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Sleeve gastrectomy in obese, Wistar rats improves diastolic function and promotes cardiac recovery independent of weight loss.

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Abstract

Background: Heart failure with preserved ejection fraction (HFpEF) is the most common cause of heart failure, and is characterized by impaired diastolic relaxation. Bariatric surgery significantly improves diastolic relaxation, but a mechanism beyond weight loss remains unknown.

Objective: We tested the hypothesis that a sleeve gastrectomy (SG) will improve diastolic dysfunction independent of weight loss due to post-operative alterations in the entero-cardiac axis.

Setting: University Research laboratory.

Methods: Male, Wistar rats were fed a high-fat diet (HFD) or low-fat diet (LFD) for 10 weeks followed by SG-HFD, pair-fed sham HFD, ad-lib sham HFD, or ad-lib sham LFD (n=9–14 per group). At least 2 months postoperatively, cardiac function, meal tolerance, glucose tolerance, and cardiac gene expression were compared between groups.

Results: Only the SG cohort showed significant improvements in post-operative diastolic relaxation (isovolumetric relaxation time pre: 14.7 ± 2.3 msec, post: 11.2 ± 1.8 msec, $p < 0.001$). SG significantly increased active glucagon-like peptide-1 ($p = 0.03$). Compared to pair-fed sham HFD rats, SG-HFD rats had significantly altered mRNA cardiac gene expression including sarco/endoplasmic reticulum Ca^{2+} -ATPase 2a (SERCA2a) ($p < 0.001$).

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Conclusions: SG improves diastolic function independent of weight loss in a rat model of obesity with beneficial alterations in cardiac gene expression of multiple known targets related to cardiac failure, including SERCA2a. These data support that a greater curve gastrectomy induces beneficial intracellular cardiac signaling for diastolic function mediated by the entero-cardiac axis that is independent of weight loss and could translate to offering metabolic surgery to patients with HFpEF.

Keywords

heart failure with preserved ejection fraction; obesity; bariatric surgery; diastolic function

Introduction

In the United States, 36% of adults and 17% of adolescent are obese ⁽¹⁾. One major comorbidity affecting obese individuals is heart failure (HF). HF with preserved ejection fraction (HFpEF) represents about 50% of all HF admissions and is characterized by diastolic dysfunction and an ejection fraction $< 50\%$ ⁽²⁾. The 5-year mortality rates of Medicare patients hospitalized for HFpEF is 75.7% ⁽²⁾. HFpEF is a complex disease of cardiomyocyte insulin resistance, inflammation, and hypertension leading to Type 1 collagen deposition ^(3,4). This causes left ventricular stiffness in diastole, which ultimately contributes to a prolonged iso-volumetric relaxation time (IVRT) and slow left ventricular filling which is characteristic of HFpEF ^(4,5).

Bariatric surgery, such as a sleeve gastrectomy (SG), almost universally improves diastolic function and reduces cardiac hypertrophy ^(6,7). The mechanisms for diastolic improvement after bariatric surgery are unknown. Unlike a SG, weight reduction through dieting alone in HF patients may improve symptoms, but often does not affect cardiac structure or function ^(8,9). As bariatric surgery produces significantly more weight loss than dieting, it could be that the massive reduction in excess weight after bariatric surgery is the prime mechanism for the improvement in diastolic function. However, rapid alterations in the post-surgical microbiome, post-prandial bile acid pool, and in enteric hormone production and secretion may produce weight-loss independent changes in the entero-cardiac axis to improve diastolic function ^(10–12).

We recently found that a SG preserves systolic function in a diet-induced rodent model of obesity and cardiac dysfunction, independent of weight loss for approximately 50% of the rodents ⁽¹³⁾. In this study, we tested the hypothesis that a SG will improve diastolic dysfunction independent of weight loss due to post-operative alterations in the entero-cardiac axis with beneficial changes in intracellular cardiac signaling using a rodent, high-fat, diet (HFD)-induced model of obesity.

Methods

Study Design.

This study, including all procedures, was approved by the Institutional Animal Care and Use Committee. Four-week-old, male, Wistar rats were fed either a HFD, Open Source Research

Diet D12492 (n=38), or a low-fat diet (LFD, n=9), Open Source Research Diet D12450J, for 10 weeks prior to SG or sham surgery as previously described (Research Diets, New Brunswick, NJ) ⁽¹⁸⁾. Prior to surgery, all rats underwent a trans-thoracic echocardiogram. Four groups were then created. Three HFD groups were assigned matching for systolic function and secondarily for body weight. These 3 groups included a SG (n=14), pair-fed (PF) sham surgery (n=12) or ad-lib sham surgery (n=12). A fourth group consisted of LFD rats only who underwent ad-lib sham surgery (n=9). All animals were kept on their assigned diet for the course of the study, except for the 48 hours after surgery, when they were switched to liquid Ensure (Abbott, Lake Bluff, IL). To control for the effect of weight loss and calorie reduction on the heart seen in SG rats, the PF sham group was fed the average daily food intake of SG rats to induce a similar weight loss and body weight by calorie restriction.

An echocardiogram and oral mixed meal tolerance test was performed eight weeks post-surgery. At 9 weeks after surgery, rats underwent an intraperitoneal (IP) glucose tolerance test. Ten weeks post-surgery, rats were sacrificed, and left ventricular cardiac tissue was collected for gene expression analysis.

Surgical Procedures.

A SG and sham surgery were performed as previously described ⁽¹³⁾. In brief, a SG was performed by removing the lateral portion of the greater curvature including the non-glandular stomach using an endoscopic stapling device (Endopath ETS-Flex, 45mm white load; Ethicon, Cincinnati, OH). Sham surgeries involved the same procedure except the stomach was not divided.

Oral Mixed Meal Test.

Rats were fasted and fed 2 mL of vanilla Ensure by oral gavage. A hand-held glucometer was used to measure glucose concentrations of tail vein blood before feeding, and 15 minutes' post-gavage. Blood was collected in an EDTA collecting tube containing a DPPIV inhibitor. Separate commercially available rat enzyme-linked immunosorbant assays (ELISAs) were used to measure insulin and active GLP-1 concentrations (Millipore Sigma, Burlington, MA).

Glucose Tolerance Tests.

After fasting, rats were injected IP with D-glucose at a dose of 2 g/kg. Glucose was measured from tail vein blood by a hand-held glucometer at: 0, 30, 60, and 120 min following the injection. Insulin concentrations were obtained using a sandwiched insulin ELISA (Millipore Sigma, Burlington, MA).

Cardiac Function Analysis.

Anesthetized rats underwent echocardiograms as previously described ⁽¹³⁾. Specific techniques and measurements for rat echocardiography are presented in the supplementary methods.

Relative Gene Expression.

Left ventricular tissue was collected at the time of euthanasia. The heart was excised and arrested in diastole using 1.5% potassium chloride. The heart was weighed after drying and sections of the mid left ventricle were used for RNA extraction.

Relative expression of several genes associated with cardiac disruption was measured using the pre-made PrimePCR Heart Failure Tier 1 plate (Bio-rad) as well as Sarco/endoplasmic reticulum Ca^{2+} -ATPase 2a (SERCA2a) by quantitative RT-PCR. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as a house-keeping gene, and fold changes in gene expression were measured utilizing the C_T method. Primer sequences and methodology for quantitative PCR are provided in the supplementary methods.

Statistics.

All values are presented as the mean $\pm$ SEM. Pre- and post-operative time points for each study group were compared using a paired t-test. A one-way analysis of variance (ANOVA) was performed to determine differences between groups at the same time point with Least Significant Difference post-hoc analysis for statistically significant F statistics. Area under the curve (AUC) was calculated using the trapezoidal rule. Values were determined statistically significant if $p < 0.05$.

Results

Sleeve gastrectomy results in reduced caloric intake, and decreased body weight, compared to high-fat controls.

Prior to surgery, there were no significant differences in BW for all 3 rat groups fed a HFD: SG-HFD: 519.5 ± 11.7 g, PF-HFD sham: 511.4 ± 13.3 g, and ad-lib HFD sham: 506.9 ± 10.4 g. All HFD rat groups weighed significantly more than those fed a LFD prior to surgery, 452.44 ± 12.8 g, $p < 0.05$. Postoperatively, SG-HFD and PF-HFD sham groups did not differ in BW at any time point. At the study end, the ad-lib HFD sham group weighed significantly more than the other three surgical groups. There were no significant differences in weight between the SG-HFD, PF-HFD sham, and ad-lib LFD sham rats at any time point after surgery. The ad-lib HFD sham group also ate significantly more calories (6744.4 ± 111.1 kcal) for the ten-week study period compared to ad-lib LFD-sham rats (5576.1 ± 137.2 kcal, $p < 0.001$), while no difference was seen between SG-HFD, PF-HFD and ad-lib LFD sham groups.

Sleeve gastrectomy and calorie restriction preserves ejection fraction.

As indicated in Table 1, pre-operatively a HFD induced an increase in EDV, SV, and a decrease in LVM/BW compared to a LFD although this did not reach significance for every HFD group due to significant variability among rats. Continuation of the HFD after surgery resulted in a significant increase in LVIDd for all HFD groups compared to the ad-lib LFD sham group 8 weeks after surgery: SG HFD 0.89 ± 0.01 cm, $p = 0.001$; PF-HFD 0.88 ± 0.02 cm, $p = 0.007$; ad-lib HFD sham 0.88 ± 0.01 cm, $p = 0.012$; compared to LFD sham 0.81 ± 0.02 cm, ($p = 0.009$). Similarly, LVIDs increased with a HFD compared to LFD postoperatively.

While only SG-HFD rats showed a significant increase in SV compared to preoperative values, both SG-HFD rats and PF-HFD shams had significantly higher post-operative SV compared to ad-lib LFD shams (SG-HFD: 1.3 ± 0.06 mL, $p=0.003$; PF-HFD: 1.23 ± 0.07 mL, $p=0.028$; ad-lib LFD sham: 1.02 ± 0.05 mL). Ad-lib HFD sham rats had no increase in SV postoperatively (ad-lib HFD sham pre: 1.16 ± 0.04 mL vs. post: 1.16 ± 0.06 , $p=0.97$). The significant post-operative increase in SV with SG-HFD and PF-HFD rats was likely due to significant increases in post-operative EDV (SG-HFD: 1.52 ± 0.07 mL, $p=0.001$; PF-HFD: 1.46 ± 0.07 mL, $p=0.009$; compared to ad-lib LFD shams: 1.19 ± 0.08 mL, $p=0.01$).

Sleeve gastrectomy improves diastolic function and cardiac mass independent of weight-loss.

Only the SG-HFD rats had a significant improvement in post-operative diastolic relaxation. As shown in Figure 1a, IVRT significantly decreased post-operatively after SG, ($p<0.001$). The SG-HFD average IVRT was actually significantly lower post-operatively than even ad-lib LFD sham rats ($p=0.03$). Before surgery, SG-HFD showed significant elevations in IVRT compared to the ad-lib HFD sham and the ad-lib LFD sham groups. Only SG-HFD and ad-lib LFD sham rats had a significantly decreased E/e' ratio post-operatively as shown in Figure 1b.

Over time, ad-lib LFD sham rats, ad-lib HFD sham rats, and PF-HFD rats had a significant reduction in LVM/BW%. Only SG-HFD rats preserved their LVM/BW% postoperatively with a pre-operative LVM/BW% of $0.31 \pm 0.01\%$ and a post-operative LVM/BW% of $0.30 \pm 0.01\%$, $p=0.4$).

Sleeve gastrectomy does not significantly alter glucose metabolism or insulin secretion but increases GLP-1 in Wistar rats.

There were no differences between groups in glucose (Figure S1a) or insulin concentrations (Figure S1b) for any time point during the IP glucose tolerance test. Similarly, there were no differences between SG-HFD rats and PF-HFD rats in glucose and insulin concentrations at 15 minutes following oral gavage of a mixed meal. However, the SG rats secreted almost twice the amount of post-prandial GLP-1, 10.69 ± 1.29 pM, compared to the PF-HFD rats, 6.84 ± 0.82 pM, $p=0.03$).

A SG induces alterations in cardiac gene expression independent of weight-loss.

Compared to PF-HFD rats, SG-HFD rats had significantly increased mRNA cardiac expression of the following tested genes, SERCA2a ($p<0.001$) and insulin-like growth factor binding protein 3 (IGFBP3) ($p=0.01$), both of which have been shown to be reduced in murine models of cardiomyopathy. Chemokine ligand 12 (CCL-12) ($p=0.04$) and secreted frizzled related protein 1 (SFRP1) ($p=0.03$) were significantly decreased after SG-HFD compared to PF-HFD sham animals as shown in Figure 2. No other genes were found significantly different between the two groups from the Heart Failure Tier 1 panel.

Discussion

Several studies have suggested that weight-loss following bariatric surgery leads to significant improvements in the heart ^(14,15). These beneficial changes in cardiac function have previously been solely attributed to post-surgical reduction in adipose tissue and body mass, which decreases pre-load and afterload, and leads to a reduction in the overall cardiac workload ⁽¹⁶⁾. In this study, we were able to isolate weight-loss dependent and independent effects of a SG on cardiac function in a diet-induced obese model of cardiac dysfunction. We found that a SG in rodents leads to weight-loss dependent benefits to systolic function but weight-loss independent benefits on diastolic function and beneficial changes in cardiac gene expression.

Although improved diastolic function was found to be weight-loss independent, the exact mechanism by which a SG leads to these benefits is unclear. One potential mechanism for improvements in diastolic function is SERCA2a, which is responsible for removing Ca^{2+} from the cytoplasm of cardiomyocytes, and leads to cardiac relaxation ⁽¹⁷⁾. SERCA2a is down-regulated in both hypertrophic and dilated cardiomyopathies, and is inversely related to IVRT ^(18–20). Increasing SERCA2a is currently being researched as a target for gene therapy ⁽²¹⁾. These findings suggest that SG-induced up-regulation of SERCA2a, if confirmed clinically, may serve as a novel therapeutic approach to treat diastolic dysfunction.

SG in this rodent model induced post-prandial increases in GLP-1 secretion. This mirrors clinical findings where post-prandial GLP-1 levels are uniquely increased after bariatric surgery unlike dieting ⁽²²⁾. GLP-1 receptors are present in cardiac tissue ⁽²³⁾. In a rat model of HFpEF, GLP-1 infusions directly led to improved diastolic function and improved survivorship ⁽²⁴⁾. Therefore, along with increased cardiac SERCA2a, it is possible that post-prandial GLP-1 is also contributing to the decrease in IVRT and E/e' that is observed in the SG animals.

A HFD increases EDV and SV, and decreases LVM/BW. Interestingly, the SG rats did not show further decreases in LVM/BW following surgery. This preservation in cardiac mass may be indicative of compensatory geometrical changes that allow the animals to overcome increased cardiac workload of body weight. A possible mechanism for this effect is through SG-induced suppression of cardiac Secreted Frizzled Related Protein 1 (sFRP1), a Wnt antagonist. SFRP1 plays a critical role in the balance between physiological compensation and cardiac hypertrophy ^(25,26). The moderate decrease in sFRP1 expression in SG cardiac tissue may explain the maintained LVM/BW ratios observed in this group only following surgery.

As a limitation, this murine model of HFpEF does not represent all of the intricacies and complexities that are associated with clinical obesity-induced HF. A stronger phenotype of HF, with hypertension and metabolic syndrome including insulin resistance and hyperglycemia, may reveal even more profound or different weight-loss independent improvements in cardiac function following SG as we found in this current study.

Conclusions

This study identifies potential weight-loss independent mechanisms for diastolic function improvement after bariatric surgery. The ability of a greater curve gastrectomy to beneficially alter cardiac gene expression and improve diastolic function suggests a potential future role of metabolic surgery as a targeted treatment for HFpEF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Echocardiograms measuring iso-volumetric relaxation times (IVRT) (**A**), and the E/e' ratio (**B**) of rats fed a high fat diet (HFD) or low fat diet (LFD), were performed before SG or sham surgery (pre-op), and 8 weeks post-operatively (post-op) (n=9–14). (*) denotes a $p < 0.05$ change compared to pre-operative values. (#) represents significant differences between the designated surgical group and ad-lib LFD shams at each time point. Data represents the mean $\pm$ SEM.

Figure 2.

Cardiac mRNA expression measured in left ventricular tissue of high-fat diet (HFD) Wistar rats 10 weeks following sleeve gastrectomy (n=3–4) or pair-feeding sham surgery (n=3–6). Real time qRT-PCR was used to measure relative expression to a housekeeping gene for (A) SERCA2a, (B) CCL-12, (C) IGFBP3, and (D) SFRP1. Values are given as the mean $\pm$ SEM. (*) represents $p < 0.05$.

Table 1.

Effect of sleeve gastrectomy or sham surgery on cardiac structure and left ventricular systolic function measured by echocardiogram pre-operatively and 8 weeks post-operatively in Wistar rats fed a high fat or low fat diet.

	IVSd (cm)	LVIDd (cm)	LVIDs (cm)	LVPWd (cm)	EDV (mL)	ESV (mL)	EF (%)	FS (%)	SV (mL)	LVM (g)	LVM/ BW x100
<i>Sleeve Gastrectomy HFD (n=14)</i>											
Pre	0.19	0.84	0.39	0.19	1.30	0.16	87.7	53.4	1.14	1.59	0.31 [#]
Post	0.19	0.89* [#]	0.44*	0.18	1.52* [#]	0.22*	85.4	50.4	1.30* [#]	1.68* [#]	0.30
<i>Pair-Fed HFD Sham (n=12)</i>											
Pre	0.19	0.84	0.41	0.18	1.30	0.19	85.5	50.7	1.11	1.60	0.31 [#]
Post	0.20	0.88 [#]	0.45	0.17	1.46* [#]	0.23	84.2	49.7	1.23 [#]	1.67 [#]	0.29*
<i>Ad-lib HFD Sham (n=12)</i>											
Pre	0.19	0.85	0.40	0.19	1.32 [#]	0.17	87.7	53.3	1.16 [#]	1.63	0.32
Post	0.19	0.88* [#]	0.45*	0.18	1.44 [#]	0.22*	84.5*	49.1*	1.16	1.65 [#]	0.27*
<i>Ad-lib LFD Sham (n=9)</i>											
Pre	0.19	0.81	0.38	0.19	1.15	0.14	88.0	53.6	1.01	1.56	0.35
Post	0.19	0.81	0.40	0.17	1.19	0.18	85.9	51.1	1.02	1.51	0.28*

Data presented as the mean. Statistical significance determined at $p < 0.05$ comparing preoperative vs. post-operative values within groups (*), or comparing the designated surgical group to the low fat diet (LFD) sham controls at the same time point (#). IVSd = inter-ventricular septum in diastole, LVIDd = left ventricular internal diameter in diastole, LVIDs = left ventricular internal diameter in systole, LVPWd = left ventricular posterior wall in diastole, EDV = end diastolic volume, ESV = end systolic volume, SV = stroke volume, LVM = left ventricle mass, LVM/BW = left ventricular mass divided by body weight, HFD = high fat diet