Sympathetic Nerve Hyperactivity Precedes Hyperinsulinemia and Blood Pressure Elevation in a Young, Nonobese Japanese Population

Kazuko Masuo, Hiroshi Mikami, Toshio Ogihara, and Michael L. Tuck

To evaluate the relationships between sympathetic nerve activity, insulin sensitivity, and blood pressure (BP) elevation, we examined BP, fasting blood glucose, plasma insulin, and norepinephrine (NE) levels in age- and body mass index (BMI)–matched 662 normotensive (NT) and 188 borderline hypertensive (BHT) subjects every year for 10 years. All measurements were taken in the supine position after an overnight fast. BP elevation (BP-E) during 10 years was defined as 10% or more elevation of mean BP when compared with BP at entry. BP-E was noted in 186 (28%) of NT and in 52 (28%) of BHT. Fasting insulin level at entry in BHT with BP-E was significantly greater than that in subjects without BP-E ($P < .01$), although fasting insulin level in NT with BP-E at entry was similar to that in NT without BP-E. Supine plasma NE level at entry period and year 10 in NT with BP-E was significantly greater than that in subjects without BP-E ($P < .05, P < .01$, respectively). Supine NE in BHT regardless of BP-E was significantly greater than that in NT at both entry and year 10. These results demonstrate that sympathetic nerve hyperactivity appears to precede hyperinsulinemia and resultant BP elevation in a young, nonobese Japanese population. © 1997 American Journal of Hypertension, Ltd. Am J Hypertens Am J Hypertens 1997;10:77–83

KEY WORDS: Sympathetic nerve activity, insulin sensitivity, blood pressure elevation, normotension, borderline hypertension, Japanese.

dyslipidemia.1–8 It is also well documented that sympathetic nerve activity is related with the etiology of hypertension9–13 and that the degree of sympathetic nerve activity is different in various stages of hypertension: increased sympathetic nerve activity being particularly prominent in the earlier hyperkinetic hypertensive stage.14 Recently, Ward et al15 reported that, in a multiple logistic regression model of 752 nondiabetic male participants of the Normative Study, aged 43 to 90 years, insulin level and sympathetic nervous system activity, as determined by measuring urinary norepinephrine excretion, are closely related with hypertension. However, they could not determine the causal relationship between increases in insulin level and increases in sympathetic nervous system activity because of its cross-sectional study de-
sign. Thus, investigations into the relationship between sympathetic nervous system activity and the insulin-resistant state or hyperinsulinemia in hypertensive patients tend to leave the “chicken-and-egg” question open, and, despite tremendous efforts, results have not yet been consistent.\(^{16-20}\) Furthermore, family history of hypertension and racial differences are also known as confounding factors for insulin-resistant states associated with hypertension.\(^{6,21-26}\)

The goal of the present longitudinal study was to clarify the problem regarding the relationship between blood pressure (BP) elevation, sympathetic nervous system activity, and insulin sensitivity; in other words, to elucidate which comes first: sympathetic nervous system hyperactivity or hyperinsulinemia. We examined the levels of NE and insulin between age- and body mass index (BMI)-matched normotensive subjects (NT) with and without BP elevation during the 10 years and, similarly, between borderline hypertensive patients (BHT) with and without BP elevations.

**SUBJECTS AND METHODS**

**Subjects** A cohort consisting of 1,568 young Japanese men working in a factory in Osaka, Japan, was studied during a biannual legal health check-up for 10 years. According to BP status, the cohort was divided into three groups: namely, 1,064 normotensive (NT), 283 borderline hypertensive (BHT), and 221 established hypertensive (EHT) subjects. The following subjects were excluded from the study: 86 subjects who had obesity (BMI \(\geq 26.0 \text{ kg/m}^2\)), 43 subjects with diabetes mellitus (HbA\(_1c\) \(> 6.0\)%), 101 subjects with a positive family history of diabetes (at least one parent had diabetes), 58 subjects with severe heart disease (CTR > 52%) or arrhythmia. Also excluded were 379 subjects on medications other than antihypertensive drugs: lipid lowering agents, 264; uric acid lowering agents, 93; medications for liver dysfunction, 72; digitalis or antiarrhythmic agents, 58. Consequently, strictly age- and BMI-matched subjects (662 NT, 188 BHT, and 136 EHT) were enrolled in this study. BHT were untreated, and EHT were untreated or stopped their medications for HT at least 2 weeks prior to the measurements each year. Those who had significant change in BMI 1.0 kg/m\(^2\) or greater (2 subjects), and an additional 31 participants were excluded, because of loss of information on plasma insulin or norepinephrine, BP, body habitus, or occupational change.

Normotension was defined as supine mean reading of less than 140/90 mm Hg. Borderline hypertension and established hypertension were defined as mean reading of 140 to 159/90 to 94 mm Hg and 160/95 mm Hg or more at entry period, respectively. The hypertensive patients were in stage I or II of the World Health Organization classification. The average BP readings of NT, BHT, and EHT at entry were 122 \(\pm 8/73 \pm 4\) mm Hg, 148 \(\pm 5/97 \pm 4\) mm Hg, and 168 \(\pm 4/101 \pm 3\) mm Hg, respectively. The mean age and BMI were strictly matched in the three groups at entry (age: 39.0 \(\pm 2.1\), 39.4 \(\pm 1.9\), 39.4 \(\pm 2.0\) years, F = 0.7132, P = .4906; BMI: 22.4 \(\pm 1.2\), 22.6 \(\pm 1.1\), 22.8 \(\pm 1.3\) kg/m\(^2\), F = 0.5000, P = .6069, respectively), and at year 10 (age: 49.0 \(\pm 2.1\), 49.4 \(\pm 1.9\), 49.4 \(\pm 2.0\) years, F = 0.6041, P = .5678; BMI: 22.3 \(\pm 1.4\), 22.6 \(\pm 1.0\), 22.7 \(\pm 1.5\) kg/m\(^2\), F = 0.7912, P = .4679, respectively).

A positive family history of hypertension or diabetes mellitus was defined as at least one parent having hypertension or diabetes as documented by previous medical records or by a direct measurement of BP or HbA\(_1c\) in the parents where possible. Studies were approved by the Ethics Committee of Osaka University Medical School, and informed consent was obtained from each subject.

**Measurements** After an overnight fast of more than 12 h, BMI, BP, pulse rate, and venous blood sampling for measurements of blood glucose levels, plasma insulin, and NE levels, triglyceride (TG), total cholesterol (Tch), HDL-ch, VLDL-ch, LDL-ch, uric acid (UA), and hematocrit (Ht) were obtained after a rest of 30 min in the supine position in a quiet room. BP was measured more than three times in each visit and was averaged. Those who had a wide variability in BP were asked to repeat measurements on more than three separate visits, to exclude chance variation.

Blood pressures and pulse rates were measured with an automated sphygmomanometer (TM-2711 or TM-2713, A & D, Tokyo, Japan) which was standardized against a mercury sphygmomanometer. Plasma NE was measured after separation by high performance liquid chromatography by the fluorometric method\(^{27}\) (intraassay CV = 2.1%; interassay CV = 3.6%; sensitivity = 0.010 to 20 ng/mL), and plasma immunoreactive insulin was measured by a standard radioimmunoassay method (insulin RIABEAD II, Dinabott, Tokyo, Japan); intraassay CV = 1.9%; interassay CV = 2.2%; sensitivity = 0.75 to 300 \(\mu\text{U/mL}\)). Blood glucose and lipid fractions were measured by autoanalyzer (Hitachi 7050, Tokyo, Japan).

**Statistical Analyses** Values are shown as mean \(\pm SD\). Changes in variables within each group and differences among groups were examined by two-way analysis of variance (ANOVA). And when significant, Dunnett’s test was used to determine whether the differences of the mean at year 10 from the values at entry period, and those among the groups were significant. The statistical analyses regarding the prevalence of BP elevations or a positive family history of hypertension were performed using the \(\chi^2\)-test. Values of P < .05 were considered significant.

**RESULTS** Table 1 shows the prevalence of BP elevation during the period of 10 years by a definition of percentage...
change in mean BP. BP elevation was defined as 10% or more elevation in mean BP compared with BP levels at entry period; no change in BP as between +10% and −10%; and BP reduction as −10% or more reduction in mean BP. The prevalence of BP elevation during the 10 years was noted in 28% of NT, 28% of BHT, and 3% of EHT. The prevalence of BP elevation in the original cohort during 10 years was 25%; no changes in BP was noted in 63%, and BP reduction was noted in 13%. With this definition, there was no subject who showed both significant elevation and reduction in BP in different years during the period.

Figure 1 shows the comparisons, between at entry and at year 10, of BP levels (upper panel), age (middle panel) and BMI (lower panel) in NT and BHT by the definition of significant BP elevation as 10% or greater during the 10 years of the study. At year 10, by the definition, BP levels in NT and BHT with BP elevation were significantly greater than those in subjects without BP elevation (NT: \( P < .001 \), BHT: \( P < .001 \)), and BP levels in subjects (NT and BHT) with BP elevation were significantly greater than those at entry period (NT: \( P < .01 \), BHT: \( P < .01 \)). At entry period, systolic (\( P < .01 \)) and diastolic BPs (\( P < .01 \))

### TABLE 1. PREVALENCE OF SUBJECTS WITH BLOOD PRESSURE ELEVATION

<table>
<thead>
<tr>
<th>BP at Entry Period</th>
<th>Maximum Changes in BP Over 10 Years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT</td>
<td>≤−10%</td>
<td>−10% −10%</td>
</tr>
<tr>
<td></td>
<td>68 (10%)</td>
<td>408 (62%)</td>
</tr>
<tr>
<td>BHT</td>
<td>22 (12%)</td>
<td>114 (61%)</td>
</tr>
<tr>
<td>EHT</td>
<td>36 (27%)</td>
<td>96 (71%)</td>
</tr>
<tr>
<td>Total</td>
<td>126 (13%)*</td>
<td>618 (63%)</td>
</tr>
</tbody>
</table>

* \( P < .01 \) v the prevalence of the subjects with no changes in BP.

BP, blood pressure; NT, normotensive; BHT, borderline hypertensive; EHT, established hypertensive.
in NT with BP elevation were significantly greater than those in NT without BP elevation, but BPs in BHT with BP elevation were similar to those in BHT without BP elevation (NS). Age and BMI in 4 groups according to BP status at entry and BP elevations during the 10 years were similar to each other. BMI in NT at year 10 did not differ from those at entry, and so were the BMI in BHT.

Figure 2 shows fasting blood glucose levels (upper panel), fasting plasma insulin (middle panel) and NE levels (bottom panel) in NT (left column) and BHT (right column) subdivided by the presence or absence of significant BP elevation. In this way, age and BMI were strictly matched at entry, in order to compare the unbiased fasting insulin and supine NE levels from the effects of age and BMI. Plasma NE levels at entry and at year 10 in NT and BHT with BP elevation were significantly greater than those in subjects without BP elevation (entry period, NT: \( P < .05 \), BHT: \( P < .05 \); year 10, NT: \( P < .01 \), BHT: \( P < .05 \)). Furthermore, fasting INS levels in BHT with BP elevation were significantly greater than those in subjects without BP elevation at both entry period \( (P < .01) \) and year 10 \( (P < .05) \), while fasting INS at entry in NT with BP elevation was similar to that in NT without BP elevation and that in NT with BP elevation at year 10 were significantly greater than that in NT without BP elevation \( (P < .05) \).

The absolute increment (left panel) in plasma insulin and NE during the 10 years and the percentile changes (right panel) in plasma insulin and NE are shown in Figure 3. The absolute increment in plasma NE in NT with BP elevation was significantly greater than that in NT without BP elevation \( (P < .01) \). Furthermore, the absolute increment in NE in NT with BP elevation was similar to those in BHT regardless of BP elevation, as were the percentile increment in plasma NE in NT with BP elevation. On the other hand, the absolute increment in plasma insulin level in NT with BP elevation and in BHT with BP elevation was significantly greater than those in subjects without BP elevation \( (P < .01, P < .05 \text{, respectively}) \) and the absolute increment in plasma insulin in BHT without BP elevation was also greater than that in NT without BP elevation \( (P < .05) \). However, the percent increment in plasma insulin in NT with BP elevation was significantly greater than that in NT without BP elevation, although the percent increments between BHT with and without BP elevation were similar to each other and similar to the values in NT without BP elevation, and were significantly less than that in NT with BP elevation.

**DISCUSSION**

The main finding from the present study is that supine plasma NE at entry in NT with BP elevation during a period of 10 years was significantly greater than that in NT without BP elevation, although fasting plasma insulin at entry in NT with BP elevation was similar to that in NT without BP elevation. In addition, in BHT with BP elevation, both plasma NE and fasting insulin were significantly greater than those in BHT without BP elevation; and in BHT regardless of BP elevation, fasting blood glucose levels, plasma NE, and insulin levels were greater than those in NT, both at entry and at year 10. In other words, prior to significant BP elevation, sympathetic nerve hyperactivity appears to precede hyperinsulinemia or impaired glucose metabolism. This study also demonstrated that the absolute and percent increments in plasma NE in NT with BP elevation were significantly greater than
those in NT without BP elevation, but they were similar to those in BHT regardless of BP elevation. On the other hand, the absolute and percent increments in plasma insulin in subjects (both NT and BHT) with BP elevation were greater than those in subjects without BP elevation. These results also indicate that the relationship between sympathetic nerve activity and insulin sensitivity might be different between NT and BHT, and between the subjects with and without BP elevation during the 10 years.

In addition to many clinical studies and epidemiological studies demonstrating a close relationship between insulin resistance and BP elevation, Denker et al. also reported a significant positive association between fasting insulin and BP levels. There is also general acceptance that both increased insulin and increased sympathetic nervous system activity are involved in hypertension, but which comes first has not yet been clearly demonstrated. It has been well documented that the degree of sympathetic nervous system activity might vary depending on the stage of hypertension: for example, increased sympathetic activity is particularly prominent in the earlier hyperkinetic stage. Julius et al. reported that, as hypertension advances with underlying hemodynamic change, sympathetic overactivity becomes less evident; and they believed that this return of plasma NE towards normal values reflects the evolving increase of vascular reactivity in hypertension. In addition, it has been reported that plasma catecholamine levels and NE spillover rates were increased only in young hypertensive patients. Julius et al. also reported that the neurogenic, hyperkinetic state could be a secondary consequence of hypertension, because hypertension in its early phase is frequently associated with a considerable decrease in the intravascular blood volume, which could trigger a secondary sympathetic adjustment. However, in the present study, hematocrit levels considered as an index of intravascular blood volume, were similar between subjects with and without BP elevation in both NT and BHT (data not shown).

In the present study, plasma NE was greater in young BHT than in young NT, and it was significantly greater in subjects with BP elevation compared to that in subjects without BP elevation. This result is in a good accor-
dance with previous studies.\textsuperscript{9–11,14,32–34} Therefore, it appears that signs of enhanced sympathetic drive are already present before the BP elevation. It is also known that the presence of obesity causes sympathetic nervous system hyperactivity\textsuperscript{13} and hyperinsulinemia.\textsuperscript{3,4,15} In NT with BP elevation, systolic and diastolic BP were significantly greater compared to those in subjects without BP elevation. We reported also that plasma NE levels correlated significantly with BP levels only in NT, but not in hypertensives.\textsuperscript{11} The differences in BP levels at entry between NT with and without BP elevation would lead us to another “chicken-and-egg” question: which of sympathetic nerve hyperactivity and BP elevation comes first in the young and normotensive subjects? However, the data from the present study indicated at least that the sympathetic nerve hyperactivity is related to BP elevation even in NT. Furthermore, in the present study, the absolute, as well as percent increment, in plasma NE in NT with BP elevation was significantly greater than those in NT without it. Moreover, absolute and percent increments in plasma insulin were significantly greater in subjects with BP elevation than those in subjects without BP elevation, regardless of BP status. Therefore, excessive sympathetic tone can induce insulin resistance and BP elevation independent of obesity and initial BP status. Thus, hypersympathetic state in the early stage of hypertension appears to precede hyperinsulinemia and obvious BP elevation.

More recently, Ward et al\textsuperscript{15} reported that in 752 nondiabetic, middle-aged and elderly men of the Normative Aging Study, fasting and postcarbohydrate plasma insulin levels and urinary NE excretion were independent predictors of hypertension. However, their study was cross-sectional in nature and hence could not determine the temporal order of events, particularly whether an increase in insulin levels precedes or comes after increases in sympathetic nervous system activity. They also stated that longitudinal data concerning the temporal order of events would be valuable, particularly for a young cohort of subjects.

In summary, the present study presents data to show that in initially normotensive subjects who had a significant BP elevation in 10 years, sympathetic nerve hyperactivity precedes the emergence of hyperinsulinemia, whereas in the early stages of hypertension (BHT), both sympathetic nerve hyperactivity and hyperinsulinemia were noted concurrently. In conclusion, these results suggest that sympathetic nerve hyperactivity appears to be the initial event, followed by hyperinsulinemia and the resultant onset and development of hypertension.

**REFERENCES**


