Effect of Energy-Restricted Diet on Sympathetic Muscle Nerve Activity in Obese Women

Björn Andersson, Mikael Elam, B. Gunnar Wallin, Per Börntorp, and Ove K. Andersson

Twenty obese women aged 45–65 years with borderline hypertension were allocated randomly to either a group with an energy-restricted diet or to a control group. Body weight, blood pressure, urinary sodium, and urinary excretion of norepinephrine and plasma volume were recorded. Resting muscle sympathetic nerve activity was measured in the peroneal nerve by tungsten microelectrodes and expressed as bursts per minute. These measurements were repeated after 3 days of semistarvation and after a body weight reduction of 7% while each patient's weight was in a steady state. After 3 days of semistarvation, only body weight was reduced, whereas after the long-term energy intake restriction, there were reductions of body weight (79.9±3.4 versus 74.1±3.4 kg; p<0.001), diastolic blood pressure (93±3 versus 86±4 mm Hg; p=0.01), and muscle sympathetic nerve activity (49±2 versus 42±3 bursts/min; p<0.05). Other variables were unchanged. There were no changes in body weight, blood pressure, or muscle sympathetic nerve activity in the control group. We conclude that body weight decrease in obesity results in a reduction of blood pressure that is at least partially caused by a reduction of sympathetic vasoconstrictor activity. (Hypertension 1991;18:783-789)

Many studies have shown that a decrease in body weight in hypertensive patients with moderate-to-severe obesity is associated with a fall in blood pressure.1,2 The mechanisms behind the blood pressure reduction are only partially understood. Some authors have suggested that a restricted sodium intake3,4 contributes to the blood pressure decrement; others have found a fall in blood pressure without a concomitant decrease of sodium intake.5 Based on measurements of circulating norepinephrine concentrations, it has also been proposed that both the acute and the long-term reduction of blood pressure are due to a reduced sympathetic vasoconstrictor drive.6–12

In a previous study13 of obese borderline hypertensive women who had been fasting for 48 hours, we made direct recordings of sympathetic neural outflow to the vascular bed of skeletal muscle and found an essentially unchanged nerve traffic in spite of a significant blood pressure reduction. The patients were energy and sodium restricted. It has been suggested previously14,15 that salt and energy intake restriction have opposite effects on sympathetic nervous activity so that the net effect of a markedly reduced sodium intake combined with a negative energy balance may be no change or even an increased sympathetic drive (expressed as increased levels of plasma norepinephrine). Our previous results are compatible with this hypothesis.

The aim of the present study was to clarify the effect of calorie restriction on sympathetic nerve activity by measuring effluent muscle sympathetic activity in a group of obese and borderline hypertensive women before and after a short-term sodium-supplemented period of fasting and also to assess the effects of a long-term negative energy balance on plasma volume, blood pressure, and effluent vasoconstrictor tone.

Methods

Subjects

Thirty moderately obese women with borderline hypertension (diastolic blood pressure 90 mm Hg or greater on at least two occasions) aged 43–66 years and with a body mass index (BMI) (kg/m²) of 26–36 were included. The mean systolic blood pressure in the examined group at baseline was 146±3 mm Hg (mean±SEM), and the mean diastolic blood pressure was 93±2 mm Hg. None of the women were on
Patients were not included if they had diabetes mellitus, overt cardiovascular disease, malignant disease, or hypertension necessitating drug management. In five patients who previously had been on antihypertensive medication, the drug was withdrawn at least 4 weeks before the study.

In seven women, baseline sympathetic nerve recordings failed for technical reasons and they were therefore excluded. Three women were excluded because of noncompliance. All patients gave their informed consent to the study, which was approved by the Ethics Committee of the University of Goteborg.

**Protocol**

Before inclusion, the subjects were allocated randomly to receive (group 1) or not to receive (group 2) diet intervention. During a run-in period of 4 weeks, blood pressure, heart rate, and body weight were measured on four separate occasions. Furthermore, four 24-hour (starting at 7:00 AM) urinary sodium and urinary norepinephrine samples were collected. The means of the measurements of these four samples were considered the baseline values. All patients were interviewed by a dietitian, and their dietary habits were recorded for 4 days.

The patients in group 1 underwent 3 days of semistarvation supervised by a dietitian. At baseline (day 1), blood pressure, heart rate, body weight, and plasma volume were determined. Muscle nerve sympathetic activity was recorded. The patients were ambulatory throughout the study. On day 4, the subjects came to the laboratory in a fasting condition, and all measurements were repeated. Twenty-four-hour urinary sodium and norepinephrine samples were collected. The patients in group 2 (control group) were not given dietary advice but were instructed to maintain their usual energy intake during these 3 days. The same measurements as in group 1 were performed. Patients from the two groups were investigated in random order, and the physicians who performed the nerve recordings (M.E. and B.G.W.) were not aware of to which group the patients belonged.

After the semistarvation period, the subjects in group 1 were placed on an individually adjusted energy-restricted diet that aimed at a weight decrease of 7% of the original body weight. This level of body weight reduction was chosen since, in previous studies of similar design, weight loss of at least 5% was considered necessary to obtain a significant fall in blood pressure. Sodium intake was not restricted. The patients visited the dietitian every fourth week on an average. Body weight was recorded during all visits. When the desired body weight decrement was achieved and the patient's weight had been stable for 4 weeks (less than ±2 kg weight change), the patient came to the laboratory; body weight, blood pressure, heart rate, and plasma volume were measured. Muscle nerve sympathetic activity was recorded. Two 24-hour urinary sodium and norepinephrine samples were collected, and the mean values of these samples were used.

The patients in group 2 were given no dietary advice and were instructed to remain on a steady-state energy intake. They were reexamined after 3-5 months, a time period that was chosen as an attempt to imitate the long-term energy restriction period in group 1. One patient in group 1 failed to cope with the semistarvation diet but accomplished the long-term energy restriction. Two patients dropped out of long-term treatment because of inability to decrease their body weight.

**Diet**

The semistarvation diet was composed of beverages of carrot, apricot, prune, and mixed fruit juices as well as a linseed supplement that totaled about 621 kJ/24 hr with a sodium content of 3 mmol and a potassium content of 7 mmol.

To provide an unchanged sodium balance during the semistarvation period, the patients received sodium...
TABLE 2. Hemodynamic and Metabolic Variables Before and After 3 Days of Either Semistarvation (Group 1) or Unchanged Energy Intake (Group 2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n=10)</th>
<th>Group 2 (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>83.5 ±4.0</td>
<td>81.0 ±3.9*</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>148 ±4</td>
<td>147 ±3</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>93 ±2</td>
<td>87 ±4</td>
</tr>
<tr>
<td>Heart rate</td>
<td>72 ±3</td>
<td>73 ±4</td>
</tr>
<tr>
<td>MSA (bursts/min)</td>
<td>48 ±2</td>
<td>53 ±3</td>
</tr>
<tr>
<td>Plasma volume (l)</td>
<td>2.82 ±0.16</td>
<td>2.75 ±0.24</td>
</tr>
<tr>
<td>Urinary norepineprine (nmol/24 hr)</td>
<td>204 ±14</td>
<td>302 ±64</td>
</tr>
<tr>
<td>Urinary sodium (mmol/24 hr)</td>
<td>168 ±21</td>
<td>127 ±20</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. SBP, systolic blood pressure; DBP, diastolic blood pressure; MSA, muscle sympathetic nerve activity.

*p<0.001 comparing before--after in each group.

Measurements

Body weight was measured to the nearest 0.1 kg with the subjects in their underwear. Systolic and diastolic blood pressures were measured automatically with a Nicon Colin Sphygmomanometer BP-203 model Y with a calibrated V-look cuff (Nippon Colin Ltd., Komachi-City, Japan) after the subject had rested at least 15 minutes in the supine position. Measurements were taken every minute during the nerve recordings at rest (10 minutes), and the mean value of the measurements was used. Heart rate was measured every minute from an electrocardiogram recorded by chest electrodes, and the mean value from the whole rest period was calculated.

All recordings of muscle nerve sympathetic activity were performed in the same room at the Department of Clinical Neurophysiology while the patient was in a comfortable supine position. The recording technique and display system have been described in detail previously.17-19 In summary, nerve recordings were made with tungsten microelectrodes with a tip diameter of a few microns. The electrodes were inserted manually through intact skin into a muscle nerve fascicle in the peroneal nerve at the knee. Small electrode adjustments were made until an optimal position was found for recording sympathetic impulses. Recordings 1 and 2 were made in different legs.

After amplification, the nerve signal was monitored on a storage oscilloscope (model 549, Teltronix, Beaverton, Ore.) and a loudspeaker and also fed through an RC-integrating network (time constant 0.1 second) to obtain a mean voltage display of the nerve activity. The analog signals of both original and mean voltage neurograms were stored together with other variables on an eight-channel, FM tape recorder (Sabre VI, Sangamo, Sarasota, Fla.).

Spontaneous sympathetic activity was recorded at rest for 10 minutes, and the mean voltage neurogram was displayed on an ink jet recorder. Records were divided into 1-minute periods, and for each period all pulse synchronous bursts that could be identified by inspection of the mean voltage neurogram were marked and counted. For each 1-minute period the strength of the sympathetic activity was expressed as the number of bursts per minute,19 and the results are presented as the mean value for all 1-minute periods.

In one patient in group 1, the nerve recording after the semistarvation period failed, but a satisfactory recording was obtained after the long-term negative energy balance. In group 2 (control group), nerve recordings after 3 days failed in one patient because of technical difficulties.

The 24-hour urine samples were collected daily in bottles containing 4N HCl as preservative. Urinary sodium was measured by flame photometry and urine norepinephrine by a high-performance liquid chromatography method with an electrochemical detector.20 Plasma volume was determined by a radioiodinated serum albumin method with J125.21

Statistics

Results are given as mean ± SEM. Statistical methods used were one-factor analysis of variance (ANOVA) with repeated measurements for comparison within groups and factorial ANOVA for comparison between groups. Multiple regression analyses were performed according to Macintosh STATVIEW. All tests were two-tailed, and values of p<0.05 were regarded as statistically significant.

Results

Baseline characteristics of the participating women are shown in Table 1. There was no difference at baseline between the treatment (group 1)
and the control group (group 2) regarding blood pressure, sympathetic nerve activity, plasma volume, or anthropometric data.

**Effects of Initial Semistarvation**

In group 1, body weight was reduced from 83.5±4.0 to 81.0±3.9 kg (p<0.001, Table 2), but no changes in systolic blood pressure, heart rate, plasma volume, or excretion of sodium and norepinephrine were observed. There was, however, a tendency for a decrease in diastolic blood pressure (93±2 versus 87±4 mm Hg, p=0.087) and an increase in muscle sympathetic nerve activity (MSA) (48±2 versus 53±3 bursts/min; p=0.092; Figure 1A). In the control group, there were no changes in the measured variables.

**Effects of Long-term Calorie Restriction**

During long-term dieting (group 1), body weight decreased from 79.9±3.4 to 74.1±3.4 kg (p<0.001; Table 3). Systolic blood pressure was unchanged, whereas diastolic blood pressure was reduced from 93±3 to 86±4 mm Hg (p<0.01). MSA decreased 14% from 49±2 bursts/min at baseline to 42±3 bursts/min after the long-term energy restriction (p<0.05; Figure 1B). The decrease was even more pronounced (21%) when MSA after the initial semistarvation period was compared with the level after the long-term negative energy balance (53±3 versus 42±3 bursts/min; p<0.01; Figure 1C). Heart rate, urinary excretion of norepinephrine and sodium, and plasma volume were unchanged (Table 3).

After a mean of 4 months, the subjects in group 2 had unchanged body weight, systolic and diastolic

### Table 3. Hemodynamic and Metabolic Variables Before and After Long-term Energy Intake Reduction (Group 1) or After 4 Months of Unrestricted Energy Intake (Group 2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n=9)</th>
<th>Group 2 (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>79.9±3.4</td>
<td>74.1±3.4*</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>146±4</td>
<td>142±5</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>93±3</td>
<td>86±4†</td>
</tr>
<tr>
<td>Heart rate</td>
<td>71±3</td>
<td>66±3</td>
</tr>
<tr>
<td>MSA (bursts/min)</td>
<td>49±2</td>
<td>42±3‡</td>
</tr>
<tr>
<td>Plasma volume (l)</td>
<td>2.68±0.20</td>
<td>2.73±0.17</td>
</tr>
<tr>
<td>Urinary norepinephrine</td>
<td>210±13</td>
<td>198±31</td>
</tr>
<tr>
<td>(nmol/24 hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary sodium</td>
<td>157±20</td>
<td>133±14</td>
</tr>
<tr>
<td>(nmol/24 hr)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SEM. SBP, systolic blood pressure; DBP, diastolic blood pressure; MSA, muscle sympathetic nerve activity.

* p<0.001, †p<0.01, ‡p<0.05, comparing before–after in each group.
blood pressure, heart rate, urinary excretion of nor-
epinephrine and sodium, and plasma volume (Table
3). The level of MSA (50±3 bursts/min) was un-
changed compared with both the initial control value
(53±3 bursts/min) and the value after 3 days (52±3
bursts/min).

Although both diastolic blood pressure and MSA
decreased during long-term dieting, the correlation
between these changes did not reach statistical sig-
ificance (r=0.56, p=0.12). There were no correla-
tions between changes in body weight and MSA or
blood pressure during treatment.

Discussion

The main findings in the present study were signif-
icant decreases of MSA and diastolic blood pressure
after long-term energy restriction and a tendency to
increased MSA and decreased diastolic blood pres-
sure after 3 days of semistarvation.

Previous reports concerning sympathetic nervous ac-
tivity after energy restriction7-9,11-12 have been based on
measurements of circulating norepinephrine, which has
been considered an indicator of sympathetic activity.
Although a correlation between plasma norepineph-
rine and MSA is usually found,22-24 there are excep-
tions,25,26 and it must be remembered that plasma
norepinephrine levels are influenced not only by cen-
tral sympathetic outflow but also by peripheral mecha-
nisms such as altered release or reuptake into nerve
terminals, regional blood flow, and spillover from dif-
f erent vascular beds.27,28

In contrast, recording MSA has an advantage in
that it gives a direct measurement of sympathetic
nerve traffic. Previous studies have shown that the
MSA level at rest is highly reproducible in repeated
recordings over several months,29,30 which is con-
firmed by the control group in the present study.
There is, however, also a limitation with the nerve
recording method. Sympathetic outflow is differenti-
ated,18 and therefore, results from one sympathetic
subdivision cannot be extended to other regions.

Effects of Semistarvation

Short-term fasting is known to reduce blood pres-
sure, and it has been suggested this effect is due to a
reduced sympathetic activity.8,9 However, in a previ-
ous study we found an essentially unchanged sympa-
thetic nerve traffic despite a decrease in blood pres-
sure after 48 hours of fasting.13 Our present results
are similar, even if the decrease in diastolic blood
pressure did not reach statistical significance.

Body weight reduction during short-term fasting is
due mainly to dehydration.31 Reduced intravascular
fluid volume may cause the initial blood pressure fall
by reducing venous return and cardiac output. Under
such circumstances it is possible that unloading of
arterial or low-pressure receptors would activate the
sympathetic vasoconstrictor system as a compensa-
tory mechanism to preserve blood pressure. In addi-
tion, a reduced sodium intake per se has been shown
to increase both MSA and plasma norepinephrine in
borderline hypertensive and normotensive subjects.32

In the present study, sodium intake was unchanged
and therefore this factor would not influence MSA,
which may explain why the changes in sympathetic
nerve activity (and blood pressure) were small.

Effects of Long-term Energy Restriction

The decrease of resting MSA after the long-term
negative energy balance provides direct support for
the hypothesis that the blood pressure decrement is
caused by a reduction of sympathetic nervous traf-
 fic.10-12 The underlying mechanisms are unclear. It
has been proposed that a low carbohydrate intake
suppresses sympathetic activity,9,33,34 whereas over-
feeding with carbohydrates or dietary fat causes an
increased sympathetic drive both in humans and rats.8,24,35,36
In the present study, the subjects were
given a diet that was reduced in dietary fat, but the
carbohydrate intake was roughly unchanged com-
pared with steady-state conditions. It is unclear
whether the reduction of fat might have influenced
the sympathetic nervous traffic.

Decreased insulin sensitivity and hyperinsulinemia
have been suggested to be one mechanism linking
obesity to hypertension.37 An independent correla-
tion between plasma insulin and blood pressure in
hypertensive patients with both normal body weight
and overweight has been reported in several studi-
ies.38-40 It has also been shown that insulin infusion
increases sympathetic nervous activity in the absence
of changes in blood glucose41 and accordingly there
might be an association between obesity with accom-
panying hyperinsulinemia, hypertension, and the
sympathetic nervous system. This could not be eval-
uated in the present study since insulin was not
assessed.

In previous reports, severe energy intake restric-
tion (1,260-1,680 kJ/24 hr) caused reduction of blood
pressure independent of sodium intake,5,11,12 whereas
more moderate energy restriction (5,040 kJ/24 hr)
failed to decrease blood pressure unless sodium
intake was restricted.4 However, contradictory to the
results of the latter study, Reisin and coworkers5
demonstrated a fall in blood pressure in patients with
only a moderately negative energy balance indepen-
dent of sodium intake. Our data are in agreement
with the findings of Reisin et al5 since a mild calorie
restriction (about 6,300 kJ/24 hr) leads to a signifi-
cant blood pressure decrease in spite of an un-
changed sodium balance. Thus, even a moderate
energy restriction is sufficient to achieve a fall in
blood pressure independent of sodium intake. How-
ever, our results do not exclude the possibility of an
additive effect of sodium restriction superimposed on
a negative energy balance.4

As mentioned above, reduced intravascular fluid
volume may contribute to the fall in blood pressure
during severe short-term energy restriction.31 How-
ever, several reports42-44 indicate that also after
long-term negative energy balance, weight loss re-
results in a contracted blood volume, leading to a decreased cardiac output and lowered blood pressure. We failed to show any contraction of plasma volume in spite of a reduced blood pressure. This may be due to a difference in study design, diet composition, and patient compliance compared with previous studies. On the other hand, our results are consistent with the findings in a previous study in which obese men with mild hypertension on an energy-reduced diet had unchanged plasma volume although weight and blood pressure were decreased.

Studies of resting MSA in essential hypertension have given varying results. In early reports on established hypertension, MSA was found to be normal, but in a recent study, MSA was increased. Similarly, in borderline hypertension two studies showed an increase and another did not. The explanation for the divergent findings may be the large interindividual differences in MSA and the increase in MSA that normally occurs with age.

In the present study, such difficulties were circumvented since each patient was her own control. Therefore, the findings of a concomitant decrease of MSA and blood pressure during dietary treatment may support the idea of a relation between MSA and the static blood pressure level.

In summary, we conclude that the blood pressure reduction observed after a long-term moderate energy restriction is associated with, and probably may support the idea of a relation between MSA and sympathetic vasoconstrictor activity.

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obese subjects treated with a low-calorie protein or mixed diet. 

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KEY WORDS • obesity • sympathetic nervous system • blood pressure • microneurographyobesity
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