyelin 22:0	$-0.28 \pm 0.09$	$-0.21 \pm 0.06$	0.52
Sphingomyelin 23:0	$-0.39 \pm 0.08$	$-0.29 \pm 0.06$	0.38
Sphingomyelin 24:0	$-0.27 \pm 0.11$	$-0.22 \pm 0.06$	0.72

Comparison based on two sample t-tests. N= 8 for Primary cohort, N=22 for validation cohort). Text in **bold** font indicates a significant *P* values.