Reactivity to Norepinephrine and Effect of Sodium on Blood Pressure During Weight Loss

Björn Fagerberg, Ove K. Andersson, Bengt Persson, and Thomas Hedner

SUMMARY

Eighteen moderately obese middle-aged men with untreated mild hypertension were randomized to two groups and placed on a low energy diet regimen for 9 to 11 weeks. In Group I (n = 10) the amount of sodium chloride in the diet maintained the urinary sodium excretion at the predieting level. Mean body mass was reduced by 9.1 ± 0.7 (SEM) kg. Mean intra-arterial pressure showed no significant change. There were significant decreases in heart rate (p < 0.05) and urinary norepinephrine excretion (p < 0.05) but not in plasma concentration of norepinephrine. In Group II (n = 8) energy as well as sodium intake was restricted, with a 95 ± 22 mmol/24 hour reduction of urinary sodium excretion. Body mass decreased by 9.3 ± 1.1 kg, and mean arterial pressure decreased by −18.9 to −4.3 mm Hg (95% confidence interval). There were also significant reductions in heart rate (p < 0.001) and plasma norepinephrine concentrations (p < 0.01) but not in urinary norepinephrine excretion. The pressor response (mean arterial pressure) to norepinephrine infusion at different dose rates was significantly elevated (p < 0.05) in Group I during dieting in comparison with baseline. The blood pressure response to norepinephrine during dieting in patients in Group II was not changed from baseline. The difference in blood pressure response to norepinephrine cannot be explained by changes in clearance rates and plasma volumes. The results indicate that the lack of hypertensive response observed in patients on moderate energy restriction with unchanged sodium intake might have been caused by increased vascular reactivity to norepinephrine. Although sympathetic vasoconstrictor tone was reduced, increased vascular reactivity may have kept the blood pressure level unchanged. Blood pressure fell in patients on combined energy and sodium restriction as the lowered sympathetic nervous activity was not offset by an increase in reactivity.

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KEY WORDS • hypertension • obesity • salt • sympathetic nervous system

WEIGHT-reducing diets have a well-known blood pressure lowering effect on obese hypertensive subjects. Although the underlying mechanisms are not clear, it has been suggested that dietary factors influence the sympathetic outflow. Thus, dietary energy restriction generally has been associated with indirect signs of reduced sympathetic outflow such as decreased plasma norepinephrine (NE) levels and decreased NE turnover.

The sympathetic nervous system is affected by the level of energy intake as well as by separate dietary constituents such as sodium, carbohydrates, and alcohol that may modify the effects of different weight-reducing regimens. The situation is further complicated by the fact that the vascular effects of sympathetic nervous system activity are determined by nervous impulse traffic which at best is mirrored by plasma norepinephrine levels, and also are influenced by changes in the adrenergic receptor level. Vascular reactivity to norepinephrine therefore has been proposed as a measure of receptor sensitivity, which may respond to changes in sodium intake.

The objective of the present study was to investigate how a moderate weight-reducing diet affects blood pressure regulation and sympathetic nervous system activity, as judged not only from measurements of catecholamine levels in plasma and urine but also from vascular reactivity assessed as the pressor response to exogenous norepinephrine. Factors other than energy restriction known to influence blood pressure and the
sympathetic nervous system (i.e., alcohol consumption, physical exercise, smoking, sodium and carbohydrate intake) were controlled. Plasma renin activity (PRA) was also assessed as it is known to reflect sympathetic activity and sodium balance as well as to affect adrenergic reactivity through angiotensin generations.

**Methods**

The experimental setting in the investigation of the hemodynamic adaptation to low energy dieting has been described previously. Twenty-three middle-aged men (mean age 51 years) with untreated hypertension fulfilled the following criteria: the body mass was 20 to 40% in excess of normal weight in an ideal Scandinavian population and the diastolic blood pressure after 5 minutes of supine rest was above 94 mm Hg and below 105 mm Hg on two separate examinations. The subjects were otherwise healthy without evidence of secondary hypertension as judged by our routine examination. The patients were randomly allocated to two groups, but because of technical problems and side effects during infusion of NE, the final study groups were reduced to 10 men in Group I and 8 men in Group II. The characteristics of the subjects are shown in Table 1. All patients gave informed consent to participate; the ethics committee at the University Hospital of Goteborg approved the study.

This ambulatory study began with a 4-week baseline period in both groups that was followed by reduced-energy diets with unchanged (Group I) or restricted sodium intake (Group II). The patients were asked not to change any habits of alcohol consumption, smoking, or physical exercise. Every second to third week they attended the hospital's hypertension clinic where they met the dietician.

During the 4-week baseline period all subjects recorded their food intake for 4 days. Four 24-hour collections of urine were obtained, the last one immediately before the baseline period ended, measurements of resting mean intra-arterial pressure (MAP), plasma NE levels, PRA, and reactivity to NE infusion also were obtained. The subjects also answered a questionnaire regarding their alcohol consumption, physical activity, and smoking habits during the 4-week baseline period.

The subjects were then divided into two groups. Group I (n = 10) was placed on an energy-restricted diet with unchanged sodium intake. The dietician used the dietary record from the basal period as the basis for the standardized but individually adjusted instructions and aimed at a weight reduction of 1 kg per week. The diet was balanced (15–20% of energy intake from protein, 25–30% from fat, and 50–60% from carbohydrates), and foods with low sodium content were selected. The habitual sodium intake was judged from the mean of the four previous 24-hour urinary sodium excretions with the addition of 10 mmol for extrarenal losses. The subjects were instructed to supplement their diet with 0.5 g sodium tablets (Natriumklorid, ACO, Sweden) and table salt in preweighed packages to maintain the prediet sodium intake (sodium excretion). The dietician monitored the patients' adherence to the regimen through repeated interviews, body mass measurements, and 24-hour urinary sodium excretions, which were determined in four specimens obtained from each patient. At the end of the period the same examinations were performed as in the baseline period.

Group II (n = 8) was placed on the same energy-restricted diet as Group I, but sodium intake also was reduced in an attempt to lower the urinary sodium excretion below 100 mmol/day. To ensure good compliance collection of 24-hour urinary specimens was identical to that in Group I. The hemodynamic investigation was repeated using the same procedures and staff as in Group I. The duration of the diet periods was governed by the time required by each patient to reduce body mass by 5% or more. The average duration of the diet was 9 to 11 weeks; the interval between the two examinations was 12 to 14 weeks.

Each subject was examined twice according to the following procedure. A standardized breakfast (tea and toast) was eaten in the morning. At 0800 hours the patient went to the laboratory. Body mass was determined with the subject dressed in trousers; thereafter, he was placed in the supine position. Percutaneous catheters were inserted in the left brachial artery and a cubital vein, and the latter catheter was advanced to the superior caval vein. The position of the venous catheter was checked with x-ray films. After silent, supine subject rested for 30 minutes. Evans blue was injected for determination of plasma volume. Thereafter, arterial and venous blood were drawn for determination of NE level and PRA. The intra-arterial blood pressure was recorded with a pressure transducer (EMT 34, Siemens-Elema, Stockholm, Sweden), and MAP was obtained from electrically damped curves. Heart rate was measured from the electrocardiogram.

After hemodynamic examinations, each patient received an i.v. infusion of 1-norepinephrine tartrate (Noradrenalin, ACO, Sweden) diluted with 5.25%...
fructose solution to a concentration of 10 µg/ml. An infusion pump was used (syringe pump, model 355, Sage Instruments Inc., Cambridge, MA, USA) with a standardized stepwise elevation of infusion speed. Infusion rate was increased when MAP had stabilized at a new level, as judged from the intra-arterial recordings. The infusion test was stopped when MAP had increased 20 mm Hg from the baseline value. The cardiovascular reactivity to NE was expressed as the change in MAP and heart rate after NE infusion at the rates of 4.3 and 7.5 µg/minute. The average values of MAP and heart rate after 2 and 4 minutes of infusion at each dose rate were used.

Reactivity to NE was also calculated as the MAP response to 2 minutes of the lowest dose rate of NE infusion corrected for individual plasma volumes.

The blood samples for determination of plasma NE levels were taken in iced tubes containing 6 mg of glutathione and 9 mg of EDTA. The plasma was separated at 4°C and stored at -70°C until the NE concentration was assayed with high performance liquid chromatography with electrochemical detection. The concentration of the urinary catecholamines, the subjects collected their urinary specimens in cans containing 16 ml of 5 M HCl. Urinary sodium and potassium concentrations were determined with flame photometry.

The coefficient of variation was 13% for epinephrine at a concentration of 10 nM and 9% for NE at a concentration of 199 nM. To avoid spontaneous degradation of the urine catecholamines, the subjects collected their urinary specimens in cans containing 16 ml of 5 M HCl. Urinary sodium and potassium concentrations were determined with flame photometry.

The data were analyzed using linear regression, Student's t test (two-tailed), and nonparametric approaches as appropriate. Statistical significance was accepted as p < 0.05. Results are expressed as mean ± SEM.

### Results

#### Patient Compliance

The subjects in Group I and Group II had a comparable habitual energy intake that was reduced to about 1200 ± 50 kcal/day (5.0 MJ) and 1250 ± 80 kcal/day (5.2 MJ) respectively in the diet periods (Table 2). There were no significant differences between the two diets in carbohydrate content (53 ± 1.8%, 52 ± 1.6% respectively) or polyunsaturated to saturated fat ratios (Group I, 0.24 ± 0.06; and Group II, 0.21 ± 0.05). The reported alcohol consumption did not differ between the groups in the postbasal period (480 ± 190 g for 4 weeks and 360 ± 230 g for 4 weeks respectively). The questionnaires showed highly varying intakes, which tended to decrease during the diet periods, but no significant differences between the groups (−220 ± 123 g for 4 weeks and −200 ± 80 g for 4 weeks respectively). There was only one smoker in each group. Physical activity remained unchanged in the two groups. Body mass decreased by an average of 9.1 ± 0.7 kg in Group I with a range of 5.5 to 11.7 kg (see Table 2). The body mass loss in Group II ranged from 6 to 15.9 kg with a mean reduction of 9.3 ± 1.1 kg, which did not significantly differ from that of Group I.

The urinary sodium excretions were comparable between the groups and did not change significantly in Group I but decreased significantly by 95 ± 22 mmol/24 hours in Group II (p < 0.001). There were no significant changes in urinary potassium excretion in the two groups.

### Table 2. Body Mass, Energy Intake, Urinary Excretion of Sodium and Potassium (mean of four 24-hour collections in each period), Intra-arterial Blood Pressure, and Heart Rate in Obese Hypertensive Men on Reduced-Energy Diets With and Without Sodium Restriction in Comparison with Baseline Periods

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (n = 10)</th>
<th>Group II (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>ERSN</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>97.7 ± 3.3</td>
<td>88.6 ± 3.1*</td>
</tr>
<tr>
<td>Energy intake (MJ/day)</td>
<td>9.7 ± 0.6</td>
<td>5.0 ± 0.2*</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/24 hr)</td>
<td>197 ± 13</td>
<td>212 ± 18*</td>
</tr>
<tr>
<td>Potassium (mmol/24 hr)</td>
<td>71 ± 5</td>
<td>69 ± 4</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>90.0 ± 2.5</td>
<td>83.9 ± 2.0</td>
</tr>
<tr>
<td>Systolic</td>
<td>152.1 ± 4.8</td>
<td>144.6 ± 5.1</td>
</tr>
<tr>
<td>Mean arterial</td>
<td>114.4 ± 3.3</td>
<td>110.8 ± 3.5</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>61.4 ± 1.8</td>
<td>57.4 ± 1.81</td>
</tr>
</tbody>
</table>

Values are means ± SEM. ERSN = energy-restricted, salt-unrestricted diet; ERSR = energy-restricted, salt-restricted diet.

*p < 0.001, †p < 0.05, ‡p < 0.01, compared with previous value.
Blood Pressure and Heart Rate

In Group I the 95% confidence interval for mean change in MAP was \(-6.2\) to \(+1\) mm Hg, while the corresponding interval in Group II was \(-18.9\) to \(-4.3\) mm Hg (see Table 2). Systolic and diastolic blood pressures fell significantly only in Group II during dieting \((p < 0.01\) respectively). In addition, diastolic blood pressure was significantly lower in Group II than in Group I \((p < 0.05\). The change in heart rate, also expressed as 95% confidence intervals, was \(-7.6\) to \(-0.4\) beats/minute in Group I and \(-10.4\) to \(-4\) beats/minute in Group II; the means were not significantly different (see Table 2).

The change in MAP that occurred in Group II after dieting was not significantly correlated to reductions of body mass \((r = 0.66\), urinary sodium output \((r = 0.69\), or NE levels in arterial plasma \((r = 0.46\) or urine.

Catecholamine Levels and Plasma Renin Activity

In all periods plasma NE levels were higher in venous than in arterial plasma \((p < 0.01\); Table 3). The arterial plasma NE concentration diminished significantly in Group II \((p < 0.01\) compared with that in the basal period, while there was no corresponding change during the diet period in Group I. Urinary excretion of NE was significantly reduced only in Group I \((p < 0.05\). Urinary output of epinephrine showed no significant changes in any of the groups. The PRA significantly decreased when energy but not sodium intake was reduced in Group I, in contrast to Group II where no significant change of PRA was found \((p < 0.05\); see Table 3).

Norepinephrine Infusions

In the baseline period there was no significant difference between groups in their response to NE infusion. In Group I, however, there was an elevated blood pressure response to NE infusion in comparison with baseline values. Thus, MAP showed a significantly higher increase during the lower \((p < 0.05\) as well as the higher \((p < 0.02\) NE infusion rate (Figure 1).

The relationship between MAP and the lowest NE infusion rate corrected for plasma volume is shown in Figure 2. As the slopes of the individual equations were different \((p = 0.01\) in Group I, MAP was greater for the same NE dose rate during energy restriction than it was on a normal diet. In Group II, on the other hand, there were no statistically significant differences in NE-reactivity during dieting in comparison with the baseline studies (see Figures 1, 2).

In both groups heart rate tended to fall during NE infusion. During dieting this tendency diminished. In Group II the average heart rate even showed a slight but not significant increase at the higher dose rate.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I ((n = 10))</th>
<th>Group II ((n = 8))</th>
<th>Group I ((n = 10))</th>
<th>Group II ((n = 8))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>ERSN</td>
<td>Baseline</td>
<td>ERSR</td>
</tr>
<tr>
<td>Plasma norepinephrine (nM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial</td>
<td>1.36 ± 0.18</td>
<td>1.30 ± 0.12</td>
<td>1.48 ± 0.12</td>
<td>0.95 ± 0.06*</td>
</tr>
<tr>
<td>Venous</td>
<td>1.60 ± 0.12</td>
<td>1.66 ± 0.18</td>
<td>1.84 ± 0.18</td>
<td>1.54 ± 0.36</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine (nmol/24 hr)</td>
<td>362 ± 39</td>
<td>292 ± 27†</td>
<td>323 ± 32</td>
<td>296 ± 37</td>
</tr>
<tr>
<td>Epinephrine (nmol/24 hr)</td>
<td>49.3 ± 4.0</td>
<td>51.7 ± 5.2</td>
<td>35.2 ± 4.5</td>
<td>38.6 ± 6.4</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>0.73 ± 0.05</td>
<td>0.44 ± 0.08†</td>
<td>0.96 ± 0.18</td>
<td>0.61 ± 0.14</td>
</tr>
</tbody>
</table>

Values are means ± SEM.
ERSN = energy-restricted, salt-unrestricted diet; ERSR = energy-restricted, salt-restricted diet; PRA = plasma renin activity.
*\(p < 0.01\), †\(p < 0.05\), compared with baseline value.
FIGURE 2. The effect of NE infusion for 2 minutes on MAP in obese hypertensive men during energy-reduced diet regimens with either unchanged (Group I; upper panel) or reduced sodium intake (Group II; lower panel) in comparison with baseline periods. The dose rate of NE was the slowest given to each patient, corrected for the plasma volume of each individual as determined in the baseline (control) and diet periods. Thin lines are individual values; heavy lines represent the mean regression lines. Values are means ± SEM.

There were no correlations between body mass, urinary excretion of sodium, plasma NE levels, PRA, and reactivity to NE infusion expressed as increase in MAP to infusion of NE.

Discussion

The validity of the results in the present study is dependent on the subjects' adherence to the regimen, particularly as the effects of two diets were compared in an ambulatory setting. We believe that the compliance was sufficient, and that opinion is based on repeated measurements of body mass and salt content in at least eight 24-hour collections of urine from each patient. Furthermore, dietary records and interviews not only showed a comparable reduction of energy intake but also indicated similarities concerning the content of diet constituents that may affect the blood pressure level. For example, polyunsaturated fat, which has been shown to reduce blood pressure possibly because of its effects on prostaglandins, was similarly reduced in both groups. Also, carbohydrates, which may offset the fall in blood pressure and circulating NE induced by low energy diets, were equally lowered in both diets. Alcohol consumption, known to cause an elevation of blood pressure and sympathetic nervous activity, was comparable in the groups according to the questionnaires. Neither were there any indications of changes in smoking habits or physical activity, which may affect blood pressure and plasma NE levels.

In confirmation of earlier reports we found that reduction of energy and sodium intake was associated with a hypotensive response. On the other hand, when sodium intake was not restricted, the same degree of weight loss caused a much smaller, or no, reduction of blood pressure, which supports the findings of Dahl et al. Before our results are discussed further, however, some basic aspects of blood pressure control must be considered.

The prevailing concept of the sympathetic vascular control used to be that of generalized, continuously present, neural impulse traffic. As a fraction of the neuronally released NE spills over into the plasma, and subsequently into the urine, the venous plasma and urinary concentrations of NE have been thought to serve as indices of neural sympathetic activity. Because it has been suggested that the sympathetic discharge is intermittent by nature as well as differentiated in terms of different vascular beds, the organs and regions thought to be central to hypertension pathogenesis (kidney, heart, and splanchnic region) seem to be responsible for no more than 35% of all NE released to plasma. The muscle sympathetic activity, on the other hand, seems to be the major determinant of peripheral venous NE levels, which have little or no relevance for blood pressure control at rest or during mental stress. The renal sympathetic discharge probably is reflected by the urinary excretion of NE. Whether metanephrine is a better index of overall sympathetic activity is not known. The point to be made is that, while measurements of plasma and urinary levels of NE remain the only practical methods to assess sympathetic activity, the data have to be interpreted with caution and in light of the experimental situation.

In the present study we found that moderate energy restriction without concomitant sodium restriction was associated with a decreased urinary excretion of NE, a decrease in PRA, and a reduction of heart rate, which is considered a good indicator of sympathetic discharge to the heart. When sodium as well as energy...
intake was restricted, there was a more pronounced fall in heart rate and the arterial plasma NE concentration diminished.

These results are in general agreement with results from earlier studies in humans and animals that demonstrated that semistarvation, irrespective of sodium intake, caused a reduction in plasma concentration of NE and urinary excretion of NE and its metabolites, as well as in cardiac NE turnover. Our results suggest that energy restriction alone decreases renal sympathetic nervous activity above all, while the combination of energy and sodium restriction mainly affects the cardiopulmonary NE outflow. Sodium restriction per se has a stimulatory effect on the renal sympathetic nervous system, which probably explains why the combined diet did not reduce the urinary NE excretion.

The observation that venous plasma NE levels were unaffected by both diets is fully understandable when it is considered that the samples were obtained in the superior caval vein, which drains the upper half of the body. The plasma concentration of NE from this sampling point is mainly determined by muscular outflow of NE, which is of no relevance for sympathetic activity to hemodynamic target organs. The arterial blood sample, on the other hand, also contains plasma from renal and coronary (through sinus coronarius) vascular beds. The lungs extract NE and are primary contributors to the total plasma level of NE. For practical purposes, the arterial plasma NE concentration has been found to provide the same information as concentrations obtained in the pulmonary artery.

The possibility that the adrenal glands contributed to the observed changes in NE levels can be refuted by the fact that the normal adrenal contribution to circulating NE is likely to be less than 2%. Furthermore, the observation that urinary epinephrine excretion remained unchanged during dieting in both groups indicates that the adrenal glands were unaffected during dieting.

The effect of the sympathetic discharge on the blood vessel ultimately is determined by the reactivity of the vascular wall to NE. We tried to assess that reactivity by measuring the blood pressor response to an infusion of NE. We could find no previous reports on the effect of different energy intake levels on pressor response to NE; however, a low sodium diet is well known to reduce the pressor response to infused NE. The arterial pressor response to NE is known to decrease the blood pressure response to NE as well as to down-regulate α-adrenergic receptors in platelets. A diminished sympathetic neural traffic is known to up-regulate α-adrenergic receptors.

Against this background, our results provide evidence that moderate energy restriction alone lowers sympathetic neural outflow with a concomitant increase in reactivity to NE, which probably is caused by an up-regulation of α-adrenergic receptors. The net result is a minor, or no, effect on the arterial pressure. In addition, blood pressure decreases when moderate energy restriction is combined with a lowered sodium intake, which prevents the up-regulation of reactivity to NE and thus permits the lowered sympathetic outflow to reduce blood pressure.

Acknowledgments

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References


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