Long-Term Sympathoinhibitory Effects of Surgically Induced Weight Loss in Severe Obese Patients

Gino Seravalle, Manuela Colombo, Paolo Perego, Vittorio Giardini, Marco Volpe, Raffaella Dell’Oro, Giuseppe Mancia, Guido Grassi

See Editorial Commentary, pp 235–236

Abstract—Weight loss improves insulin sensitivity and exerts sympathomodulatory effects. No data, however, are available on the effects of the weight loss induced by vertical sleeve gastrectomy on sympathetic neural drive, insulin sensitivity, and their reciprocal cross talks. In 10 severe obese hypertensives (age, 54.0±2.3 years [mean±SEM]), we measured sphygomonanometric blood pressure, heart rate, body mass index, homeostatic model assessment index, plasma leptin, muscle sympathetic nerve traffic (microneurography), and baroreflex sensitivity (vasoactive drug technique). Measurements were performed 2 to 3 days before surgery and repeated 6 and 12 months after the procedure. Ten matched hypertensive obeses not undergoing gastrectomy served as controls. Six months after bariatric surgery, a significant (P<0.05) reduction in body mass index (−9.1±1.4 kg/m²), sphygomonanometric systolic blood pressure (−10.2±4.5 mm Hg), heart rate (−11.0±2.4 bpm), homeostatic model assessment index (−3–3±1.3 AU), plasma leptin (−53.6±8.8 μg/L), and muscle sympathetic nerve traffic (−15.0±3.4 bursts/100 heart beats) was observed. The weight loss, the plasma leptin reduction, and the sympathetic inhibition were maintained after 12 months, whereas homeostatic model assessment index showed a tendency to return toward presurgery values. A significant improvement in baroreflex control of sympathetic nerve traffic was observed both 6 (+32.1%; P<0.05) and 12 months (+60.7%; P<0.01) after gastrectomy. No significant changes in the above-mentioned variables were detected in the control group. These data provide evidence that massive weight loss induced by sleeve gastrectomy triggers profound sympathoinhibitory effects, associated with a stable and significant reduction in plasma leptin levels, whereas the improvement in insulin sensitivity was attenuated with time and unrelated to the sympathoinhibition. (Hypertension. 2014;64:431-437.) • Online Data Supplement

Key Words: bariatric surgery ■ baroreflex ■ body weight ■ insulin resistance ■ leptin ■ obesity ■ sympathetic nervous system

Long-term prospective studies have recently shown that bariatric surgery significantly reduces the risk of death in severely obese patients.1 This has been confirmed by retrospective analyses of a large cohort of obese individuals in whom surgery-related reductions in body weight were associated with a significant reduction in death rate compared with obese individuals followed under dietary and medical treatment.2-4 It is a widespread belief that the protective effect of bariatric surgery in obese patients may perhaps be related to a reduction of body weight per se but that the concomitant improvement of the array of risk factors commonly associated with obesity, for example, alterations in lipid and glucose metabolism, is likely to play a major role.5-7 In this context, however, little attention has to date been given to whether bariatric surgery is also associated with the improvement of another adverse phenomenon of obesity (ie, sympathetic activation).8,9 The only information available comes from 3 studies that assessed sympathetic tone by making use of spectral analysis of heart rate signal or 24-hour norepinephrine urinary excretion10-12 (ie, approaches that display major intrinsic limitations not allowing to provide any direct insight on the effects of the intervention on central sympathetic outflow, as the microneurographic technique only allows to achieve13.) The issue has pathophysiological and clinical relevance because sympathetic activation has been shown to be an adverse prognostic factor in several clinical conditions.14-17 Furthermore, evidence has been obtained that sympathetic overdrive may cause or worsen insulin resistance,18,19 thus contributing to a common metabolic alteration in obesity.
A time-honored hypothesis maintains that, although increasing energy wasting and thus initially opposing the increase in body weight, at a later stage sympathetic stimulation majorly contributes to the life-threatening complications of obesity, such as diabetes mellitus and hypertension. Primary aim of the present study was to investigate the effect of surgically induced reduction of body weight on central sympathetic neural outflow directly assessed by the micro-neurographic technique in severely obese patients. Secondary aims were to see whether changes in sympathetic activity (1) were persistent over the long term and (2) correlated with, and thus were possibly responsible for, surgically induced modifications of reflex sympathetic control, body weight, blood pressure (BP), and metabolic profile.

Methods

Study Population

Our study was performed in patients selected from 35 severe obese individuals evaluated between September 2011 and February 2012 by the Obesity Care Unit of the San Gerardo Hospital of Monza, Italy. Five patients were excluded for psychiatric abnormalities, 4 for the high risk posed by anesthesia to surgical intervention, and 6 for severe obstructive sleep apnea. Of the remaining 20 patients 10 were found to be suitable for vertical sleeve gastrectomy to which they consented. The other 10 patients refused to surgical procedure and were thus kept under the previously prescribed caloric restricted diet protocol (1500 calories/d) to serve as controls. Periodic checks allowed to determine that the dietary caloric restriction was followed by the patients belonging to the active or control group along the entire period of the study. No patient had a history of cardiovascular, cerebrovascular, renal, or pulmonary disease, and none had diabetes mellitus, was a heavy smoker, or reported excessive alcohol consumption. All patients were hypertensives. Eight of them in the surgically treated and 7 in the control group were under antihypertensive treatment with dihydropyridines, renin–angiotensin blockers, and diuretics. Dihydropyridines were not withdrawn, whereas the other drugs were stopped 2 weeks before the experimental sessions (see below). The patients recruited agreed to participate in the study after being informed of its nature and purpose. The study protocol was approved by the Ethics Committee of one of the institutions involved (Istituto Auxologico Italiano).

Measurements

In all patients, multiunit recordings of efferent sympathetic nerve activity to skeletal muscle (muscle sympathetic nerve activity [MSNA]) were obtained by a single operator (G.S.) through a tungsten microelectrode inserted into the right or left peroneal nerve as previously described. MSNA was quantified either as number of bursts per minute and as serum insulin (standard methods), homeostatic model assessment of the insulin resistance (HOMA) index (calculated with the following formula: plasma glucose [mmol/L]×serum insulin [μU/mL]/22.5), plasma leptin (ELISA, DRG Instruments GmbH, Marburg, Germany), plasma norepinephrine and epinephrine (high-performance liquid chromatography), plasma renin activity (radioimmunoassay), as well as plasma aldosterone (radioimmunoassay).

Simultaneous MSNA, beat-to-beat heart rate, and beat-to-beat BP recordings also allowed to study the baroreflex. To this aim, phenylephrine was infused in an antecubital vein at the doses of 0.3, 0.6, and 0.9 μg kg⁻¹ min⁻¹ to increase BP, stimulate baroreceptors, and reflexly induce a reduction of MSNA and heart rate. Nitroprusside was infused at the doses of 0.4, 0.8, and 1.2 μg kg⁻¹ min⁻¹ to reduce BP, deactivate baroreceptors for their ongoing level of activity, and reflexly induce an increase of MSNA and heart rate. The dose–response curves were selected randomly, and each infusion was maintained for 5 minutes. Mean arterial pressure (diastolic BP+1/3 pulse pressure), MSNA, and heart rate were averaged for the 5 minutes before and the 5 minutes of each infusion. Baroreceptor modulation of MSNA and heart rate was calculated by the ratio of the MSNA (percent integrated activity) or heart rate and the mean BP changes separately for the condition of baroreceptor stimulation and deactivation.

Protocol and Data Analysis

Anthropometric data, blood sample for routine blood chemistry, and the echocardiographic data were obtained few days before the study proper, which in patients undergoing surgery was performed 1 to 2 days before the intervention. Patients were brought to the laboratory in the morning after an overnight abstinence from food. They were placed in a supine position and fitted with the intravenous cannula and the BP, heart rate, and respiratory measuring devices. After a 45-minute interval, the blood sample was withdrawn to assay plasma glucose, insulin, leptin, norepinephrine, epinephrine, plasma renin activity, and plasma aldosterone. Microelectrodes were then manipulated until MSNA was obtained. After a 20-minute interval, BP, heart rate, respiratory rate, and MSNA were continuously measured during (1) a 15-minute baseline condition, (2) the intravenous infusion of one vasoactive drug, (3) a 30-minute recovery period, (4) a second 15-minute baseline condition, and (5) the infusion of the other vasoactive drug. Data were collected in a semidark and quiet room at a constant temperature of 20°C to 21°C. The study was repeated according to the same experimental sequence of interventions 6 and 12 months after surgery. The same protocol was followed in the control group.

Data were analyzed by a single investigator who was not involved in data collection and unaware of the nature of the study (M.V.). Values from individual subjects were averaged for either group and expressed as means±SE. Continuous variables with uneven distribution were analyzed by the t test for paired or unpaired data and Pearson correlation test. Categorical variables were analyzed by the χ² test or Fisher exact test, as appropriate. Multiple regression analysis was performed only on data that were significantly correlated in univariate analysis. All statistical tests were 2-tailed, and a P<0.05 was considered significant.

Results

Table 1 shows the demographic and baseline clinical characteristics of the patients undergoing bariatric surgery or remaining under dietary treatment. Patients undergoing surgery were on average middle age and as expected had a marked increase in body mass index, waist circumference, and waist-to-hip ratio. Systolic BP values were in the grade I hypertension range, whereas heart rate, echocardiographic data (left ventricular mass index and ejection fraction), plasma glycohemoglobin, plasma norepinephrine and epinephrine, plasma renin activity, and aldosterone were all normal in the high normal range. In contrast, fasting plasma glucose, plasma leptin, plasma insulin, and HOMA index were above the reported normal values, this being the case also for MSNA both when quantified as bursts/min and as bursts/100 heart beats. In no instance were baseline values significantly different between patients undergoing surgery and the control patients.
Table 1. Demographic and Baseline Clinical Characteristics of the 2 Groups of Obese Patients Who Underwent Bariatric Surgery (Surgery) or Remained Under Dietary Therapy (Control)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgery</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (males/females)</td>
<td>10 (6/4)</td>
<td>10 (5/5)</td>
</tr>
<tr>
<td>Age, y</td>
<td>54.0±2.3</td>
<td>53.1±2.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>112.4±7.1</td>
<td>113.0±6.9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>160±3.5</td>
<td>162±3.0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>43.3±1.8</td>
<td>43.1±1.7</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>127.1±4.9</td>
<td>128.0±4.0</td>
</tr>
<tr>
<td>Waist-to-hip ratio, cm</td>
<td>1.02±0.03</td>
<td>1.03±0.03</td>
</tr>
<tr>
<td>LVMi, g/m²</td>
<td>103.3±1.9</td>
<td>103.9±2.0</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>66.1±0.9</td>
<td>65.0±0.9</td>
</tr>
<tr>
<td>Sphygmonanometric SBP/DBP, mmHg</td>
<td>150.1±6.0</td>
<td>151.1±5.5</td>
</tr>
<tr>
<td>Finger SBP/DBP, mmHg</td>
<td>144.6±7.6</td>
<td>145.0±5.4</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>76.1±2.3</td>
<td>78.0±2.5</td>
</tr>
<tr>
<td>Respiration rate, breaths/min</td>
<td>17.8±0.6</td>
<td>18.2±0.6</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>52.1±3.4</td>
<td>50.5±3.1</td>
</tr>
<tr>
<td>MSNA, bursts/100 heart beats</td>
<td>69.2±3.5</td>
<td>64.7±3.3</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>292.6±42.3</td>
<td>284.1±39.5</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>34.9±8.9</td>
<td>30.1±7.9</td>
</tr>
<tr>
<td>Plasma renin activity, ng/mL</td>
<td>2.4±0.5</td>
<td>2.5±0.5</td>
</tr>
<tr>
<td>per hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma aldosterone, ng/dL</td>
<td>6.8±0.31</td>
<td>7.12±0.36</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>6.3±0.6</td>
<td>6.1±0.5</td>
</tr>
<tr>
<td>Glycohemoglobin, %</td>
<td>5.18±0.06</td>
<td>5.03±0.05</td>
</tr>
<tr>
<td>Plasma insulin, μU/mL</td>
<td>19.3±6.0</td>
<td>17.8±5.4</td>
</tr>
<tr>
<td>HOMA index, AU</td>
<td>5.3±1.7</td>
<td>4.82±0.9</td>
</tr>
<tr>
<td>Plasma leptin, μg/L</td>
<td>81.5±9.7</td>
<td>78.3±8.8</td>
</tr>
</tbody>
</table>

Data are shown as mean±SE. DBP indicates diastolic blood pressure; HOMA, homeostatic model assessment; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; MSNA, muscle sympathetic nerve activity; and SBP, systolic blood pressure.

The modifications of the baseline variables after 6 and 12 months in the bariatric surgery and control groups are shown in Table 2 and for waist circumference, plasma leptin, HOMA, and MSNA data, also in Figure 1. In the control group, that is, the group maintained under low-caloric diet, body weight and the other measured variables did not significantly modify. In the bariatric surgery group, however, body weight, body mass index, waist circumference, and waist-to-hip ratio showed a marked reduction after 6 months from the intervention. Plasma norepinephrine, epinephrine, renin activity, and plasma aldosterone did not change significantly, whereas systolic BP, heart rate, plasma leptin, plasma glucose, plasma insulin levels, and HOMA index exhibited significant lower values than before surgery. The postsurgery decrease included, and was particularly marked, sympathetic nerve traffic: −38.0% when MSNA was quantified as bursts/min and −29.6% when it was quantified as bursts/100 heart beats (Table 2 and right lower panel of Figure 1). The changes detectable after 6 months for bariatric surgery were either maintained or further potentiated after 12 months, with the exception of plasma insulin and HOMA index, which increased in the opposite trend and at 12 months were no more significantly different from the values seen in the presurgery state (Table 2 and left lower panel of Figure 1).

Figure 2 shows the heart rate and MSNA responses to baroreflex stimulation and deactivation induced by vasoactive drugs. Compared with the nonsignificant changes from baseline values seen in the control group (Figure 2, right), both baroreflex heart rate and MSNA modifications improved after 6 months from bariatric surgery (Figure 2, left), a further improvement being observed after 12 months when both reflex responses became significantly different from baseline. Similar results were obtained when data were expressed as baroreflex sensitivity values (Figure S1 in the online only Data Supplement). After 12 months from surgery, the MSNA reduction was significantly related to the decrease in body mass index (r=0.78; P<0.02). A relationship close to statistical significance was found between the MSNA reduction and the decrease in waist circumference and plasma leptin (r=0.67 and r=0.69, respectively, P<0.06 for both). A significant relationship of inverse nature was, however, observed between the MSNA reduction and the improvement of baroreflex MSNA modifications (r=−0.69; P<0.05).

Discussion

The major novel findings of the present study are that (1) the marked reduction in body weight induced by bariatric surgery in severely obese subjects is accompanied by a marked reduction in the elevated sympathetic nerve activity typical of the obese state21,23,30 and (2) the evidence that the sympathoinhibitory effect remains substantially stable or even increases with time. This provides the first direct demonstration obtained via the microneurographic technique that the favorable effects of surgical treatment of obesity include reversal of the sympathetic overdrive seen in individuals with a marked increase in body weight. This allows to more directly and unequivocally document the evidence recently provided by a study showing the lower levels of MSNA in obese subjects 3 years after bariatric surgery compared with a control group.31

In our obese subjects, bariatric surgery was accompanied by a 6- and 12-month BP reduction (particularly of systolic BP), the size of which was related to the concomitant reduction in MSNA. The relationship, however, did not achieve the level of statistical significance (r=0.43 and r=0.36; P=not significant) presumably because of the small sample size of the present study. Furthermore, after surgery, there was a reduction in plasma leptin levels and, at the sixth month, in plasma insulin and insulin resistance. This suggests that the sympathoinhibition may play a role in the favorable cardiovascular and metabolic effects of this therapeutic procedure reported in previous studies5–7,10 and largely confirmed in the present one. This is not unexpected because the importance of sympathetic hyperactivity in the pathogenesis of hypertension is well documented32–34 and so is, both in experimental animals and in man, its stimulating influence on leptin and insulin secretion,35–37 as well as its ability to cause or worsen insulin resistance.18,19 In the case of leptin, however, prevailing evidence suggests that the opposite is also true, namely that leptin may trigger central and peripheral sympathoexcitation.38,39 This possibility has been recently strengthened by the results of a microneurographic study showing that in healthy normoweight subjects acute infusion of leptin triggers a significant increase in MSNA.40 It is thus conceivable
to conclude that the sympathoinhibitory effects of sleeve gastrectomy are mediated, at least in part, by the reduction in the elevated levels of plasma leptin, which activate the sympathetic nervous system. Our study, however, also allows to discuss other possible mechanisms involved in the sympathoinhibitory effect of the surgically induced weight loss. First, we can exclude that the consistent, persistent, and marked reduction in sympathetic nerve activity seen in our obese patients after surgery was as a result of a decline of the sympathoexcitatory effect of the renin–angiotensin system because the postsurgery modifications of plasma renin activity were inconsistent and on average not statistically significant. It is also unlikely that despite its documented sympathoexcitatory effect, insulin is involved because, as discussed below, the reduction in plasma insulin levels was not sustained over the postbariatric surgery observation period, whereas that of sympathetic nerve traffic was. A further factor can be, however, the baroreflex because its persistent improvement in the postbariatric surgery period exhibited a rather close relationship with the reduced sympathetic activity. It should be mentioned, however, that our data cannot allow to determine which is the cause and the effect of these 2 phenomena and that not necessarily an improvement in baroreflex function triggers...
almost invariably a sympathetic deactivation. Our results, however, also suggest that in the postbariatric state insulin levels and insulin resistance are not persistently governed by the degree of sympathetic activation. This is because after their combined and related 6-month reduction at the twelfth month after surgery, sympathetic nerve activity remained lower, whereas plasma insulin levels returned toward the higher presurgery values with also a trend for impaired insulin sensitivity to reverse. Thus, in more chronic conditions factors other than autonomic influences may be involved in the regulation of glucose metabolism with a partial disappearance of the initial favorable effects, despite the maintenance of an effective body weight reduction. The nature of these factors is not clarified by our study.

Several other results of our study deserve a brief mention. First, in our patients, the reduction in MSNA induced by sleeve gastrectomy was not accompanied by a concomitant decrease in plasma norepinephrine and epinephrine. This may suggest that, as shown in other clinical conditions, plasma catecholamines may be unable to reflect central sympathetic drive fully and its changes induced by interventions. It may also imply, however, that the sympathetic inhibition after sleeve gastrectomy is not generalized to the entire cardiovascular system and that it does not necessarily take place in regional vascular districts other than the muscle one, such as the heart, the kidney, the adipose tissue, or the liver. Second, bariatric surgery was also accompanied by a reduction in heart rate, which persisted throughout the follow-up period. Because heart rate lowering has a favorable effect on the energy–performance balance of the cardiac organ, this can be included in the favorable consequences bariatric surgery has on the cardiovascular system. It can further be suggested that the heart rate–lowering effects originate from the postsurgery improvement of the baroreflex heart rate control.

**Perspectives**

Our study has some limitations but also a clinical implication. The first limitation refers to the fact that our results apply to vertical sleeve gastrectomy only, and thus it remains to be seen whether a similar behavior of MSNA accompanies other forms of bariatric surgery. Another limitation refers to the fact that in our patients we did not assess plasma ghrelin levels, which have been shown to exert sympathoexcitatory effects and to be reduced by sleeve gastrectomy. Finally, although the MSNA data were calculated by an investigator unaware of the experimental design, our study has the intrinsic limitations of a study with an unblinded study design. The clinical implication refers to the fact that removal of the sympathetic...
activation by sleeve gastrectomy may eliminate a factor that is involved in the high prevalence of hypertension, congestive heart failure, ischemic heart disease, and sudden death typical of the severe obese state.48–50

None.

References


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**Novelty and Significance**

**What Is New?**

- The present study assesses for the first time the effects of vertical sleeve gastrectomy on muscle sympathetic nerve traffic, baroreflex sensitivity, plasma leptin, as well as metabolic profile in severe obese subjects.
- It also assesses the time course of the various responses to determine whether and to what extent the sympathetic changes correlate with, and thus are possible responsible for, surgically induced modifications of reflex sympathetic control, body weight, blood pressure, and metabolic profile.

**What Is Relevant?**

- Massive weight loss induced by bariatric surgery triggers profound sympathoinhibitory and eumetabolic effects, reducing elevated plasma leptin levels and improving also baroreflex cardiovascular control.
- In the long-term follow-up period, however, the sympathoinhibitory and the metabolic effects seem to follow a different time course, indicating that the sympathoinhibition accompanying weight loss is not necessarily related to insulin sensitivity changes.

**Summary**

Weight loss induced by bariatric surgery triggers marked sympathoinhibitory effects associated with a marked reduction in plasma leptin and an improvement in baroreflex cardiovascular control and metabolic profile as well. The sympathetic changes, however, display a time course different from the one characterizing the metabolic modifications (specifically insulin sensitivity), suggesting that in the long-term period the 2 phenomena might be unrelated each other.
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Gino Seravalle¹, Manuela Colombo², Paolo Perego³, Vittorio Giardini³, Marco Volpe², Raffaella Dell’Oro², Giuseppe Mancia¹,⁴, Guido Grassi²,⁴,⁵.

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Running Title: Sympathetic and metabolic responses to gastrectomy

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S1. Bar graphs showing the overall sensitivity of the baroreceptor-heart rate (HR) (left panel) and muscle sympathetic nerve activity (MSNA) (right panel) reflex before and after 6 and 12 months (mo) of bariatric surgery (surgery) or dietary treatment (control). MBP, mean blood pressure; %i.a., percentage integrated activity. Data are shown as mean±SEM. * P < .05, ** P < .01 vs baseline.