The Limited Value of Plasma B-type Natriuretic Peptide for Screening for Left Ventricular Hypertrophy Among Hypertensive Patients

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Background: Several reports have suggested that plasma B-type natriuretic peptide (BNP) levels are elevated in hypertensive patients especially with left ventricular (LV) hypertrophy. However, few data have been available concerning the utility of plasma BNP measurement to identify LV hypertrophy in hypertensive patients in a general population screening context.

Methods: We measured plasma BNP concentrations in 1112 volunteers in a health screening program (mean age, 57 years). All subjects underwent electrocardiography, chest X-ray, and echocardiography. Among the sample, 284 subjects were designated as hypertensive because they were on antihypertensive drugs or showed elevated systemic blood pressure. By echocardiography, 36 of the hypertensive patients showed significant LV hypertrophy.

Results: There were no significant differences in age and sex between the LV hypertrophy and non-LV hypertrophy groups. Plasma BNP levels in the LV hypertrophy group were significantly higher than in the non-LV hypertrophy group (19.4 ± 18.9 vs 28.2 ± 28.2 pg/mL; P < .05). However, the ability of plasma BNP levels to discriminate between LV hypertrophy and non-LV hypertrophy patients was not sufficient as the area under the receiver operating characteristic curve was 0.588 (95% CI: 0.528 – 0.646) with sensitivity of 50.0% and specificity of 69.0%. Positive and negative predictive values for detecting LV hypertrophy among hypertensive patients were 18.9% and 90.5%, respectively. This ability did not improve significantly when the screening was limited to patients with untreated LV hypertrophy or concentric LV hypertrophy.


Key Words: Natriuretic peptide, left ventricular hypertrophy, screening, general population.
large number of unselected hypertensive subjects. The present study has therefore examined whether measurement of plasma BNP is an appropriate test for this purpose in a hypertensive cohort with various etiologies.

**Methods**

**Study Population**

The sample consisted of 1112 consecutive subjects (705 men and 407 women; mean age, 57.2 years; range, 25 to 83 years) who attended a multiphasic health checkup program carried out in Iwate, northern Japan, between April 1999 and March 2001. Most of the subjects were recruited through a Japanese agricultural cooperative association (JACA) in northern Iwate prefecture. Because the fee for the health checkup was supported by JACA and participation was voluntary, the sample was deemed to be representative of the local population. There were no limitations on participant selection on the basis of medical history or ongoing medications, but hospital inpatients were excluded from the study population.

**Measurements**

All subjects underwent physical examination, chest radiography, standard 12-lead electrocardiogram, and BP measurement. Blood pressure in a sitting position was measured twice in the right arm after a 5-min rest period, using a manual sphygmomanometer. The mean value was calculated. Venous blood samples were obtained during the morning of attendance, and were taken from a forearm with the patient in a sitting position. Blood samples for plasma BNP measurement were collected into a test tube containing EDTA-2Na and centrifuged immediately, and the plasma was stored at −80°C until BNP assay was carried out. Plasma BNP concentrations were measured by direct radioimmunoassay using monoclonal antibodies specific for human BNP (Shiono RIA BNP kit, Shionogi, Japan). Cross-reactivity of the antibody was 100% for human BNP and 0.001% for human atrial natriuretic peptide. The intra-assay and interassay coefficients of variation were 5% and 6%, respectively.

Echocardiographic examination was performed with a high performance machine (Acuson 512 Sequoia, Mountain View, CA) with a 3V2C transducer (3.5 MHz with harmonic image). All data were analyzed for LV geometry and function, which were measured according to guidelines of the American Society of Echocardiography. The LV mass was calculated according to Devereux et al. and normalized for body surface area and shown as a LV mass index. End-diastolic relative wall thickness (RWT) was calculated as the ratio of posterior wall thickness to one-half of the left ventricular internal dimension. Left ventricular ejection fraction was calculated by Teichholz’s rule. The echocardiographic data were reported immediately after the test by an echo-technician, with video-recorded figures being checked after this by an experienced echo-specialist. The median variation between two readings by the same observer or by different observers for LV geometry and function was within 10%. These procedures were performed with no knowledge of plasma BNP levels.

**Hypertension**

Hypertension was defined as follows: systolic BP $\geq$140 mm Hg or diastolic BP $\geq$90 mm Hg, or self-reported current treatment with an antihypertensive drug. Subjects who met the criteria for hypertension but showed any overt heart disease such as cardiomyopathy, previous myocardial infarction, valvular heart disease, or atrial fibrillation were excluded from the study.

**Statistics**

Because the distribution of plasma BNP levels was skewed, log transformation values were used for statistical analysis. In the text and figures, all data are shown in actual values as mean ± SD. Receiver operating characteristic (ROC) curves were constructed to assess the sensitivity and specificity of plasma BNP throughout the range of concentrations as an indicator of LV hypertrophy. The area under the curve with the 95% confidence interval (CI), and positive and negative predictive values of each test were calculated to provide a measure of the overall diagnostic accuracy of the test.

**Results**

**Healthy Controls**

Six hundred eighty-six subjects (mean age, 55.3 ± 9.4 years; 426 men and 260 women) who were free from any cardiovascular history (hypertension, angina, myocardial infarction, myocardial disease, valvular heart disease, cerebrovascular events, or arrhythmia) or diabetes mellitus were selected from the present cohort to determine the normal range of LV mass index and of RWT. In the control group, the mean ± SD of LV mass index was 95.1 ± 18.5 g/m² for men and 85.5 ± 17.2 g/m² for women, respectively. Ninety-five percentile values of LV mass index in this cohort were 130 g/m² for men and 120 g/m² for women, and these values were thus defined as partition values for LV hypertrophy. The mean value of RWT in this cohort was 0.41 ± 0.06 for men and 0.38 ± 0.07 for women. The 95 percentil value of RWT was 0.53 for both sexes, and thus concentric and eccentric LV geometry were defined as upper and lower values, respectively.

**Hypertensive Patients**

Two hundred eighty-four patients met the criteria for hypertension in the present cohort (mean age, 60.6 ± 8.8 years; 174 men and 110 women) (Fig. 1). Among these hypertensives, 36 patients (13%) showed LV hypertrophy as defined by the partition values. In the LV hypertrophy group, 12 patients had untreated hypertension, 13 patients
had hypertension despite antihypertensive medication, and 11 patients had well-controlled hypertension. The type of LV hypertrophy was concentric in 12, and eccentric in 24 subjects.

No significant differences in age, sex, body weight, height, and smoking status were found between the LV hypertrophy and non-LV hypertrophy groups (Table 1).

**Table 1. Comparison of clinical parameters between hypertensive subject groups with and without LV hypertrophy**

<table>
<thead>
<tr>
<th></th>
<th>LVH (−)</th>
<th>LVH (+)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>60.6 ± 8.8</td>
<td>60.8 ± 9.3</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>155/93</td>
<td>19/17</td>
<td></td>
</tr>
<tr>
<td>BH (cm)</td>
<td>159 ± 8.7</td>
<td>158 ± 9.7</td>
<td></td>
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<tr>
<td>BW (kg)</td>
<td>64.9 ± 11.2</td>
<td>66.5 ± 12.0</td>
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<tr>
<td>BSA (m²)</td>
<td>1.67 ± 0.17</td>
<td>1.68 ± 0.19</td>
<td></td>
</tr>
<tr>
<td>Smoking (non/ex/current)</td>
<td>137/57/54</td>
<td>20/8/8</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>136.5 ± 15.7</td>
<td>140.8 ± 15.6</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>77.8 ± 8.7</td>
<td>80.6 ± 10.6</td>
<td></td>
</tr>
<tr>
<td>CTR (%)</td>
<td>49.1 ± 3.9</td>
<td>49.3 ± 3.9</td>
<td></td>
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<tr>
<td>FBS (mg/dL)</td>
<td>101.3 ± 14.7</td>
<td>103.4 ± 28.1</td>
<td></td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>210.4 ± 35.1</td>
<td>217.7 ± 34.6</td>
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<tr>
<td>Serum Cr (mg/dL)</td>
<td>0.96 ± 0.17</td>
<td>0.91 ± 0.15</td>
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</tbody>
</table>

BH = body height; BW = body weight; BSA = body surface area; BP = blood pressure; CTR = cardiothoracic ratio; FBS = fasting blood glucose; TC = total cholesterol; Cr = creatinine. P = not significant for all parameters.

Systemic BP did not differ between the groups (systolic BP, 136 ± 15 vs 140 ± 15 mm Hg; diastolic BP, 77 ± 8 vs 80 ± 10 mm Hg; both P = not significant [NS]). Biochemical data including fasting blood sugar, serum total cholesterol, and serum creatinine did not differ between the LV hypertrophy and non-LV hypertrophy groups. In echocardiographic data, values of LV ejection fraction and E/A ratio were similar between the two groups (Table 2). The LV geometric data including RWT and LV mass was significantly higher in the LV hypertrophy group than in the non-LV hypertrophy group.

**Plasma BNP and LV Hypertrophy**

Plasma BNP concentrations were significantly increased in the LV hypertrophy group compared to the non-LV hypertrophy group (19.4 ± 18.9 vs 28.2 ± 28.2 pg/mL; P < 0.05). However, no significant relationship was found between LV mass index and plasma BNP levels (r = 0.10, P = NS). The validity of plasma BNP measurement for distinguishing the LV hypertrophy group from the non-LV hypertrophy group was low, as the area under the ROC was 0.588 (95% CI: 0.528–0.646) with sensitivity of 50.0% and specificity of 69.0%. Positive and negative predictive values for selection of LV hypertrophy among hypertensive patients were 18.9% and 90.5%, respectively. The ability did not improve when the test was applied for patients with untreated hypertensive LV hypertrophy (area under ROC: 0.611). Furthermore, we have examined the utility of plasma BNP testing for identifying concentric LV hypertrophy from non-LV hypertrophy in hypertensive patients (Table 3). The ability of plasma BNP testing for this purpose was not sufficient as the area under ROC was 0.581 (95% CI: 0.518–0.641).

When an established LVH partition values (>110 g/m² for women, >134 g/m² for men) for US populations was applied in this model, the main results are as follows:
sensitivity = 48.9 (95% CI: 34.1–63.9); specificity = 72.6 (95% CI: 66.4–78.1); positive predictive value = 26.1%; negative predictive value = 87.8%; area under ROC = 0.623 (95% CI: 0.564–0.680). These values do not differ significantly from our original findings.

**Discussion**

LV hypertrophy is known to be an independent risk factor for all the cardiovascular complications of hypertension.\(^1\)\(^–\)\(^3\)\(^\text{19}\)

Because hypertensive LV hypertrophy is a reversible geometric abnormality, early detection and intervention are important to improve outcomes for hypertensives. When hypertensive structural LV abnormalities characterized by preserved LV ejection fraction with diastolic dysfunction are present, plasma BNP levels appear to be increased.\(^20\)

This means that elevated plasma BNP levels may serve as a marker of LV hypertrophy in a hypertensive population. Several previous studies have shown that plasma levels of natriuretic peptides were elevated in LV hypertrophy subjects within a general population,\(^21\)\(^–\)\(^22\) and in heart disease\(^23\) and hypertension.\(^12\)\(^–\)\(^13\) However, these reports have not described the diagnostic ability of plasma natriuretic peptide testing for distinguishing between LV hypertrophy and non-LV hypertrophy patients in terms of sensitivity and specificity. The present study has demonstrated that plasma BNP measurement is unlikely to be a useful screening test for that purpose in patients with hypertension in a general population. Plasma BNP levels have been reported to decrease with LV mass in hypertensive subjects receiving long-term antihypertensive treatment, specifically angiotensin-converting enzyme inhibitors.\(^24\)

However, the present unexpected result was consistent when patients receiving antihypertensive drugs were excluded from this analysis.

Yamamoto et al\(^23\) have shown that the sensitivity and specificity of plasma BNP testing for identifying LV hypertrophy patients showing LV mass index ≥120 g/m\(^2\) among patients with various kinds of heart disease were 81% and 85%, respectively. The diagnostic ability of BNP testing for LV hypertrophy has been reported to be reliable as the area under the ROC was >0.9. Although this finding contrasts with the present results, their subjects and ours had differing clinical characteristics. The subjects in the present study were mildly to moderately hypertensive, whereas a large proportion of their subjects had coronary heart disease, including hypertrophic cardiomyopathy. In accordance with our results, Bettencourt et al\(^25\) have demonstrated in a small number of hypertensive patients that plasma BNP measurement was unable to differentiate between patients with and without LV hypertrophy.

Vasan et al\(^26\) recently reported that the performance of plasma BNP testing for detection of LVH within a community-based sample was suboptimal. This finding is consistent with our present results. However, they did not investigate the ability for selection of nontreated LVH or concentric LVH within a hypertensive subgroup. Several studies have shown that plasma BNP concentrations in concentric LV hypertrophy were higher than in eccentric LV hypertrophy.\(^27\)\(^–\)\(^28\) The present study therefore examined the ability of plasma BNP testing to distinguish between patients with concentric LV hypertrophy and those without LV hypertrophy. However, the screening power for this subset of LV hypertrophy was not improved.

The reasons for the low validity of plasma BNP testing for selecting LV hypertrophy patients regardless of the type of LV hypertrophy from hypertensive patients remains unknown. However, in a rat experimental model of LV hypertrophy, myocardial expression of BNP mRNA was not observed in an early phase showing LV hypertrophy alone, whereas mRNA levels increased in a late phase presenting both LV hypertrophy and hemodynamic deterioration.\(^29\) In addition, several studies have suggested that a gene polymorphism such as angiotensin-converting enzyme gene deletion allele was related to LV hypertrophy independent of systemic BP in patients with essential hypertension.\(^30\)\(^–\)\(^31\) Moreover, Suzuki et al\(^32\) have reported an elevation of plasma BNP concentrations before the establishment of LV hypertrophy in patients with essential hypertension, suggesting that plasma BNP levels would increase in some cases without LV hypertrophy. These confounding factors in LV hypertrophy relative to plasma BNP levels may reduce the validity of the plasma BNP test for LV hypertrophy screening in a hypertensive population.

In conclusion, plasma BNP testing in a mass screening context is of limited use for identification of LV hypertrophy patients among hypertensive patients with heterogeneous etiology.
References


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