B-Type Natriuretic Peptide and Arterial Stiffness in Healthy Japanese Men

Minoru Yambe, Hirofumi Tomiyama, Yutaka Koji, Kohki Motobe, Kazuki Shiina, Zaydun Gulnisia, Yoshio Yamamoto, and Akira Yamashina

Background: Recent evidence suggests that even a slight increase in the plasma level of B-type natriuretic peptide (BNP) may be a marker of cardiovascular risk; however, the mechanisms underlying the association are currently unclear. Because increased arterial stiffness, as reflected by an increase of the pulse wave velocity (PWV) or pulse pressure (PP), may contribute to increasing plasma BNP levels, in the present study we investigated the relationships between the plasma BNP level and the PWV and PP, all of which are known markers of cardiovascular risk, in a healthy male Japanese cohort.

Methods: This was a cross-sectional study of 725 healthy Japanese men (age, 54 ± 4 years). The PWV was assessed by the volume-rendering method. Plasma BNP levels were determined with a high-sensitivity noncompetitive immunoradiometric assay.

Results: A univariate linear regression analysis demonstrated that the plasma BNP level was significantly correlated with age (r = 0.20, P < .01), PWV (r = 0.12, P < .01), and PP (r = 0.17, P < .01). A stepwise multivariate linear regression analysis demonstrated that both the PWV and PP were significantly associated with the plasma BNP level, independent of age.

Conclusion: In healthy Japanese men, stiffening of large arteries, as evidenced by an increase of the PWV or PP, may account at least in part for elevated plasma BNP levels, even within the so-called normal range.

Key Words: Atherosclerosis, cardiovascular diseases, natriuretic peptide, pulse wave velocity.
The detection threshold of the BNP assay was 1.0 pg/mL the interassay coefficient of variation was 2.1% and intra-assay coefficient of variation was 10.0%,11 with a reported interobserver coefficient of variation of 11.0J (SPSS Inc., Chicago, IL). P values < .05 were considered to indicate statistical significance.

**Results**

The clinical characteristics of the 725 subjects screened for the study are summarized in Table 1. Their plasma BNP levels ranged from 1.0 to 98.0 pg/mL. The results of the linear regression analyses revealed that the plasma BNP level was significantly correlated with brachial–ankle PWV ($r = 0.12$, $P < .001$) and PP ($r = 0.17$, $P < .001$). Table 2 shows the regression coefficients obtained in the univariate linear regression analysis between the plasma level of BNP and other cardiovascular risk factors, including the heart rate. The variables of age, body mass index, mean blood pressure, heart rate, and total cholesterol level showed significant correlations with the plasma BNP level. The results of stepwise multivariate linear regression analysis revealed that the brachial–ankle PWV and PP were significantly correlated with the plasma BNP level independent of age, heart rate, or other parameters identified by univariate linear regression analysis (Table 3).

**Discussion**

This is the first study to examine the association between brachial–ankle PWV and the plasma BNP level within the so-called normal range. In recent years plasma BNP levels >100 pg/mL have come to be widely regarded as an adverse prognostic biomarker in patients with heart fail-

### Table 1. Clinical characteristics of the study subjects

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR</td>
<td>-0.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.05</td>
<td>0.17</td>
</tr>
</tbody>
</table>

**Abbreviations as in Table 1.**
ure or acute myocardial infarction. Wang et al. reported that a plasma BNP level /H11022 20 pg/mL in men in a general population double the risk of a future cardiovascular event (initial cardiovascular event, stroke, or atrial fibrillation), and Nielsen et al. suggested that even a level of /H11022 8 pg/mL may be a marker of asymptomatic cardiac systolic dysfunction. However, the pathophysiologic basis for considering a slight increase in the plasma BNP level, within the so-called normal range, as a marker of cardiovascular risk has not yet been clearly elucidated. The present study showed that the brachial–ankle PWV may indeed bear a weak but significant correlation with the plasma BNP level in healthy Japanese men.

Although aging is an important determinant of arterial stiffness, in as much as brachial–ankle PWV and PP were associated with plasma BNP levels independent of age, arterial stiffness may be associated with plasma BNP levels independent of the aging process. Brachial–ankle PWV reflects both arterial stiffness at peripheral sites in the upper and lower limbs and central arterial stiffness; it is strongly correlated with aortic PWV. An increase in central arterial stiffness leads to earlier arrival of the reflected pulse waves, causing increased ventricular afterload with concomitant decreased coronary perfusion but increased myocardial oxygen demand. These alterations related to increased arterial stiffening can stimulate the synthesis and release of BNP.

On the other hand, PP is presented as the formula: PP = cardiac stroke volume/arterial compliance. Thus, cardiac performance is also an important determinant of PP. Ventricular–arterial coupling maintains cardiac stroke volume in the presence of increased arterial stiffening, and it has been demonstrated that ventricular–arterial uncoupling increases the production of BNP. In addition, our previous study demonstrated a significant association between the brachial–ankle PWV and the cardiac diastolic function, which is a known marker of cardiac stiffness. Therefore we speculated that in our study cohort also, this adaptive coupling may explain the increase in the plasma level of BNP.

The present study suggested that increased brachial–ankle PWV and PP are equally reliable markers of elevated plasma BNP level in a general population. However, compared with PP, the PWV is a more robust marker of arterial stiffness and also of the severity of atherosclerosis. Furthermore, increased arterial stiffness acts as an atherogenic factor by itself, apart from its unfavorable effect on the cardiovascular system via elevation of the plasma BNP level. Therefore, a longitudinal study must be conducted in the future to confirm whether the plasma level of BNP and markers of arterial stiffness (PWV and PP) are related or independent markers of increased cardiovascular risk in a general population.

In addition to BNP, plasma C-reactive protein and matrix metalloproteinase–9 levels have also been reported to be predictors of future cardiovascular events. These parameters have also been shown to be significantly associated with PWV, and their significant associations may be related to the finding that vascular inflammation or vascular connective tissue metabolism may be involved in the arterial stiffening process. Both of these parameters were even more closely associated with PWV than the association between brachial–ankle PWV and plasma

---

### Table 3.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>β</th>
<th>t Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.16</td>
<td>4.46</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HR</td>
<td>−0.17</td>
<td>−4.41</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>baPWV</td>
<td>0.18</td>
<td>4.45</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TC</td>
<td>−0.12</td>
<td>−3.19</td>
<td>.001</td>
</tr>
<tr>
<td>Not significant variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBP</td>
<td>—</td>
<td>1.06</td>
<td>.29</td>
</tr>
<tr>
<td>BMI</td>
<td>—</td>
<td>−1.49</td>
<td>.14</td>
</tr>
</tbody>
</table>

Including brachial–ankle pulse wave velocity as a covariate (total $R^2 = 0.09$)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>β</th>
<th>t Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.18</td>
<td>5.00</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PP</td>
<td>0.17</td>
<td>4.68</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HR</td>
<td>−0.12</td>
<td>−3.27</td>
<td>.001</td>
</tr>
<tr>
<td>TC</td>
<td>−0.10</td>
<td>−2.81</td>
<td>.005</td>
</tr>
<tr>
<td>Not significant variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBP</td>
<td>—</td>
<td>1.57</td>
<td>.12</td>
</tr>
<tr>
<td>BMI</td>
<td>—</td>
<td>−1.76</td>
<td>.08</td>
</tr>
</tbody>
</table>

Including pulse pressure as a covariate (total $R^2 = 0.09$)

Abbreviations as Table 1.
BNP level. However, the results of our study suggest that slight increases in arterial stiffness observed in a general population may not be a major determinant of increases in plasma BNP level within the high normal range. This significant but weak association between brachial–ankle PWV and plasma BNP level can be explained by the finding that BNP directly reduces arterial stiffness through its favorable effects on arterial properties, and the effects of BNP that counter the arterial stiffness may blunt the positive association between arterial stiffness and plasma BNP level.

There are three major limitations of the present study. The first is that the possibility of asymptomatic cardiac dysfunction was not fully evaluated. Another study that would examine the association between cardiac systolic or diastolic function and plasma BNP level within the high normal range is proposed. The second limitation of our study is that the brachial–ankle PWV is a surrogate of the carotid–femoral PWV, which is an established marker of aortic stiffness. As mentioned earlier here, although the brachial–ankle PWV bears a close correlation with the aortic PWV, the possibility that the carotid–femoral PWV may show a closer association with the plasma BNP level cannot be neglected. Therefore, confirmation of the present results using the carotid–femoral PWV is proposed. The third limitation was that the study was conducted in Japanese men, and the results may not be applicable to women or to other ethnic groups.

In conclusion, the brachial–ankle PWV and PP were found to be significantly associated with the plasma BNP level, independent of age. In healthy Japanese men, stiffening of the large arteries, as evidenced by an increased PWV or PP, may account at least in part for elevated BNP levels, even within the so-called normal range.

References


