Association of Insulin Resistance With Salt Sensitivity and Nocturnal Fall of Blood Pressure

Masaaki Suzuki, Yuko Kimura, Motoo Tsushima, Yutaka Harano

Abstract—Insulin resistance was demonstrated in hypertensive patients and in salt-sensitive subjects. It was recently reported that the salt-sensitive state was related to a reduced fall in blood pressure during the night in essential hypertension. In the present study, the relationship among insulin sensitivity, blood pressure response to salt intake, and nocturnal fall in blood pressure was examined in 20 subjects with nondiabetic and nonobese essential hypertension during a low-salt and a high-salt diet. The subjects were maintained on a low-salt diet (50 mmol/d) and a high-salt diet (255 mmol/d) for 1 week each, in random order. On the sixth day of each diet, blood pressure was measured every hour for 24 hours with an automatic device. Insulin sensitivity was measured according to the steady-state plasma glucose (SSPG) method on the seventh day of each diet. Salt-induced increase in blood pressure, which we defined as the change in 24-hour mean arterial pressure between the low and the high dietary salt intakes, was significantly correlated with SSPG (r = 0.60, P < 0.01) during the high-salt period. There was a significant negative correlation (r = −0.61, P < 0.01) between SSPG and a nocturnal fall in mean arterial pressure during the high-salt period. Salt-induced increase in blood pressure was inversely correlated with a nocturnal fall in mean arterial pressure (r = −0.52, P < 0.02) with the high-salt diet. These results suggest that insulin resistance, salt sensitivity, and failed nocturnal fall in blood pressure are associated with each other in subjects with essential hypertension. (Hypertension. 2000;35:864-868.)

Key Words: blood pressure ■ sodium, dietary ■ insulin resistance ■ hypertension, essential ■ risk factors

Insulin resistance associated with hyperinsulinemia has been found in patients with essential hypertension.1,2 Previous studies indicate that in a group of essential hypertensives, salt-sensitive subjects have severe insulin resistance compared with salt-resistant subjects.3–5 It was recently reported that the salt-sensitive state was related to reduced blood pressure (BP) fall during the night in essential hypertension.6,7 These reports suggest that insulin resistance, salt sensitivity, and failed nocturnal BP fall might coexist in some hypertensive subjects. Hypertension,8 insulin resistance,9–12 salt sensitivity,5 and failed nocturnal BP fall13,14 were considered to be risk factors of cardiovascular disease. Thus, these patients are considered part of one of the strongest risk groups for cardiovascular disease. There has been no study of the relationship among insulin sensitivity, salt sensitivity, and nocturnal BP fall in subjects with essential hypertension.

The aim of the present study was to clarify the relationship between nocturnal fall in BP and insulin resistance in hypertensive subjects. We also wanted to test the hypothesis that in patients with essential hypertension, insulin resistance, salt sensitivity, and failed nocturnal fall in BP are associated with each other.

Insulin resistance was demonstrated in hypertensive patients and in salt-sensitive subjects. It was recently reported that the salt-sensitive state was related to a reduced fall in blood pressure during the night in essential hypertension. In the present study, the relationship among insulin sensitivity, blood pressure response to salt intake, and nocturnal fall in blood pressure was examined in 20 subjects with nondiabetic and nonobese essential hypertension during a low-salt and a high-salt diet. The subjects were maintained on a low-salt diet (50 mmol/d) and a high-salt diet (255 mmol/d) for 1 week each, in random order. On the sixth day of each diet, blood pressure was measured every hour for 24 hours with an automatic device. Insulin sensitivity was measured according to the steady-state plasma glucose (SSPG) method on the seventh day of each diet. Salt-induced increase in blood pressure, which we defined as the change in 24-hour mean arterial pressure between the low and the high dietary salt intakes, was significantly correlated with SSPG (r = 0.60, P < 0.01) during the high-salt period. There was a significant negative correlation (r = −0.61, P < 0.01) between SSPG and a nocturnal fall in mean arterial pressure during the high-salt period. Salt-induced increase in blood pressure was inversely correlated with a nocturnal fall in mean arterial pressure (r = −0.52, P < 0.02) with the high-salt diet. These results suggest that insulin resistance, salt sensitivity, and failed nocturnal fall in blood pressure are associated with each other in subjects with essential hypertension. (Hypertension. 2000;35:864-868.)

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Methods

Subjects
The clinical study was performed in 20 subjects (9 men and 11 women) with essential hypertension (Table 1). All subjects were selected according to the following criteria: (1) a systolic or diastolic BP of >140 or >90 mm Hg, respectively, or both (mean of pressures for first 3 days on admission between 6 and 8 AM; Table 1), (2) a body mass index (BMI) of <28.5 (weight [in kg]/height [in m2]), (3) the absence of diabetes mellitus (exclusion according to American Diabetes Association criteria15,16), and (4) the absence of secondary hypertension and cardiovascular, cerebrovascular, renal, hepatic, or other endocrine diseases. Previous antihypertensive medications were discontinued for ≥4 weeks before hospitalization. The study was approved by the Ethics Committee of the National Cardiovascular Center, and all subjects gave informed consent.

Study Protocol
After hospitalization, the subjects were administered a regular diet containing 140 mmol/d NaCl daily for 1 to 2 weeks to allow BP stabilization. The subjects were maintained on a low-salt diet (50 mmol/d) and a high-salt diet (255 mmol/d) for 1 week each, in random order. A nurse checked the remaining food to confirm complete food intake. Compliance to the prescribed diet was assessed with measurements of 24-hour urinary Na+ excretion during the last 3 days of each diet. On the fifth day of both the low- and the high-salt period, the 75-g oral glucose tolerance test (OGTT) was carried out. On the sixth day of each period, BP was measured every hour...
hour for 24 hours with an automatic oscillometric device (model BP-203i; Nippon Colin). Mean arterial pressure (MAP) was calculated as diastolic BP plus one third of pulse BP, and the average of the 24 daily MAPs was calculated (24-hour MAP). Insulin sensitivity test was performed on the seventh day of each period.

Assessment of Salt-Induced Increase in BP and Nocturnal Fall in BP

To perform correlations between BP sensitivity to salt and other variables, we defined a salt-induced increase in MAP as the change in 24-hour MAP between the low and the high dietary salt intakes. A nocturnal decline in BP was defined as a nocturnal fall in MAP. The daytime MAP was obtained as the average of the 17 MAPs measured between 6 AM and 10 PM, and nighttime MAP was the average of the remaining 7 MAPs. The nocturnal fall in MAP was defined as the difference between daytime and nighttime MAPs.

Insulin Sensitivity Test

Glucose utilization in response to insulin was evaluated with a newly modified steady-state plasma glucose (SSPG) method16–18 with octreotide acetate (Sandostatin; Novartis) after an overnight fasting period of ≥12 hours. Sandostatin (9.8-pmol bolus followed by a constant infusion of 73.5 pmol/h) and Novolin R insulin (45-pmol/kg bolus [7.5 mU/kg] followed by a constant infusion at a rate of 4.62 pmol · kg⁻¹ · min⁻¹ [0.77 mU · kg⁻¹ · min⁻¹]; Novo Nordisk S/A) were infused intravenously for 120 minutes. Glucose in a final 12% solution containing KCl (0.5 mEq/kg) was infused at a rate of 0.033 mmol · kg⁻¹ · min⁻¹ (6 mg · kg⁻¹ · min⁻¹) through an antecubital vein via a constant infusion pump. Blood samples were drawn routinely at 0, 30, and 120 minutes (9:00, 9:30, and 11:00 AM) for the determination of glucose, insulin, and lipids. The value of glucose at 120 minutes (SSPG) was used as a marker of insulin sensitivity to glucose utilization. High SSPG levels indicate peripheral insulin resistance. SSPG provides a good estimate of glucose clearance, one that is very similar to those obtained with the glucose clamp method as shown in control subjects.19 Furthermore, Greenfield et al20 demonstrated in 30 subjects that SSPG and M values (glucose utilization) determined with the glucose clamp method are highly correlated (r = −0.93, P < 0.001). Theoretically, (infusion rate of glucose/SSPG) is the formula to calculate glucose clearance. With the glucose clamp method, the numerator is obtained as the fixed fasting blood glucose, whereas with the SSPG method, SSPG (denominator) is obtained as the fixed dose of the numerator (glucose infusion).

Results

Baseline characteristics of the hypertensive subjects are shown in Table 1. Body weight, BP, and fasting plasma glucose and lipid levels were measured on the second day between 6 and 8 AM after hospitalization.

The result for each parameter during a low- or high-salt period is shown in Table 2. Mean body weight was on average 0.4 kg higher during a high-salt than a low-salt period (P < 0.05). Nocturnal MAP fall in the low-salt period tended to be higher compared with that in the high-salt period, but the difference did not reach statistical significance. No difference was observed between high- and low-salt study periods for SSPG, steady-state plasma insulin, or AUC of glucose or insulin during OGTT. Mean 24-hour urinary sodium excretion was significantly higher in the high-salt period than in the low-salt period (P < 0.0001). Plasma epinephrine and norepinephrine levels were significantly higher during low-salt than during high-salt intake at both 0 and 120 minutes during the insulin sensitivity test (P < 0.01).
The salt-induced increase in MAP was significantly correlated with SSPG \( (r=0.60, P<0.01) \) during the high-salt period (Figure 1). SSPG during the low-salt period did not correlate with the salt-induced increase in MAP. There was a significant negative correlation \( (r=-0.61, P<0.01) \) between nocturnal MAP fall and SSPG during the high-salt period (Figure 2). SSPG had no relationship with nocturnal MAP fall during the low-salt period.

Partial correlation coefficients were calculated to evaluate the independent association of insulin sensitivity with salt-induced increase in MAP and with nocturnal fall in MAP. Significant partial correlation \( (r=0.63, P<0.01) \) was observed between SSPG during the high-salt period and salt-induced increase in MAP, eliminating the effects of age, BMI, and 24-hour MAP during the high-salt period. Partial correlation analysis was also performed between nocturnal MAP fall and SSPG during the high-salt period, and significant negative correlation was noted \( (r=-0.75, P<0.01) \), eliminating the effects of age, BMI, and 24-hour MAP during the high-salt period. No significant partial correlation was observed between SSPG during the low-salt period and salt-induced increase in MAP or nocturnal MAP fall during the low-salt period.

Regarding insulin response during OGTT, no simple or partial correlations were observed between the salt-induced increase in MAP and AUC of insulin during low- and high-salt intake periods. There were no simple and partial correlations between nocturnal MAP fall and AUC of insulin during the low- and high-salt periods. No simple and partial correlations were noted between AUC of glucose and salt-induced increase in MAP or nocturnal MAP fall during the low- and high-salt periods.

**Discussion**

The results of the present study demonstrate that insulin resistance is associated with both diminished nocturnal BP fall and salt-induced increase in MAP in nontreated hypertensive subjects.

Eleven of 20 subjects were classified as salt sensitive on the basis of a salt-induced increase in MAP of \( \geq 3 \) mm Hg. An additional 9 subjects were classified as salt resistant. The SSPG levels \( (13.1 \pm 1.4 \text{ mmol/L}) \) of salt-sensitive subjects were significantly \( (P<0.05) \) higher than the SSPG levels \( (9.5 \pm 1.5 \text{ mmol/L}) \) of salt-resistant subjects. Therefore, salt sensitivity was closely associated with insulin resistance.

The SSPG levels \( (12.1 \pm 0.9 \text{ mmol/L}) \) of the subjects whose nocturnal MAP fall was \( <10\% \) \( (n=17) \) tended to be higher \( (P=0.06) \) than the SSPG levels \( (7.9 \pm 0.2 \text{ mmol/L}) \) of the subjects whose nocturnal MAP fall was \( \geq 10\% \) \( (n=3) \).

In the present study, salt-induced increase in MAP was significantly and inversely correlated with nocturnal MAP fall \( (r=-0.52, P<0.02) \) during high salt intake (simple correlation). Significant partial correlation was also observed between salt-induced increase in MAP and nocturnal MAP fall \( (r=-0.59, P<0.01) \) in the high-salt period after correction for the effects of age, BMI, and 24-hour MAP in the high-salt period. There was no significant correlation between salt-induced increase in MAP and nocturnal MAP fall during the low-salt period. Therefore, insulin resistance, salt sensitivity (salt-induced increase in BP), and failed nocturnal decline in BP were associated with each other in hypertensive subjects.

The association between insulin resistance and salt sensitivity was demonstrated in hypertensive subjects in several studies. This association was also found in young normotensive subjects. However, there was only 1 report that indicated a relationship between insulin sensitivity and nocturnal BP fall. Chen et al reported that insulin resistance and \( \beta \)-cell dysfunction were both noted in nondippers. They measured plasma glucose and insulin levels during OGTT; plasma insulin levels were higher in dipper hypertensive patients than in nondippers. These results did not prove there is insulin resistance in the nondipper group; the study just showed that the ratio of fasting insulin to glucose was higher in nondippers. Insulin resistance should be evaluated with a more precise method. There has been no study that demonstrated the relationship among insulin sensitivity, salt sensitivity, and nocturnal BP fall in subjects with essential hypertension.

The exact mechanism for the association between insulin resistance and salt sensitivity is unclear. It is possible that increased intracellular \( \text{Ca}^{2+} \) plays an important role in essential hypertension. Increased intracellular \( \text{Ca}^{2+} \) during sodium loading was described in salt-sensitive subjects with hyper-
It was reported that the reduced insulin action (insulin resistance) was associated with high intracellular Ca\(^{2+}\) due to the decreased Ca\(^{2+}\)-ATPase and Na\(^+\),K\(^+\)-ATPase, which are insulin sensitive. Intracellular Ca\(^{2+}\) metabolism might contribute to a disturbed circadian rhythm of BP.

Plasma epinephrine and norepinephrine levels at 0 and 120 minutes during insulin sensitivity test did not correlate with SSPG or MAP for low- and high-salt diets. Changes in plasma epinephrine and norepinephrine levels at 0 and 120 minutes in response to salt loading did not correlate with salt-induced changes in SSPG or MAP. Although plasma catecholamines were higher during the low-salt than during the high-salt intake, no difference in SSPG levels was observed between low- and high-salt periods. Thus, altered activity in sympathetic nervous system does not seem to directly relate to insulin resistance or BP. However, insulin sensitivity may be influenced by an increased activity of sympathetic nervous system; Laakso et al. reported that epinephrine affects insulin sensitivity.

In the present study, no relation was observed between insulin resistance and salt sensitivity or nocturnal MAP fall during the low-salt period; during the low-salt period, increased activity of sympathetic nervous system, as demonstrated with the higher level of plasma catecholamines, affected insulin sensitivity, and the relations shown in the high-salt period disappeared.

Gaboury et al. demonstrated that dietary salt restriction had no effect on insulin sensitivity as measured with the euglycemic glucose clamp method in hypertensive subjects. Using the same method, Gomi et al. showed that strict dietary salt reduction worsened insulin sensitivity by increasing sympathetic nervous activity in hypertension. In the present study, SSPG and AUC of insulin tended to be higher during the low-salt period than during the high-salt period (Table 2). The BMIs of the subjects in the present study and the study of Gaboury et al. were higher than those in the study of Gomi et al. Insulin resistance based on the higher BMI might weaken the effect of increasing sympathetic nervous activity on insulin sensitivity.

There were no significant simple and partial correlations between salt sensitivity and AUC of insulin during the low- and high-salt periods. Salt sensitivity tended to correlate with AUC of insulin for a high-salt diet (partial correlation coefficient=0.35, P>0.1; eliminating the effects of age, BMI, and 24-hour MAP). These results suggest that insulin resistance rather than hyperinsulinemia is more closely associated with salt sensitivity. We have reported a similar tendency between insulin resistance and hypertension, indicating that insulin resistance rather than hyperinsulinemia was more closely associated with high BP.

In the present study, our data demonstrated that insulin resistance, salt sensitivity (salt-induced increase in BP), and decreased nocturnal BP fell were associated with each other. Insulin resistance, \textsuperscript{9}–\textsuperscript{12} salt sensitivity, \textsuperscript{5} and reduced nocturnal BP decline\textsuperscript{13,14} were all described as risk factors for cardiovascular diseases. Therefore, increased salt sensitivity and nondipper circadian BP pattern were considered additional factors of the multiple risk factor syndrome based on insulin resistance, such as syndrome X. It is important to improve insulin sensitivity in hypertensive patients who exhibit salt sensitivity and reduced nocturnal BP decline to prevent cardiovascular diseases. In addition, the restriction of dietary salt intake might shift the circadian rhythm of BP from a nondipper to a dipper pattern, resulting in amelioration of the risks.

References


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