Role of Sympathetic Activity in Blood Pressure Reduction With Low Calorie Regimen

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To investigate the effects of a low calorie regimen on sympathetic function and its relation to blood pressure response, 22 untreated obese essential hypertensive patients (50±2 years, body mass index 29±1 kg/m²) were hospitalized and a diet was prescribed of 2,000 kcal/day for 5 days (control period) followed by 800 kcal/day for 21 days without changing salt intake (8–10 g/day). The dose of intravenous phenylephrine infusion needed to elevate systolic blood pressure 20 mm Hg (CD20) and the 24-hour urinary excretion of norepinephrine (UNE) were measured. During the low caloric period, blood pressure normalized in 14 patients (responder group, 124±3/79±4 mm Hg) and eight remained hypertensive (poor responder group, 158±6/103±3 mm Hg). At the control period, blood pressure and body mass index were similar, but the responder group had higher UNE (134±15 µg/day) and CD20 (127±11 µg) than the poor responder group (89±6 µg/day and 79±13 µg, respectively). During the low caloric period, both UNE (87±15 µg/day) and CD20 (74±10 µg) decreased in the responder group; no change was seen in the poor responder group. Changes in UNE and systolic blood pressure were correlated (r=0.6, p<0.05). In conclusion, suppression of sympathetic activity plays a role in blood pressure reduction during moderate caloric restriction. (Hypertension 1991;17:965–968)

Incidence of hypertension is two to three times more frequent among obese subjects than in nonobese individuals,1 and weight reduction is an effective nonpharmacological antihypertensive measure; however, the precise mechanism of blood pressure change associated with weight reduction is yet to be determined.

Roles of the sympathetic nervous system in the pathogenesis of hypertension-associated obesity have been implied,3–5 and Tuck et al6 demonstrated that urinary norepinephrine excretion decreased with weight reduction during a protein-sparing modified fasting diet. However, it is not clear whether the enhanced sympathetic activity observed in obese subjects contributes to their hypertension, because the sympathetic activity is influenced by changes in energy, sodium intake, or both.7,8 Also, observed differences in sympathetic activity in obese subjects could be merely a reflection of their altered food intake profile and may not be related to hypertension. Moreover, it is uncertain that the decrease in sympathetic activity during a low caloric regimen contributes to blood pressure change, because the caloric restriction or weight reduction itself may be responsible for the change in sympathetic activity. Longitudinal investigations concerning the relation of changes in sympathetic activity and in blood pressure may help to solve the issue.

This study was conducted to elucidate the relation between alteration in sympathetic activity and change in blood pressure during a low caloric diet in obese hypertensive patients.

Methods

Twenty-two untreated mild-to-moderate essential hypertensive patients (12 men and 10 women) whose weight was at least 20% in excess of the ideal body weight were hospitalized in Surugadai Nihon University Hospital. Their mean age was 50±2 years, and their mean body mass index was 29±1 kg/m². None of them had an obvious hypertensive complication, and their blood chemistry data, including blood urea nitrogen, creatinine, and fasting glucose, were within normal limits. The study protocol was explained, and agreement to participate in the study was obtained from every patient before admission.

For the first 5 days after admission, a regular diet of approximately 2,000 kcal/day (70 g protein, 300 g carbohydrate, and 60 g fat) was given, followed by a...
A 3-week period of a low calorie diet of 800 kcal/day (60 g protein, 100 g carbohydrate, and 20 g fat). Salt intake was maintained at 8-10 g/day throughout both diet periods. Blood pressure was measured every morning by auscultation using an appropriately sized cuff. Twenty-four-hour urinary excretion of norepinephrine was measured by high-performance liquid chromatography at the end of the control diet and at days 4, 7, 14, and 21 of the low calorie diet.

At the end of both periods, pressor responses to intravenous phenylephrine were assessed. After 20 minutes of rest in a supine position, the patient was infused intravenously with phenylephrine using an infusion pump (Harvard Apparatus, South Natick, Mass.). The infusion was started at a dose of 25 µg in a 2-minute period, and blood pressure was measured by auscultation at the end of each infusion period. The dose of phenylephrine was increased in a stepwise fashion until systolic pressure became 20 mm Hg higher than in the preinfusion period, and the final dose of the drug was determined as CD20.

Data are expressed as mean±SEM. The Scheffe's test and Student's t test were used for statistical analysis for comparison of values from repeated examinations in the same patients and for comparison of values from patients of different groups, respectively. A value of p<0.05 was considered significant.

**Results**

Patients were divided into two groups according to blood pressure response characteristics during the low calorie period: the responder group (n=14), whose blood pressure normalized (both systolic and diastolic pressures became less than 140 and 90 mm Hg, respectively), and the poor responder group (n=8), whose blood pressure did not normalize. During the control diet, blood pressure did not change significantly in either group, and the pressure at the end of the control period was 164±5/100±3 mm Hg in the responder group and 170±4/104±3 mm Hg in the poor responder group. In the responder group, the blood pressure markedly decreased in the first week, and their pressure at the end of the third week was 124 ±3/79 ±2 mm Hg. No significant change in blood pressure was seen in the poor responder group, and their blood pressure in the third week was 158±6/103±3 mm Hg (Figure 1).

Body mass index and sex distribution (eight males and six females in the responder group) were not different between the two groups. Both groups did not show a significant change in body weight during the control diet, and weight reductions with the low calorie diet were almost identical. In the first week, patients lost approximately 2 kg, losing 1.6 kg/week thereafter; the total weight reduction in 3 weeks was approximately 5.2 kg in both groups.

During the control diet, the responder group had significantly larger norepinephrine excretion (134±15 µg/day) than the poor responder group (89±6 µg/day). As compared with the control diet, the responder group showed a significant decrease after day 4 of the low calorie diet. There was not a significant change in the poor responder group, and norepinephrine excretion during the low calorie diet was not significantly different between the two groups (87±15 µg/day in the responder group and 86±10 µg/day in the poor responder group) (Figure 2). When patients of both groups (n=22) were combined, there was a strong correlation between the changes in norepinephrine excretion during the low calorie diet from the control diet and levels of norepinephrine excretion at the control diet. At day 4 of the low calorie diet, the correlation coefficient was 0.8 (p<0.01). The change in systolic pressure and percent change of norepinephrine excretion from the control diet in all patients were significantly correlated after day 7 of the low calorie diet (r=0.6, p<0.05).

In the control diet, CD20 of the responder group (127±11 µg) was significantly larger than that of the poor responder group (79±13 µg). Although CD20 of the responder group became significantly smaller at
the low calorie diet (74±10 µg), it did not change in the poor responder group (61±6 µg). There was not a significant difference between the two groups at the low calorie diet (Figure 3).

Discussion

Several investigators have focused on the relation between changes in blood pressure and sympathetic activity during a low calorie regimen in obese hypertensive patients. Tuck et al demonstrated a consistent decrease in urinary excretion of norepinephrine during a protein-sparing modified fast. Andersson et al observed changes in blood pressure as well as in catecholamine levels during modest caloric restriction with or without sodium restriction. Blood pressure decreased only in patients who underwent concomitant sodium restriction; however, plasma and urinary excretion of norepinephrine decreased irrespective of blood pressure change. In the study of Andersson et al, caloric restriction was modest (5 MJ/day), and the difference between their data and the present investigation may be related to the different energy intakes.

In the present study, patients were hospitalized, and calorie and sodium intake were under strict control. The observed data that the blood pressure was normalized in 63% of patients and that of Andersson et al was normalized in 63% of patients, and that the of Andersson et al (approximately 1,300 kcal/day); these differences may contribute to the different blood pressure and catecholamine responses to the regimens.

A larger CD20 at the control diet in the responder group than in the poor responder group may suggest that the peripheral vascular sensitivity to α-agonist is decreased in the responder group, because blood pressures in the two groups were similar at this period. It is difficult to assess the vascular reactivity to the agonist by pressor responsiveness to exogenous α-agonist when baseline blood pressures are different; therefore, it is not clear whether the change in CD20 associated with caloric restriction in the responder group is related to the change in peripheral vascular sensitivity to the agonist.

The fact that the responder group had a larger urinary norepinephrine and CD20 as compared with the poor responder group at the control diet may indicate enhanced sympathetic activity and down-regulated α-receptor function in the responder group. Although it is possible to assume that the organic change in vascular beds caused a secondary increase in sympathetic activity, this is unlikely because urinary norepinephrine excretion as well as blood pressure decreased only a few days after the initiation of the low calorie diet. Egan et al demonstrated enhanced vasodilator response to α-receptor antagonist in obese hypertensive subjects, and these data also suggest the abnormality is functional. Fagerberg et al demonstrated that the pressor response to intravenous norepinephrine became attenuated after weight reduction in patients receiving low calorie and low salt diets. It seems difficult to reconcile these observations with our data; however, differences in calorie intake and sodium status between the two studies might be responsible.

Insulin has been receiving attention, as it causes sodium retention and contributes to salt sensitivity in obese hypertensives. It is interesting to note that the sympathetic nervous system regulates insulin secretion, and insulin has been shown to modulate sympathetic function. But the effect of insulin on peripheral vascular tone is still controversial, because acute administration of insulin causes vasodilation and attenuates the vasopressor responses to various vasoconstrictive agents, including norepinephrine, and chronic administration of insulin did not raise blood pressure in normotensive dogs. Decreased insulin secretion during a low calorie diet may be another possible mechanism to explain the increased pressor sensitivity to phenylephrine. The pathophysiological relations of the sympathetic nervous system and insulin in hypertension associated with obesity should be elucidated by further investigations.

In conclusion, among obese hypertensive patients, blood pressure is likely to respond to moderate caloric restriction in those patients who have enhanced sympathetic activity associated with down-regulated α-receptor function. Furthermore, suppression of the sympathetic activity plays a role in blood pressure reduction.

References


**KEY WORDS** • blood pressure • sympathetic nervous system • diet • essential hypertension • obesity
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