Brief Communication

MOLECULAR METABOLISM

Vertical sleeve gastrectomy corrects metabolic perturbations in a low-exercise capacity rat model

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ABSTRACT

Objective: Bariatric surgery is currently our most effective strategy at weight loss, yet the mechanisms for its success remain unknown. Low exercise capacity, in humans and rodents, predicts poor metabolic outcome. The objective of this manuscript was to determine if bariatric surgery could restore metabolic perturbations in rats with low intrinsic exercise capacity.

Methods: We performed vertical sleeve gastrectomy (VSG) or sham surgery in high fat-fed rats selectively bred for low running capacity.

Results: We found that VSG reduced body mass through a reduction in fat mass, caused early reductions in food intake, and shifted macronutrient preference away from fat and toward carbohydrates. VSG had no impact on basal glucose but did improve the return to baseline after an oral glucose load. As has been shown previously, VSG increased postprandial insulin, GLP-1, and bile acids. There was no significant impact of VSG on plasma triglycerides, hepatic triglycerides, or cholesterol. Interestingly, the brown adipose tissue to white adipose tissue ratio tended to be greater in VSG compared to sham surgery animals. While VSG positively impacted several aspects of metabolism, it did not enhance maximal oxygen capacity and seemed to lower metabolic efficiency as indicated by lower resting oxygen consumption and fat and carbohydrate oxidation.

Conclusion: VSG can improve the metabolic status of animals with a low exercise capacity independently of exercise capacity.

Keywords Bariatric surgery; Metabolism; Exercise

1. INTRODUCTION

Increasing rates of obesity and type 2 diabetes mellitus (T2DM) threaten our health and overburden our health care system. A large part of this threat comes from the relative dearth of effective therapies for both conditions. Although a variety of lifestyle interventions and medications can produce some weight loss and improvements in glucose regulation [1], none of them provides the long-term benefits observed with bariatric surgery. The fastest growing bariatric surgery procedure performed worldwide is vertical sleeve gastrectomy (VSG), a procedure in which ~80% of the stomach along the greater curvature is removed. This procedure produces sustained weight loss and rapid improvements in glucose and lipid metabolism [2]. While the VSG procedure is quite effective, the mechanism(s) underlying this success are unclear. Understanding the mechanism(s) for this success could lead to less invasive treatments as well as expand our current knowledge of the pathophysiology of obesity.

Low exercise capacity and cardiovascular fitness are highly predictive of poor metabolic health, including higher fat mass, reduced insulin sensitivity, increased blood pressure, and, importantly, increased age-adjusted mortality [3]. Evidence for the impact of inherent exercise capacity has been extensively studied in a rat model derived from a founder population of N:NIH stock rats and artificially selectively bred for intrinsic (untrained) treadmill running capacity [4]. In this model, as in humans, exercise capacity is a heritable trait [5,6], and, like humans who differ in running capacity, rats with low vs. high capacity running ability (LCR vs. HCR) diverge in susceptibility to metabolic disease [7–10]. Specifically, compared to HCR, LCR weigh significantly more and despite similar food consumption have decreased capacity for substrate oxidation throughout their lifespan [11]. The phenotype of LCR is coincident with a host of metabolic problems [12] along with a 28–40% decreased lifespan [7]. Given the widespread metabolic benefits of VSG, we hypothesized that VSG would induce weight loss and correct the metabolic perturbations associated with LCR.

2. MATERIAL AND METHODS

2.1. Animals

LCR rats were developed as previously described [4]. In the running capacity selection process, rats were exercise tested across 5 consecutive days so that estrous cycle dropped out as a random variable [4]. Twenty-two female LCR rats aged 4–5mos old were individually housed and maintained on a 12:12-h light–dark cycle (lights off at 1400) at 25 °C and 50–60% humidity with ad libitum access to water and a high-fat butter diet (HFD, 4.54 kcal/g; 41% fat; Research Diets, New Brunswick, NJ) for 12 weeks. Only female rats

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were used in this study as 80% of bariatric surgery patients are women. After 12-weeks of high fat feeding, body fat and lean mass were assessed using NMR (Echo MRI, Houston, TX), and surgical groups (VSG, n = 11 vs. sham, n = 9) were assigned in a counter-balance fashion based on fat mass. All procedures for animal use were approved by the University of Michigan Institutional Animal Care and Use Committee. Two VSG animals died within 2-weeks of surgery. All of their data have been eliminated from the study. Besides the exercise selection process, estrous cycle was not assessed on days of testing. The rationale for this is that we wanted to determine the overall impact of surgery on metabolic responses and were not interested in the potential variation across the estrous cycle.

2.2. Surgeries

VSG was performed as described previously [13–17]. Briefly, a laparotomy incision was made in abdominal wall, allowing the stomach to be isolated outside the abdominal cavity and placed on saline-moistened gauze pads. Loose, gastric connections to the spleen and liver were released along the greater curvature, and the suspensory ligament supporting the upper fundus was severed, widening the angle between lower esophagus and the fundus. The lateral 80% of the stomach was excised using an ETS 35-mm staple gun, leaving a tubular gastric remnant in continuity with the esophagus and the pylorus and duodenum. This gastric sleeve was then reintegrated into the abdominal cavity. Finally, the abdominal wall was closed in layers.

Sham surgery was performed as described previously [13–17] and involved abdominal laparotomy incision and removal of the stomach from the abdominal cavity followed by manually applying pressure with blunt forceps along a vertical line between the esophageal sphincter and the pylorus of the stomach.

For 3 days preoperatively, the high-fat diet was replaced with Ensure Plus liquid diet (Abbott Nutrition, Columbus, OH). After recovery from surgery, animals were studied using a battery of *in vivo* physiological studies described below. Body mass was measured weekly throughout the study, and food intake was measured weekly for the first 4-weeks postoperatively. Body composition was assessed again at 4, 8, and 24 weeks after surgery.

2.3. Macronutrient preference

We previously demonstrated that bariatric surgery alters macronutrient preference. To determine whether the LCR rats responded similarly, approximately 18 weeks after surgery, we provided three pure macronutrient diets casein, high fat lard, and cornstarch; (Harlan Teklad, Madison, WI), which were presented in separate containers simultaneously and assessed food intake for each macronutrient for 4d.

2.4. Glucose tolerance tests

7-weeks after surgery, an oral glucose tolerance test was performed. Prior to each test, rats were fasted for 5h and blood glucose was measured via a hand-held glucose analyzer (Accuchek; Roche Diagnostics, Indianapolis, IN) from tail vein samples at 0, 15, 30, 45, 60, and 120 min after administration of 25% dextrose (2 g/kg). Fifteen minutes after the nutrient load, blood was collected in tubes containing 1 ml of a cocktail made of EDTA (4.65 g), aprotinin (92 mg), heparin (40,000 U), and a DPP4-Inhibitor (1 μL; Millipore # DPP4-010) for assessment of plasma glucagon levels.

2.5. Mixed meal tolerance test

Approximately 12 weeks after surgery, 4–5-hour fasted rats were gavaged with 3 mL (4.46 kcal) Ensure Plus Liquid diet. This load was based on the volume of liquid diets rats will voluntarily consume [17]. Fifteen minutes after the nutrient load, blood was collected in tubes containing 1 ml of a cocktail made of EDTA (4.65 g), aprotinin (92 mg), heparin (40,000 U), and a DPP4-Inhibitor (1 μL; Millipore # DPP4-010). Blood glucose was assessed using the hand held glucometer as in the OGTT. Plasma levels of total bile acids (Genway Biotech, San Diego, CA) and insulin (Crystal Chem, Downers Grove, IL) were assessed using commercially available ELISA kits while GLP-1 (7–36) was measured by an electrochemiluminescence assay (Meso Scale Discovery, Gaithersburg, MD).

2.6. Lipid metabolism

Ad lib-fed and 24h-fasted blood was taken from the tail vein for subsequent analysis of plasma triglycerides and cholesterol. At the end of the study liver from ad lib-fed rats was harvested and immediately flash frozen in liquid N_2 for subsequent analysis of hepatic triglyceride levels.

Briefly, hepatic lipids were folch extracted, and tissue and plasma triglycerides and cholesterol were assayed by the University of Cincinnati MMPC using commercially available kits (Cholesterol: Infinity® Cholesterol, Fischer Scientific, Waltham, MA; Triglycerides, Randox Trigs, Randox Laboratories, Crumlin, UK).

2.7. Estimation of endurance running capacity

Maximum oxygen consumption (VO_{2max}) was measured by the UM Animal Phenotyping Core using an integrated open-circuit calorimeter (CLAMS, Columbus Instruments). All exercise tests were performed between 0900 and 1500h. Rats were weighed and placed into the treadmill chambers ($305 \times 51 \times 44$ mm^3) for approximately 10 min to acclimate them to the treadmill environment. The slope of the treadmill was set at 10° to the horizontal for each rat within the initial speed set at 10 m/min and increased every 2 min until the rat sat on the electric shocker for 5 consecutive seconds indicating exhaustion. VO_2 and VCO_2 were sampled every 5s.

2.8. Statistical analysis

Normally distributed data were analyzed utilizing standard parametric statistics including One- and Two-way ANOVAs with repeated measures and t-tests where applicable. Statistical analyses were performed using either GraphPad Prism v.6.02 or Statistica v.13 for Windows. Data are expressed as mean ± SEM, and statistical significance was accepted when $p < 0.05$.

3. RESULTS

3.1. Body mass & composition changes

VSG caused a significant decrease in body weight at week 1, compared to presurgery values, and at week 24, compared to their sham surgery counterparts, whether shown as absolute or as a % delta over time (Figure 1A,B; surgeryXtime interaction; $p < 0.05$). Further, sham but not VSG animals had greater body mass over presurgical values at weeks 11–24 (Figure 1A,B; surgeryXtime interaction; $p < 0.05$). Fat mass was significantly lower at 24 weeks after the surgery in VSG vs. Sham animals (surgeryXtime interaction; $p < 0.05$), and there were no significant differences between surgeries in lean mass at any post-operative time point (Figure 1C,D).

3.2. Food intake & preference

Similar to what we have previously reported [13,17], food intake was significantly lower in VSG vs. sham animals the first two weeks after surgery but was similar thereafter (Figure 1E; surgeryXtime interaction; $p < 0.05$). Twenty-weeks after surgery when body mass changes

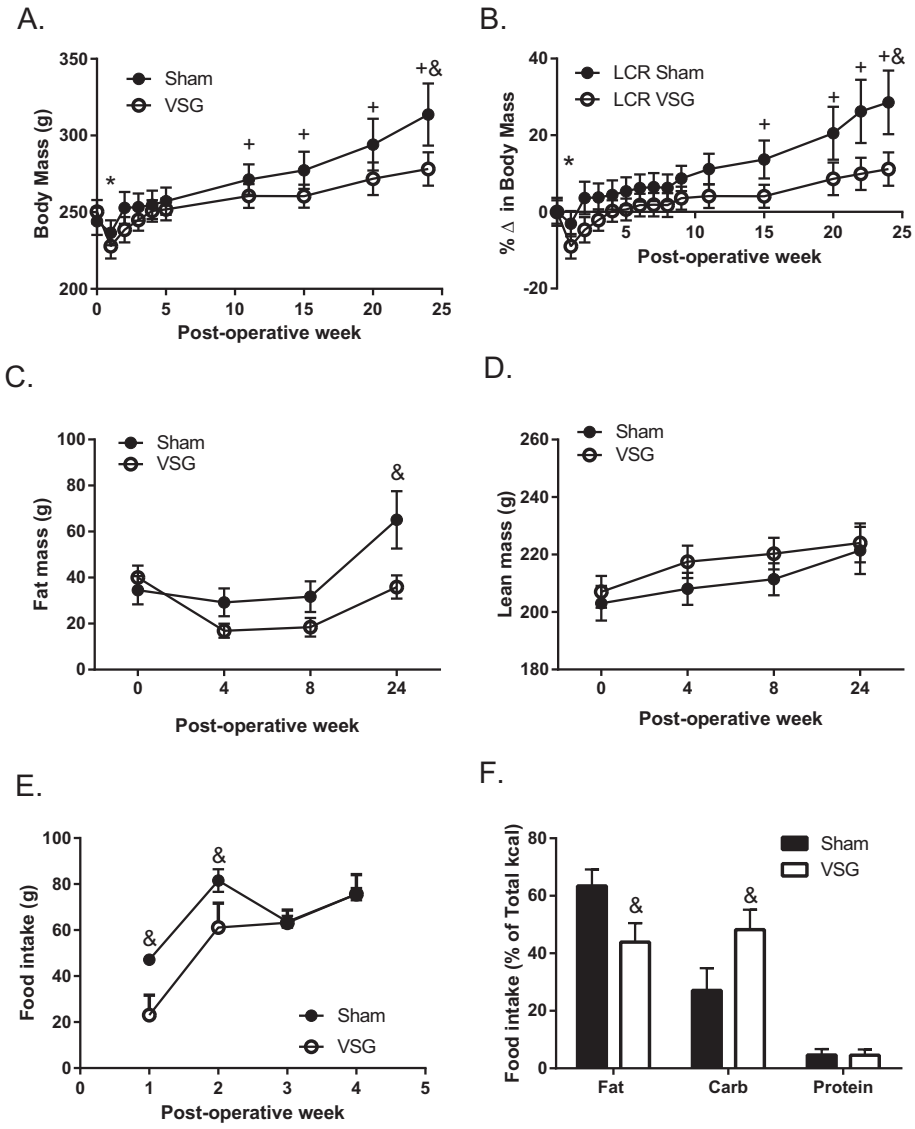

Figure 1: Body mass and composition and feeding changes after VSG or sham surgery. A. VSG caused a significant reduction in body weight compared to pre-surgical values at week 1 and compared to their sham surgery counterparts at week 24 (surgeryXtime interaction). Sham animals significantly increased body mass compared to pre-surgical values at weeks 11–24. B. VSG caused a significant change from baseline in body weight at 1 compared to pre-surgical values and compared to their sham surgery counterparts at week 24 (surgeryXtime interaction). C. Fat mass was significantly lower 24 weeks in VSG vs. Sham animals (surgeryXtime interaction). D. There was no significant difference in lean mass across time or between VSG vs. sham surgery. E. Food intake was significantly lower in VSG vs. sham animals in the first two weeks after surgery but was similar thereafter (surgeryXtime interaction; $p < 0.05$). F. When given a choice between fat, carbohydrate, and protein, VSG animals ate less fat and more carbohydrates compared to sham surgery animals (unpaired t-test within a macronutrient; $p < 0.05$). open circles, VSG; closed circles, sham. *$p < 0.05$ vs. pre-surgical values in VSG; &$p < 0.05$ in VSG vs. sham; +$p < 0.05$ vs. pre-surgical values in sham animals. N = 11 VSG and 9 sham for all data.

were stable, we assessed whether LCR rats would modify macronutrient preference in response to VSG. Indeed, and similar to what we have seen in Long-Evans rats, when given a choice between fat, carbohydrate, and protein, VSG animals ate less fat and more carbohydrates compared to sham surgery animals (Figure 1F; unpaired t-test within a macronutrient; $p < 0.05$).

3.3. Glucose, insulin, GLP-1, bile acids

We next examined the hormonal and metabolite response to a mixed meal gavage (Ensure Liquid Meal©). Similar to the glucose gavage data, basal glucose levels were similar (109 ± 3 vs. 114 ± 2 mg/dl; $p > 0.05$) while glucose levels were significantly higher 15 min after the gavage in VSG vs. sham animals (210 ± 10 vs. 178 ± 7 mg/dl; $p < 0.05$, surgeryXtime interaction). Insulin and GLP-1 levels were both significantly greater 15 min following the mixed liquid meal, in VSG vs. sham animals (Figure 2A,B; unpaired t-test; $p < 0.05$). VSG also significantly increased both basal and meal-stimulated bile acid levels (Figure 2C; main effect of surgery; $p < 0.05$).

We also performed an OGTT and again found that peak glucose levels were significantly higher after VSG but returned to basal levels quicker than sham surgery animals (Figure 2D). This is a glucose response pattern that is similar to what we have previously observed with the early rise being due to rapid gastric emptying rate [16]. Glucagon levels were significantly reduced at 0 and 15 min after the glucose gavage in

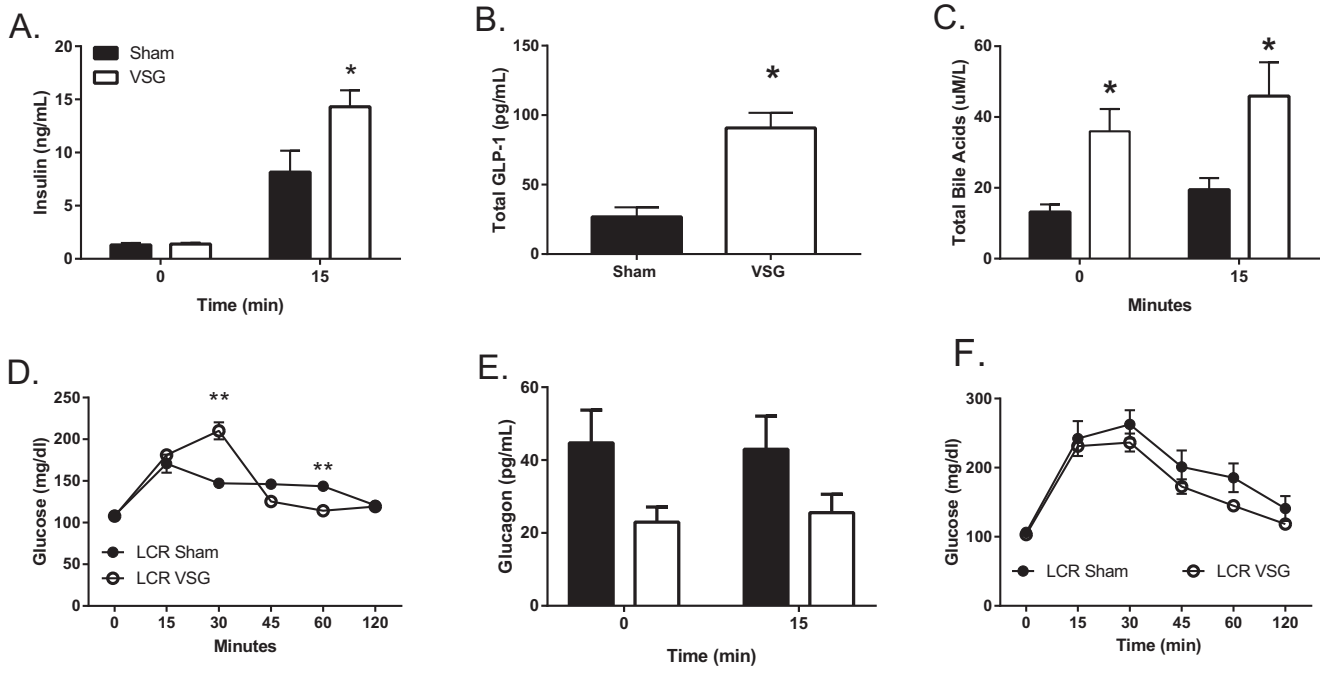

Figure 2: Hormone and metabolite responses to a meal. Insulin (A), and GLP-1 (B) levels were significant greater 15-minutes following a mixed liquid meal gavage in VSG vs. Sham animals (unpaired t-test). C. Plasma bile acid levels were significantly higher in fasted (time 0) and postprandial conditions in VSG vs. sham animals (main effect of surgery). D. Glucose response to an oral glucose load was significantly higher at 30 but significantly lower at 60 min following a glucose gavage in VSG vs. sham surgery animals (surgeryXtime interaction). E. Glucagon levels were significantly reduced at 0 and 15 min after the oral glucose load (main effect of surgery). F. Glucose response to an IP glucose load was similar between VSG and sham animals. Open circles, VSG; closed circles, sham. N = 11 VSG and 9 sham for all data. *p < 0.05 VSG vs. sham.

VSG vs. sham rats (Figure 2E). In response to an IP glucose load, a route of administration that limits the contribution of gut-secreted factors to glucose clearance, there were no significant differences in glucose levels between sham and VSG animals (Figure 2F).

3.4. Lipid homeostasis

9-weeks after surgery, we assessed ad lib fed and fasted plasma lipids levels. Fasting significantly reduced plasma triglycerides (Figure 3A; main effect of feeding status; $p < 0.05$) with no additional effect of surgery. In addition, hepatic triglyceride and cholesterol content were not altered by VSG (Figure 3B). Subcutaneous and visceral adipose tissue weight was significantly reduced by VSG with no significant change in brown adipose tissue weight (Figure 3C). Interestingly, there was a trend for the ratio of the weight of the brown adipose to white adipose weight to be greater after VSG vs. sham surgery (Figure 3D; $p = 0.06$).

3.5. Exercise capacity

Maximum oxygen consumption was measured 14-weeks post-operatively. There were no significant differences in time to exhaustion (Figure 4A) or maximal oxygen capacity (VO_{2max}) whether expressed relative to total body mass or fat free mass (Figure 4B) between sham and VSG animals. Interestingly, for a given workload, submaximal oxygen consumption was significantly lower in VSG vs. sham surgery animals (Figure 4C; main effects of surgery and time; no interaction; $p < 0.05$). However, when the data were expressed relative to baseline, there were no longer differences between surgeries (Figure 4D). Similarly, whether expressed in absolute terms, or relative to body mass or lean mass, energy expenditure was reduced by VSG (data not shown; main effect of surgery and time; no interaction; $p < 0.05$). Fat and carbohydrate oxidation expressed relative to lean mass was significantly greater in sham vs. VSG animals (Figure 4E&F), but, again, this difference disappeared when expressed relative to baseline (data not shown).

4. DISCUSSION

In this study, we examined whether LCR rats, a rat model with known metabolic deficiencies including obesity and impaired glucose tolerance [4,18,19], would respond favorably to bariatric surgery. We performed VSG or sham surgery in HFD-fed female rats. Similar to what we have previously reported, rats who received VSG surgery lost weight due specifically to fat mass, had early reductions in food intake, and shifted macronutrient preference towards carbohydrates and away from fat. Regarding specific changes in glucose and lipid metabolism, VSG vs. sham animals had significantly greater peak blood glucose followed by a more rapid return to baseline levels after a glucose gavage. VSG also caused greater plasma GLP-1, insulin, and bile acids in response to a nutrient load. All of these results are similar to what we have previously reported in response to VSG in either male or female rats [13,17,20]. These metabolic changes were independent of any changes in exercise capacity in LCR rats. Together these data suggest that the pathways that drive metabolic improvements after VSG are distinct from the metabolic impairment in LCR rats.

Like what we have observed in several studies, peak glucose levels after a glucose or liquid mixed meal (Ensure) gavage were higher in VSG compared to sham animals [16,17,20]; an effect we attribute to rapid gastric emptying rate [16]. Unlike what we have seen previously, the LCR rats did not have improved basal glucose levels or reduced glucose response to an IP glucose load. The difference between the glucose responses to the oral vs. the IP glucose load suggests that VSG drives improvements in gut-derived signals that regulate glucose

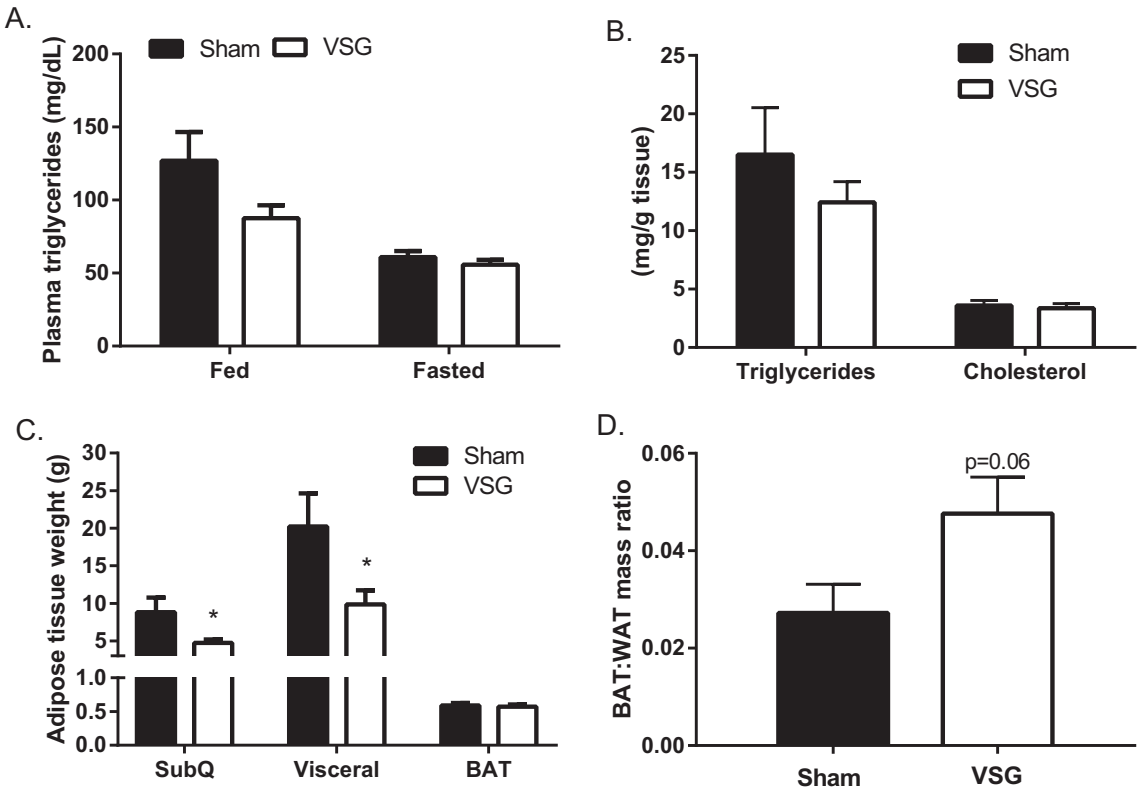

Figure 3: Changes in plasma and tissue lipids in response to VSG. A. Fasting significantly reduced plasma triglycerides (main effect of feeding status; $p < 0.05$). There were no independent effects of VSG on plasma triglycerides. B. Hepatic triglyceride and cholesterol content were not altered by VSG. C. Subcutaneous and visceral adipose tissue weighed significantly less in VSG vs. sham animals. There were no significant differences in brown adipose tissue weight between groups. D. There was a trend for the weight of the brown adipose to white adipose tissue ratio to be greater in VSG vs. sham surgery ($p = 0.06$). Open circles, VSG; closed circles, sham. $N = 11$ VSG and 9 sham for all data.

homeostasis; e.g. GLP-1. Another possibility is that VSG is not able to overcome all of the metabolic abnormalities associated with inherently lower exercise capacity. One example is that VSG did not significantly reduce hepatic triglycerides as we and others have reported previously [20,21]. Ectopic storage of lipids in the liver are strongly correlated with hepatic insulin resistance and thought to be a factor in driving type 2 diabetes mellitus [22]. Interestingly, low aerobic capacity is also associated with poor insulin sensitivity, greater visceral adiposity, and fatty liver disease [22], with the latter being due to reduced hepatic mitochondrial content and increased lipogenesis [20]. Thus, it is possible that the impact of VSG on hepatic lipid metabolism is limited in LCR rats. If true in humans, it might suggest that patients that both have both increased hepatic lipid storage and lower exercise capacity might not be as responsive the positive impact of VSG on hepatic lipid metabolism.

One caveat to this is that while VSG has been found to lead to weight loss and improve plasma glucose and lipid levels for both males and females, hepatic lipid handling is significantly different between the sexes [20]. Specifically, VSG also causes less triglyceride export from the liver to peripheral tissues in fasting resulting in far greater retention of hepatic triglycerides in female compared to male rats. Thus, the lack of changes in hepatic triglycerides in the current study suggest that the lack of reduction in hepatic triglycerides may be more tightly linked to biological sex differences in hepatic lipid handing in rodents than it is about the inability of VSG to improve metabolism in LCR rats.

Total body fat was significantly reduced by the end of the study; this was via reductions in both subcutaneous and visceral adiposity. Despite this fat loss, weight of brown adipose tissue was not significantly altered by VSG. This is interesting, because previous work has shown that female rats bred for high aerobic capacity have greater amounts of weight-adjusted brown adipose tissue compared to LCR females [23]. We found a trend of a greater ratio of brown adipose tissue weight to white adipose tissue weight in VSG animals compared to sham animals. Together, these data suggest the interesting possibility that part of how surgery improves metabolism, at least in LCR rats, is by increasing or maintaining brown adipose tissue weight.

While we did not assess daily energy expenditure in these rats, we examined baseline VO_2 from the VO_{2max} test. We do not typically see changes in energy expenditure in our rodent models of VSG [13], and here we paradoxically saw a decrease in baseline and submaximal VO_2 in the VSG animals. Further, although maximal VO_2 was similar, basal and submaximal fat and carbohydrate oxidation was reduced in VSG vs. sham animals. Previous work has proposed that LCR rats have an increased capacity to store fuel and reduced capacity to oxidize fat [24]. That VSG would further contribute to increased fuel storage efficiency could be concerning as it suggests that inherently low exercise capacity could result in weight re-gain after surgery.

Body weight is controlled by a balance of food intake and energy expenditure and the predominance of literature suggests that bariatric surgery drives more robust changes in food intake than energy expenditure [25], although recent data suggest energy expenditure can be more critically involved in body mass changes in mice [26]. With extreme weight loss, energy expenditure decreases to compensate for the reduction in food intake and in some cases the reduction is greater

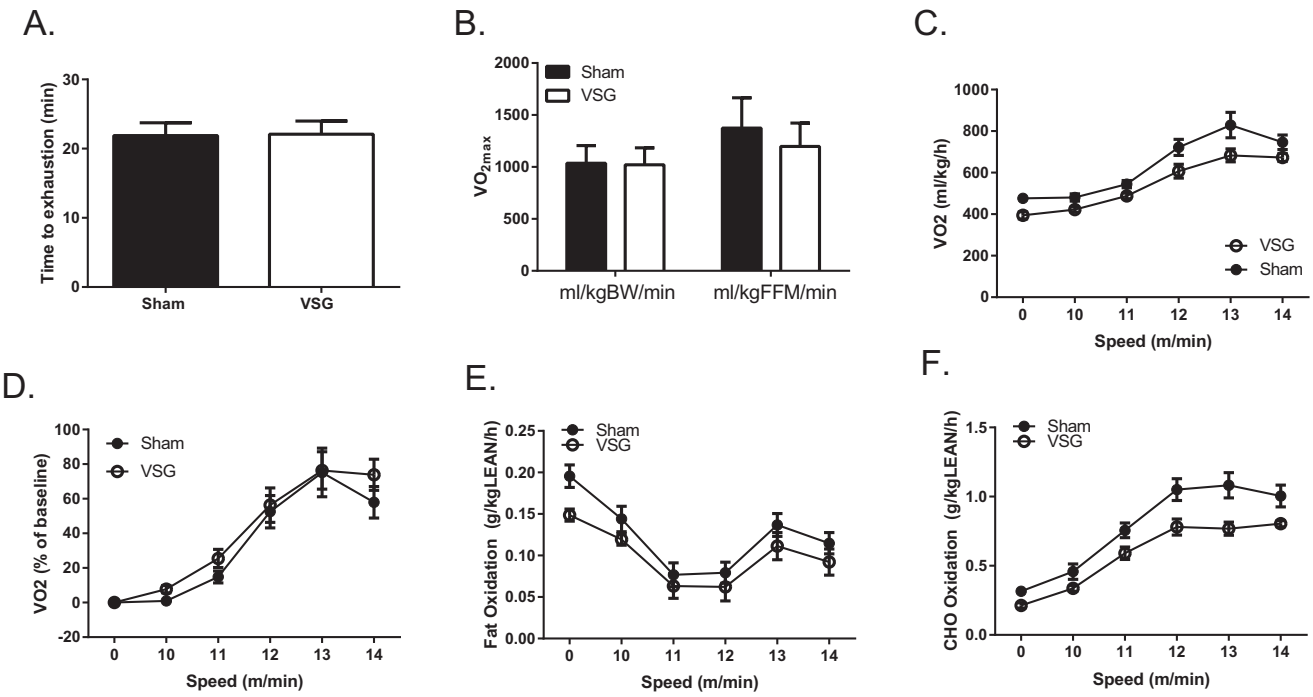

Figure 4: Changes in exercise capacity after sham vs. VSG surgeries. A. Time to exhaustion was also similar between sham and VSG animals. B. There were no significant differences in maximal oxygen capacity (VO_{2max}) whether expressed relative to body or fat free mass. C. Oxygen consumption (VO_2) over time was significantly lower in VSG vs. sham surgery animals (main effects of surgery and time; no interaction). D. There were no significant differences in VO_2 when expressed relative to baseline. Fat (E) and carbohydrate oxidation were significantly lower in VSG vs. sham animals (main effects of surgery and time; no interaction). Open circles, VSG; closed circles, sham. N = 11 VSG and 9 sham for all data.

than the reduction in caloric intake minimizing weight loss, i.e. adaptive thermogenesis [27]. Pharmacological administration of glucagon has demonstrated effects on increasing energy expenditure [28]. While we saw a reduction in glucagon after VSG in LCR rats, it is unclear whether physiological reductions in glucagon will drive a reduction in energy expenditure. Regardless, together with the somewhat delayed reduction in adiposity in the LCR rats after VSG, the reduction in VO_2 suggests that inherently low exercise capacity may increase susceptibility to adaptive thermogenesis limiting weight loss. We did not include a group of HCR rats in this experiment. While it may have been interesting to determine whether VSG could improve the metabolic phenotype of the LCR rats to the level of HCR rats, given the distinct differences between LCR and HCR metabolism, it is clear from our data that this did not happen. The LCR animals did lose body fat and have improvements in oral glucose tolerance in response to VSG, but this was not due to changes in aerobic capacity or basal oxygen consumption. Maximal aerobic capacity can be up to 60% higher in HCR vs. LCR rats [12], and HCR animals have *increased* basal VO_2 compared to LCR rats [29] while in response to VSG, the LCR animals had even further *reductions* oxygen consumption compared to sham animals. These differences are thought to be key differences that drive the downstream metabolic phenotypes of HCR vs. LCR rats. One other response is that the LCR animals also have 33% higher liver triglycerides compared to HCR rats [19], but the LCR rats did not have a significant decrease in hepatic triglycerides after VSG. Thus, altogether, our data demonstrate that VSG improved some parameters of metabolism in the LCR rats but at least some of these improvements are independent of the metabolic dysfunction caused by lower intrinsic aerobic capacity.

RYGB has been found to have greater effects on increasing brown adipose tissue volume and metabolic activity compared to VSG in male mice [30]. Another study suggested that with weight loss there is a decrease in brown adipose tissue thermogenic gene expression and that this decrease is blunted in RYGB in rats [31]. Because female LCR rats did not seem to get the full beneficial effects of VSG, future work should determine whether RYGB might be a more effective surgery for patients with low inherent exercise capacity.

5. CONCLUSION

In conclusion, our results indicate that VSG caused weight loss and some metabolic improvements in LCR female rats and this occurred independent of any changes in exercise capacity. Indeed, it seems that basal energy expenditure and fat and carbohydrate oxidation was reduced by VSG making these animals more efficient at storing energy, an effect that would limit weight loss. If true in humans, these data suggest that low exercise capacity could either minimize weight loss or contribute to weight-regain after bariatric surgery. They also suggest the interesting possibility that inherent exercise capacity could be used as a potential screening tool for who might benefit most from bariatric surgery.

ANIMAL RIGHTS

All animal experiments complied the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978).

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DECLARATION OF INTEREST

DAS has received research support from Ethicon Endo-Surgery, Novo Nordisk, and Boehringer Ingelheim. DAS has been a paid speaker for Novo Nordisk. SLB has been a paid speaker for Charles River.

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