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Sympathetic Inhibition Following Bariatric Surgery

Allyn L. Mark, Andrew W. Norris, and Kamal Rahmouni

Departments of Internal Medicine (ALM, KR), Pediatrics (AWN), Pharmacology (KR), and Biochemistry (AWN); the Obesity Research and Education Initiative (ALM, AWN, KR); and the Fraternal Order of Eagles Diabetes Research Center (ALM, AWN, KR). University of Iowa Carver College of Medicine Iowa City, Iowa and the Department of Cell and Developmental Biology, Weill Cornell Medical College, New York, NY (ALM).

Starting in 1967, Edward E. Mason, a surgeon at the University of Iowa, boldly advocated and performed gastric bypass for intractable morbid obesity (1). Since then, bariatric surgery has emerged as the only proven effective treatment for morbid obesity, resulting in substantial and sustained weight loss and striking beneficial effects on the metabolic syndrome, particularly type 2 diabetes mellitus. In recent years, research on the beneficial effects of gastric bypass and vertical sleeve gastrectomy (VSG) has shifted from the contribution of simple gastric diversion and restriction to an energetic pursuit of the contribution of gastrointestinal hormones, secretions and microbiome.

In this issue of *Hypertension*, Seravalle et al (2) from Grassi's laboratory extend their impressive body of work on the sympathetic nervous system in human hypertension and obesity with the demonstration of another beneficial effect of bariatric surgery, namely pronounced and sustained sympathoinhibition after VSG in patients with severe obesity.

Using direct, intramural recording recordings of sympathetic nerve activity (SNA) to the skeletal muscle, Seravalle et al report that VSG produces pronounced and sustained decreases in muscle SNA, body weight, plasma leptin, and systolic blood pressure (BP) at 6 and 12 months following surgery, whereas their measure of insulin sensitivity was improved at 6 but not 12 months. Seravalle et al conclude that the sympathoinhibition may be related to decreases in plasma leptin attendant to reduction in adiposity. The investigators highlight the temporal dissociation of changes in muscle SNA and insulin sensitivity and suggest that changes in insulin sensitivity and SNA following VSG are unrelated.

Microneurographic recordings of SNA and measurement of norepinephrine (NE) spillover are the most direct and powerful methods for measurement of sympathetic activity in humans. There have been multiple reports of measurement of muscle SNA or whole body NE spillover during diet-induced weight loss, but this is the first study employing one of these methods to measure SNA before and after weight loss produced by bariatric surgery. This permits comparison of the sympathoinhibitory effects of bariatric surgery vs dietary therapy for severe obesity. As expected, weight loss with VSG was much greater than that

CORRESPONDING AUTHOR Allyn L. Mark, M.D. University of Iowa Carver College of Medicine 3187 MERF Iowa City, Iowa 52242-1101 Ph: 319 594 5560 Fax: 319 335 6969 allyn-mark@uiowa.edu.

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with dietary therapy in previous studies. Decreases in muscle SNA following VSG were likewise pronounced and sustained. However, it is worth noting that the sympathoinhibition with VSG in the current study is of similar magnitude to that observed with dietary therapy in a previous study by these investigators despite smaller decreases in body weight with dietary therapy (3).

Indeed, when the percent decrease in muscle SNA is expressed in terms of the percent decrease in body weight, the sympathoinhibitory effect of VSG is less than that reported in several studies with diet-induced weight loss. A similar observation has been noted for the decreases in BP with bariatric surgery (4). Although bariatric surgery may reduce BP beyond that with dietary therapy, the relative antihypertensive effect is significantly less than expected from the degree of weight loss (4). This suggests that the magnitude of decrease in body weight or even total body fat is not the proximate cause of the decreases in SNA and BP. Instead, negative energy balance which decreases visceral, hepatic and intramyocellular fat and inflammation appears to be more decisive (5).

Removal of large amounts of abdominal subcutaneous adipose tissue by liposuction does not reduce visceral, hepatic or intramyocellular fat or markers of inflammation and does not improve insulin action, BP and other components of the metabolic syndrome (5). In contrast, during 12 weeks of low calorie diet, there are greater decreases in visceral than subcutaneous fat, and the improvement in BP and glucose metabolism correlates with reduction in visceral fat and not with the change in body weight (6). In this regard, muscle SNA correlates with visceral but not subcutaneous adiposity (7).

Dietary restriction may also play a role. Overfeeding stimulates and fasting suppresses SNA independent of changes in body mass (8). Dietary restriction *per se* may thus decrease SNA and BP independent of weight loss. This may help explain two interesting phenomena (9). First, dietary therapy for obesity is often associated with a prompt reduction in BP with only modest reductions in body weight. Second, for a given body mass index (BMI), BP is lower when the BMI is attained during dieting and weight loss than when the same BMI is attained during increased food intake and regain of weight.

A notable finding in the study by Seravalle et al was the magnitude of decrease in plasma leptin following VSG: decreasing by ~66% at 6 months and ~80% at 12 months reflecting the massive decrease in adipose tissue mass. In addition to its effects on appetite, metabolism and adiposity, leptin increases regional SNA and BP and contributes to obesity-induced sympathetic overdrive and hypertension in animal models of obesity (10). A recent study of healthy lean men provided the first direct evidence that acute experimental hyperleptinemia increases muscle SNA in humans (11). This supports the suggestion of Seravalle et al that the pronounced decreases in muscle SNA following VSG may be mediated at least in part by the striking decreases in plasma leptin.

Seravalle et al remark on the bidirectional interaction of the sympathetic nervous system and insulin action. As noted by Seravalle et al, insulin acts in the central nervous system to increase regional SNA, whereas sympathetic vasoconstriction in skeletal muscle decreases glucose uptake and promotes a functional insulin resistance. Presumably the investigators

expected concomitant decreases in muscle SNA and insulin resistance during the massive weight loss following VSG. Indeed, the decreases in muscle SNA were accompanied by reduction in plasma insulin and the homeostasis model assessment insulin resistance index (HOMA-IR) at 6 months, but surprisingly plasma insulin, blood glucose and HOMA-IR did not differ from baseline at 12 months following VSG. This prompted the investigators to suggest that changes in SNA and insulin sensitivity after VSG are unrelated. There are cautions regarding this conclusion. HOMA-IR is an estimate of insulin resistance that is based solely on fasting glucose and insulin. Since bariatric surgery primarily changes physiology as regards the fed state, HOMA-IR may not reflect the full impact of bariatric surgery on insulin action.

None of the patients in this study had diabetes. Both VSG and gastric bypass are significantly better than medical therapy for improving glycemic control in obese patients with type 2 diabetes, an advantage that is maintained for at least 3 years (12). The physiologic mechanisms underlying improvement in diabetes following VSG have not been clearly elucidated, but the antidiabetic effect of gastric bypass is related to remarkable improvements in β -cell responsiveness and insulin sensitivity when measured with robust techniques 1 to 2 years after surgery (13,14). Thus, the data on the effects of VSG on insulin action in the study of Seravalle et al may not exclude an interaction between insulin-mediated glucose metabolism and SNA following bariatric surgery, particularly in diabetic patients.

Interestingly, although SNA has potential impact on insulin action, insulin secretion, and energy balance, there is little information regarding its role in remission of diabetes after bariatric surgery.

In the past five decades, bariatric surgery has spurred advances in understanding the pathophysiology of obesity and its complications. Seravalle et al have expanded this understanding with the first demonstration of pronounced and durable sympathoinhibitory effects of bariatric surgery.

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