Role of Insulin Resistance in Nondipper Essential Hypertensive Patients

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In hypertensive patients, diminished nocturnal blood pressure (BP) fall is associated with poor prognosis for cardiovascular events. However, the relation of insulin resistance with the etiology of nondipper essential hypertension remains unclear. The aim of the present study was to assess the role of insulin resistance in diminished nocturnal BP fall, left ventricular hypertrophy (LVH), and increased plasma atrial (ANP) and brain natriuretic peptides (BNP) in essential hypertensive patients. One hundred and three patients with essential hypertension were divided into dippers (n = 57; age: 57 ± 5 years, mean ± SD) or age-matched nondippers (n = 46; 57 ± 4 years), based on ambulatory BP (ABP) monitoring. Although the systolic and diastolic ABP values were similar during the day, those at night were higher in nondippers than in dippers (p < 0.0001 for each). Echocardiographic findings revealed that the left ventricular mass index (LVMI) was higher in nondippers (p < 0.0001). Plasma ANP and BNP were also higher in nondippers (p < 0.0001 for each). Fasting plasma concentrations of glucose and insulin (p < 0.0001 for each) and the homeostasis model assessment (HOMA) index (p < 0.0001) were also higher in nondippers. Multivariate analysis revealed that systolic ABP at night was a significant factor for LVMI, ANP and BNP. In addition, the HOMA index was a significant factor for LVMI and BNP. These observations suggest that diminished nocturnal BP fall is closely related to the development of LVH with concomitant increase in BNP in essential hypertensive patients, and that insulin resistance may play a key role in these processes. (Hypertens Res 2003; 26: 669–676)

Key Words: insulin resistance, essential hypertension, nondippers, brain natriuretic peptide

Introduction

Hypertension is a major risk factor for the development of cardiovascular diseases (1, 2). Nondippers, who show a diminished nocturnal blood pressure (BP) fall, have been shown to have an increased frequency of damage to target organs including the brain, heart, and kidney, and poorer prognosis for cardiovascular events, when compared with dippers with appropriate nocturnal BP fall (3–5).

Nondippers have been reported to show an increased incidence of left ventricular hypertrophy (LVH) (6). On the other hand, LVH is known to cause an increase in plasma levels of atrial and brain natriuretic peptides (ANP and BNP) in patients with essential hypertension (7–9). Accumulating evidence suggests that insulin resistance plays an important role in the development of essential hypertension (10, 11). Therefore, we hypothesized that LVH with concomitant increase in plasma concentrations of ANP and BNP may occur more easily in nondipper essential hypertensive patients than in dippers, and that insulin resistance may play an essential role in these processes. In this study, we analyzed 24-h ambulatory blood pressure (ABP), echocardiographic findings, plasma ANP and BNP levels, and insulin resistance in untreated patients with essential hypertension.

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Table 1. Clinical Characteristics of Studied Patients

<table>
<thead>
<tr>
<th>Dippers (n = 57)</th>
<th>Nondippers (n = 46)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 5</td>
<td>57 ± 4</td>
</tr>
<tr>
<td>Gender (women/men)</td>
<td>37/20</td>
<td>22/24</td>
</tr>
<tr>
<td>Family history (%)</td>
<td>28</td>
<td>67</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.1 ± 2.1</td>
<td>24.7 ± 2.2</td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
<td>5.5 ± 0.5</td>
<td>5.9 ± 0.3</td>
</tr>
<tr>
<td>F-IRI (pmol/l)</td>
<td>5.9 ± 1.0</td>
<td>7.4 ± 1.2</td>
</tr>
<tr>
<td>HOMA index</td>
<td>1.4 ± 0.3</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>IGT (%)</td>
<td>16</td>
<td>48</td>
</tr>
<tr>
<td>T-Chol (mmol/l)</td>
<td>5.7 ± 0.6</td>
<td>5.7 ± 0.4</td>
</tr>
<tr>
<td>TGL (mmol/l)</td>
<td>1.7 ± 0.3</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>HDL-c (mmol/l)</td>
<td>1.3 ± 0.1</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>UA (mmol/l)</td>
<td>0.35 ± 0.04</td>
<td>0.39 ± 0.04</td>
</tr>
<tr>
<td>Creatinine (µmmol/l)</td>
<td>63.7 ± 16.9</td>
<td>68.7 ± 17.7</td>
</tr>
<tr>
<td>ANP (pg/ml)</td>
<td>67.6 ± 13.5</td>
<td>82.8 ± 12.2</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>15.6 ± 5.5</td>
<td>31.3 ± 12.0</td>
</tr>
</tbody>
</table>

Data are mean ± SD. BMI, body mass index; FPG, fasting plasma glucose; F-IRI, fasting immunoreactive insulin; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; T-Chol, total cholesterol; TGL, triglyceride; HDL-c, high-density lipoprotein cholesterol; UA, uric acid; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide.

Methods

Patients

One hundred and three patients with essential hypertension (age: 57 ± 5 years, mean ± SD; 59 women and 44 men) who were admitted to our hospital were enrolled in this study. Seventy-four of the studied patients were admitted for coronary angiography. The remaining 29 patients were admitted to the Department of Orthopedics and found to have essential hypertension. No patients had been treated with antihypertensive medication prior to enrollment in this study. The clinical characteristics of these patients are summarized in Table 1. None of these patients had organic heart disease except for LVH as determined by physical examination, chest X-ray, 12-lead ECG and echocardiography. Patients showing organic coronary artery stenosis were excluded. Essential hypertension was defined as mean 24-h systolic ABP (sABP) greater than 135 mmHg or mean 24-h diastolic ABP (dABP) greater than 85 mmHg (12).

Patients with renal failure, pulmonary disease, liver dysfunction, or a history of symptomatic cerebrovascular disease were excluded from the study. The diagnosis of diabetes mellitus was based on a 75 g oral glucose tolerance test (OGTT) (13). Briefly, blood samples were obtained before and 30, 60, 90, and 120 min after the oral administration of 75 g glucose. Individuals with diabetes mellitus, which was defined as a fasting glucose level of 7.0 mmol/l or greater and/or a plasma glucose level at 2 h after glucose administration of 11.1 mmol/l or greater, were excluded from the study.

All subjects gave their written informed consent to participate in the study, and the study protocol was approved by the ethics committee of the Oita Medical University.

Twenty-Four Hour ABP Monitoring

During admission, 24-h ABP was measured by the cuff-oscillographic method using an ABP monitoring system (Fukuda Denshi, Tokyo, Japan) with CO2 gas-powered cuff inflation. BP was measured every 30 min from 6:00 AM to 10:00 PM, and every 60 min from 10:00 PM to 6:00 AM of the following day (14, 15). BP was obtained as the mean value during the awake period between 6:00 AM and 10:00 PM and during the sleep period between 10:00 PM and 6:00 AM (14, 15). The waking time, time of falling asleep, and quality of sleep were assessed by interview with each patient. Patients who complained of sleep disturbance during ABP monitoring were excluded from analysis.

Definitions of Dippers and Nondippers

Subjects whose mean night-time sABP fell by more than 10% compared with their mean day-time sABP value were defined as dippers. The remaining subjects were defined as nondippers (16).

Echocardiography

M-mode 2-dimensional echocardiography and cardiac Doppler recordings were obtained by means of a phase-array echo-Doppler system. Echocardiograms were obtained in a standard manner using standard parasternal, short axis, and apical views. Left ventricular mass was calculated as follows...
according to a previous study (17): left ventricular mass = 1.04 \cdot \left( \left[ LVIDd + IVSTd + PWTd \right]^3 - LVIDd \right)^{1/3} + 14 g, where LVIDd, left ventricular internal dimension at end-diastole; IVSTd, intraventricular septal thickness at end-diastole; PWTd, posterior wall thickness at end-diastole. Left ventricular mass was divided by body surface area to calculate the left ventricular mass index (LVMI). Pulsed Doppler recordings were made from the standard apical 4-chamber view. Mitral inflow velocity was recorded with the sample volume at the mitral annulus level; the average of ≥3 cardiac cycles taken.

The following measurements were made: peak velocity of early ventricular filling (E), peak velocity of late ventricular filling (A), their ratio (E/A), and deceleration time.

Measurement of Plasma ANP and BNP

After 30 min of supine rest, 10 ml blood was drawn from an antecubital vein and immediately transferred into two chilled glass tubes, one containing EDTA (1 mg/ml) and one containing aprotinin (500 U/ml) for measuring plasma ANP and BNP, respectively. Blood was centrifuged immediately at 4 °C, and the plasma was frozen and stored at -80 °C until assayed. Plasma ANP and BNP were measured with specific immunoradiometric assays (Shiono RIA assay kit; Shionogi, Osaka, Japan) (18–20).

Insulin Resistance

Insulin resistance was evaluated by the homeostasis model assessment (HOMA) index: HOMA index = (fasting plasma insulin [pmol/l] \cdot fasting plasma glucose [mmol/l])/22.5 (21).

Statistical Analysis

Data are presented as the mean \pm SD. Differences between the two groups were analyzed by unpaired Student’s t-test, \chi^2 test, or Fisher’s exact probability test. Correlations between two variables were assessed by simple linear regression analysis. Multiple linear regression was carried out to determine the independence of association with other variables. Adjustments of variables between the groups were performed by analysis of covariance (ANCOVA). Values of p < 0.05 were considered to indicate statistical significance.

Results

Clinical Characteristics of the Patients

As demonstrated in Table 1, the mean age was similar between the groups. No significant differences were observed between the two groups with respect to gender or body mass index. The family history of essential hypertension was greater in nondippers than in dippers (p < 0.0001). The fasting plasma glucose and insulin, and the HOMA index were higher in nondippers than in dippers (p < 0.0001 for each). The percentage of patients revealing impaired glucose tolerance was higher in nondippers than in dippers (p < 0.001). Plasma total cholesterol, triglyceride, and high-density lipoprotein (HDL)-cholesterol were not significantly different between the two groups. However, the level of uric acid was higher in nondippers than in dippers (p < 0.0001). Plasma creatinine was not significantly different between the two groups.

Plasma ANP and BNP

The levels of ANP and BNP in nondippers were higher than in dippers (p < 0.0001 for each, Table 1).

ABP Monitoring Data

The ABP data are shown in Table 2. The sABP, dABP, and heart rate during the day were similar between the groups. In contrast, those at night were higher in nondippers than in dippers (p < 0.0001, p < 0.0001, and p < 0.0005, respective-
ly). As a result, the 24-h mean sABP and dABP were higher in nondippers than in dippers (p < 0.0001 and p < 0.001, respectively).

**Echocardiographic Findings**

Table 3 summarizes the echocardiographic findings. The left atrial dimension (p < 0.0001), and left ventricular dimensions at end-diastole and end-systole (p < 0.0001 for each), the interventricular septal thickness and posterior wall thickness at end-diastole (p < 0.0001 for each), and the LVMI (p < 0.0001) were greater in nondippers than in dippers. However, the left ventricular ejection fraction was similar between the two groups. With respect to the left ventricular diastolic function, the E/A ratio was lower (p < 0.0001) and the deceleration time was greater (p < 0.0005) in the dippers than in the nondippers.

**Relation of LVMI and ABP**

LVMI correlated with all parameters of ABP monitoring (Table 4). Multiple stepwise regression analysis revealed that the sABP at night was a significant predictor for the LVMI (p < 0.0001, multiple r = 0.77). To exclude the possibility that higher 24-h BP caused greater LVMI in nondippers, the same analysis was performed after adjustment of the 24-h sABP by ANCOVA. The analysis also revealed that the sABP at night was a significant predictor for the LVMI (p < 0.005).
Relation between LVMI and Plasma ANP and BNP

As demonstrated in Fig. 1, the LVMI correlated with plasma ANP and BNP \((r = 0.60, p < 0.0001\) and \(r = 0.82, p < 0.0001\), respectively).

Relationship of the HOMA Index with LVMI, and ANP and BNP

As demonstrated in Fig. 2, the LVMI correlated with the HOMA index \((r = 0.76, p < 0.0001)\). The plasma concentrations of ANP and BNP also correlated with the HOMA index \((r = 0.50, p < 0.0001\) and \(r = 0.75, p < 0.0001\), respectively; Fig. 3).

Multivariate Analysis

Multivariate analysis was performed using the LVMI, ANP, and BNP as dependent variables and the sABP at night and HOMA index as independent variables. As shown in Table 5, sABP at night was found to be a significant factor for LVMI, ANP, and BNP, while the HOMA index was also a significant factor for LVMI and BNP, but not for ANP.

Discussion

Main Findings

The main findings of the present study were that LVMI, ANP, BNP, fasting plasma concentrations of glucose and insulin, and the HOMA index were higher in nondippers than in dippers. Multivariate analysis revealed that sABP at night was a significant factor for LVMI, ANP, and BNP. In addition, the HOMA index was also a significant factor for LVMI and BNP.

Table 5. Multivariate Analysis

<table>
<thead>
<tr>
<th>Dependent variables</th>
<th>Independent variables</th>
<th>(\beta)</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI</td>
<td>Night sABP</td>
<td>0.459</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>HOMA index</td>
<td>0.422</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>ANP</td>
<td>Night sABP</td>
<td>0.568</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>HOMA index</td>
<td>0.081</td>
<td>0.4887</td>
</tr>
<tr>
<td>BNP</td>
<td>Night sABP</td>
<td>0.565</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>HOMA index</td>
<td>0.330</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

LVMI, left ventricular mass index; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; sABP, systolic ambulatory blood pressure; HOMA, homeostasis model assessment.
Nondippers and LVH

The LVMI in nondippers was greater than that in dippers. The levels of sABP and dABP during the day were similar between the two groups. Therefore, we speculated that the significantly increased BP at night contributed to the increased LVMI in nondipper hypertensive patients. In fact, multiple stepwise regression analysis revealed that sABP at night was a significant predictor for the LVMI. This finding was consistent with the recent report of an inverse relationship between nocturnal BP decline and LV mass in a large population of unselected and untreated patients with essential hypertension (16). Exposure for a long duration to increased BP may underlie the pathogenesis of LVH in essential hypertensive patients.

Relationship between LVMI and the Levels of ANP and BNP

In hypertensive patients with LVH, both plasma ANP and BNP levels were higher than in those without LVH (7). ANP is released by the atria in response to stretching and is also released by the ventricle in response to pressure and volume overload (22, 23). In contrast, BNP is predominantly released from the ventricle in response to pressure and volume overload, and BNP secretion is markedly enhanced in the presence of congestive heart failure as well as moderate to severe LVH (24). In the present study, the LVMI also correlated with both ANP and BNP, suggesting that these hormonal parameters well reflect the degree of LV pressure and volume overload in patients with essential hypertension.

Role of Insulin Resistance

Recently accumulated evidence suggests that insulin resistance plays an important role in the development of essential hypertension (11, 25). However, the role of insulin resistance in circadian BP regulation has not been fully elucidated. Chen et al. studied 24-h BP monitoring and OGTT in 50 essential hypertensive patients and reported that postprandial glucose levels during OGTT were higher in nondippers than in dippers (26). Similarly, the present study demonstrated that fasting plasma levels of glucose and insulin, and the HOMA index were higher in nondippers than in dippers. Taken together, these results suggest that insulin resistance plays an essential role in the etiology of nondipper hypertension.

Sustained activation of the sympathetic nervous system may be involved in the development of nondipper hypertension in patients with insulin resistance. In fact, in the present study, the heart rate at night was higher in nondippers than in dippers, whereas that during the daytime was not significantly different between the two groups, as shown in Table 2. This finding indicates that the sympathetic nervous system was activated even at nighttime in nondippers. Consistent with these findings, we recently reported in non-insulin dependent type 2 diabetic patients that the presence of essential hypertension was associated with both a higher HOMA index and increased clearance of cardiac $^{125}$I-metiodobenzylguanidine when compared to normotensive patients (27). In the present study, the fasting plasma insulin and HOMA index in nondipper patients were not markedly elevated, and the differences in these values between the two groups were modest. However, our results may suggest that even a modest increase in insulin resistance has importance for the etiology of nondipper hypertension.

Other Risk Factors

Although plasma total cholesterol, triglyceride, and HDL-cholesterol values were not significantly different between the two groups, the level of uric acid was higher in nondippers than in dippers. A growing body of evidence suggests that the plasma level of uric acid is associated with a greater incidence of cardiovascular events and higher systolic BP (28). Hyperuricemia is associated with low-density lipoprotein oxidation and an increase in reactive oxygen species, both of which play a role in the development of atherosclerosis and hypertension (29). Further studies are required to assess the role of hyperuricemia in the pathogenesis for the nondipper pattern of hypertensive patients.

Relevance

The present study demonstrated that insulin resistance contributes to the development of the nondipper pattern of essential hypertension and LVH. Conversely, interventions which increase insulin sensitivity may decrease the incidence of an abnormal circadian pattern of BP and subsequent LVH in patients with essential hypertension. In addition to physical training and diet, several drugs, including antihypertensive drugs, have been reported to improve insulin resistance (30, 31). Future studies are needed to clarify the interventions that improve insulin sensitivity, and which may thereby result in an improvement of circadian regulation of BP and prevention of LVH in essential hypertensive patients.

Limitations

There were several limitations in this study. First, we used the HOMA index as a conventional indicator of insulin resistance. The best method for assessment of insulin resistance is the glucose clamp technique (32). However, a recent study revealed that the HOMA index is significantly correlated with insulin resistance as measured using the glucose clamp technique in Japanese type 2 diabetic patients (33), indicating the validity of the HOMA index as an indicator of insulin resistance. Second, our study included 29 patients who were admitted to the Department of Orthopedics in addition to 74 patients who underwent coronary angiography, suggesting...
the heterogeneity of the cohort. However, when the patients were separated into these two respective groups for analysis, no essential difference was found between them (data not shown).

In conclusion, these observations suggest that diminished nocturnal BP fall is closely related to the development of LVH with concomitant increase in BNP in essential hypertensive patients, and that insulin resistance may play a key role in these processes.

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