Plasma Brain Natriuretic Peptide Levels and Blood Pressure Tracking in the Framingham Heart Study


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Plasma Brain Natriuretic Peptide Levels and Blood Pressure Tracking in the Framingham Heart Study


Abstract—Increased brain natriuretic peptide (BNP) expression in the ventricles antedates elevated blood pressure (BP) in experimental studies. We hypothesized that higher plasma BNP levels in nonhypertensive individuals may be associated with a greater likelihood of future BP increase and/or hypertension. We evaluated the relations of plasma BNP to longitudinal BP tracking and incidence of hypertension in 1801 nonhypertensive Framingham Heart Study participants (mean age, 56 years; 57% women) by using gender-specific multivariable logistic regression. Progression of BP stage was defined as an increment of one or more BP categories, as classified by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). Hypertension was defined as a systolic BP ≥ 140 or diastolic BP ≥ 90 mm Hg or use of antihypertensive medications. On follow-up 4 years from baseline, progression of BP category was observed in 36.2% of men and 33.1% of women; hypertension developed in 16.4% of men and 15.5% of women. In multivariable models adjusting for known risk factors, elevated plasma BNP level was associated with increased risk of BP progression in men (odds ratio of 1.15 for trend across categories, P=0.046) but not in women (P=0.82). There were no significant trends of increasing incidence of hypertension across BNP categories in men or women. In our community-based sample, higher plasma BNP levels were associated with increased risk of BP progression in men but not women. Additional investigations are warranted to confirm these findings and elucidate the basis for these gender-related differences. (Hypertension. 2003;41:978-983.)

Key Words: natriuretic peptides ■ blood pressure ■ hypertension, essential ■ epidemiology ■ hemodynamics

The natriuretic peptide (NP) family plays a key role in salt and water homeostasis and blood pressure regulation through direct vasodilator, diuretic, and natriuretic properties.1–2 Brain natriuretic peptide (BNP), in particular, is a sensitive indicator of ventricular wall stress.3–6 Experimental studies suggest that induction of BNP gene expression is one of the earliest responses to hemodynamic pressure overload and occurs before the development of left ventricular (LV) hypertrophy.7 Indeed, in spontaneously hypertensive rats, increased BNP expression antedates the development of hypertension itself and precedes LV hypertrophy.8 Therefore, it is not surprising that in several cross-sectional studies, plasma BNP and atrial natriuretic peptide levels have been reported to be elevated in subjects with hypertension and in individuals with LV hypertrophy.9–15 To our knowledge, the relations of plasma BNP levels to the incidence of hypertension or to longitudinal blood pressure tracking in the community have not been investigated.

Investigators have reported that individuals prone to development of high blood pressure often have a hyperdynamic circulation antedating the onset of hypertension by several years.16 Other researchers have underscored the role of increased conduit artery stiffness as a precursor of systolic hypertension in middle-aged and elderly individuals.17 The recent demonstration of favorable effects of BNP on vascular smooth muscle cells and conduit artery properties18,19 and the beneficial effect of neutral endopeptidase inhibitors (that increase BNP levels) on conduit artery stiffness20 support the notion that plasma BNP may be an important correlate of altered vascular wall properties.

We hypothesized that hypertension-prone individuals may have higher levels of plasma BNP as a result of elevated ventricular wall stress or increased vascular stiffness early in the course of the disease. If this hypothesis is true, plasma BNP level could serve as a marker of future hypertension risk. Accordingly, we evaluated the relation of plasma BNP obtained at a routine examination to longitudinal changes in blood pressure on follow-up (including the incidence of hypertension) in a large community-based sample of nonhypertensive individuals.
Methods

Subjects
The Framingham Offspring Study is a prospective cohort study established in 1971 to evaluate potential risk factors for coronary heart disease in 5124 participants. We retained the sample for the present investigation consisted of all 3532 Framingham Offspring Study participants who attended the sixth examination cycle between 1995 and 1998. Subjects were excluded from the present investigation for the following reasons, in hierarchical fashion: hypertension, as defined by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) and the World Health Organization-International Society of Hypertension (WHO-ISH) (systolic blood pressure ≤140 mm Hg, or diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication) (n = 1468); missing blood pressure at the baseline examination (n = 11); nonattendance, missing blood pressure, or missing covariates at the next follow-up Heart Study visit (examination cycle 7) 4 years later (n = 186); prevalent heart failure/recognized myocardial infarction (n = 39); atrial fibrillation (n = 21); serum creatinine >2.0 mg/dL (n = 1) at the baseline examination; and unavailable plasma BNP levels (n = 5). We excluded individuals with heart failure or myocardial infarction at baseline because these conditions (and medications used to treat them) may be associated with lower blood pressure but elevated plasma BNP levels. After these exclusions, 1801 subjects (mean age, 56 years; 57.5% women) remained eligible. Informed consent was obtained from study participants, and the research protocol was reviewed and approved by the institutional review board of Boston University School of Medicine.

Baseline Measurements
At the index examination, all attendees underwent a routine physical examination, anthropometry, electrocardiography, laboratory assessment of cardiovascular disease risk factors, and transthoracic echocardiography. A physician using a standardized protocol measured systolic and diastolic blood pressures twice in the left arm of seated subjects with a mercury column sphygmomanometer. The average of 2 such readings constituted the examination blood pressure. Body mass index was calculated as the weight in kilograms divided by the square of height in meters.

At baseline, eligible subjects were categorized into 3 groups, based on their examination blood pressure: optimal (systolic <120 mm Hg and diastolic <80 mm Hg), normal (systolic 120 to 129 mm Hg or diastolic 80 to 84 mm Hg), or high normal blood pressure (systolic 130 to 139 mm Hg or diastolic 85 to 89 mm Hg). Left ventricular mass was calculated on the basis of results of M-mode echocardiography: LV mass = 0.8 [1.04 (LVIVD + IVST + PWT)² – (LVIVD)²] + 0.6, where LVIVD represents LV end-diastolic internal dimension and IVST and PWT indicate the end-diastolic thickness of the interventricular septum and LV posterior wall, respectively.

Plasma BNP Measurements
At the baseline examination, venous blood was drawn from fasting study subjects between 8 AM and 9 AM. Specimens were drawn into ethylenediamine tetracetic acid containing tubes and immediately stored at −70°C without repeat freeze-thaw cycles until their assay in 1998. A noncompetitive immunoradiometric assay based on a 2-site sandwich antibody system (Shionogi) was used to measure BNP levels from unextracted plasma. The lower limit of the measurement of BNP for the assay was 4 pg/mL, with an average interassay coefficient of variation of 12.2%.

Blood Pressure Outcomes on Follow-Up
Approximately 4 years after the baseline examination, study subjects attended the seventh examination cycle (1998 to 2001), on which occasion they underwent routine assessment of blood pressure (using the same standardized protocol as at the prior examination). Blood pressure was reclassified according to JNC VI categories/WHO-ISH grades. We examined occurrence of 2 different blood pressure outcomes: (1) progression of blood pressure by one or more JNC VI categories on follow-up and (2) incidence of hypertension.

Statistical Analyses
At baseline, subjects were divided into 4 categories, based on the distribution of plasma BNP values. All analyses were gender-specific because of differences in plasma BNP values between the 2 genders. Because of the truncation of plasma BNP values at the lower detection limit of the assay, we defined all individuals with plasma BNP values equal to 4 pg/mL as category 1. We then divided the remaining subjects into 3 equal categories, based on their plasma BNP values.

We used gender-specific logistic regression models to examine the relations of plasma BNP category at baseline to the risk of developing the blood pressure outcomes on follow-up. Separate analyses were performed for each blood pressure outcome. The multivariable models adjusted for the following covariates (all defined at baseline) that are known to influence plasma BNP levels as well as blood pressure and blood pressure changes over time: age, blood pressure category, systolic and diastolic blood pressure, smoking, diabetes mellitus, and body mass index (BMI). The criteria for these covariates have been previously defined.

We examined multivariate models in which risk of a blood pressure outcome in each of categories 2 to 4 was compared with that in category 1. We also evaluated trend models that tested for a linear trend for increased risk of developing the blood pressure outcomes across categories of plasma BNP.

Additional Analyses
Because low plasma BNP levels may be associated with increased hypertension risk, statistical models incorporating squared terms for BNP were constructed to evaluate potential U-shaped relations between plasma BNP and the blood pressure outcomes. We performed secondary analyses in which we adjusted for left ventricular mass (LV mass), in addition to all other covariates defined above, because plasma BNP is associated positively with LV mass, and increased LV mass has been associated with incidence of hypertension in some prior reports.

Because prior investigators have reported low plasma BNP levels in obese hypertensives, we examined statistical models incorporating interaction terms (BNP×BMI) to assess effect modification by BMI. A 2-sided probability value of <0.05 was considered statistically significant. All statistical analyses were performed with the use of SAS statistical software on a SUN Ultra-Sparc computer (Sun Microsystems Inc).

Results

Baseline Characteristics of Study Subjects
The baseline characteristics of our study subjects are displayed in Table 1. More than 50% of the women and ~40% of the men had optimal blood pressure (as defined by the JNC VI/WHO-ISH guidelines) at the baseline examination. A very small proportion of subjects were being diuretics (0.9%) or β-blocking agents (2.5%) for indications other than high blood pressure. Although subjects with a recognized myocardial infarction were excluded at baseline, a small proportion of participants (1.6%) had other manifestations of coronary heart disease.

BNP and Increase in Blood Pressure Category on Follow-Up
On follow-up, 277 men (36.2%) and 343 women (33.1%) had an increase to a higher JNC VI blood pressure category.
proportions of individuals within each blood pressure category who had progression of blood pressure are shown in Table 2.

In men, in multivariable models comparing each plasma BNP category with the first, risk of progression to a higher blood pressure category was increased in the third and fourth categories of plasma BNP (point estimates of the odds ratio exceeded 1), but the results were not statistically significant (Table 3). However, in models evaluating trend for blood pressure increase across categories of plasma BNP, there was a 15% increased risk of progression to a higher blood pressure group per category increase in plasma BNP (Table 3, $P=0.046$). The association of plasma BNP category with progression of blood pressure category persisted after adjustment for baseline LV mass (odds ratio for trend across categories of 1.15; 95% CI, 1.01 to 1.32; $P=0.04$).

In women, plasma BNP was not associated with blood pressure progression in multivariable analyses (Table 3).

Additional Analyses
We did not find any evidence of a U-shaped relation of plasma BNP and risk of blood pressure progression or incidence of hypertension in either gender (all probability values $>0.35$). Furthermore, there was no evidence of effect modification by BMI in either gender and for either blood pressure outcome (probability value for interaction terms exceeded 0.10). In secondary analyses adjusting for the use of diuretics or $\beta$-blocking drugs and for prevalent coronary

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**TABLE 1. Baseline Characteristics of Study Sample**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n=766)</th>
<th>Women (n=1035)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>55±9</td>
<td>56±9</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>121±10</td>
<td>117±12</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>75±7</td>
<td>71±8</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>28.0±4.3</td>
<td>26.3±5.0</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td><strong>Blood pressure category</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal, %</td>
<td>41.1</td>
<td>53.7</td>
</tr>
<tr>
<td>Normal, %</td>
<td>29.8</td>
<td>26.5</td>
</tr>
<tr>
<td>High normal, %</td>
<td>29.1</td>
<td>19.8</td>
</tr>
<tr>
<td><strong>Biochemical features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.2±0.2</td>
<td>1.1±0.2</td>
</tr>
<tr>
<td>Brain natriuretic peptide, pg/mL</td>
<td>9.0±9.5</td>
<td>13.2±13.0</td>
</tr>
<tr>
<td><strong>Echocardiographic characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular mass, g/m$^2$*</td>
<td>183±36</td>
<td>134±27</td>
</tr>
</tbody>
</table>

Values are mean±SD unless otherwise indicated. *Available in 1436 (79.7%) of 1801 subjects.

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**TABLE 2. Plasma BNP Categories and 4-Year Incidence of Blood Pressure Outcomes**

<table>
<thead>
<tr>
<th>BNP Category</th>
<th>Men BNP, Mean (range)</th>
<th>No. at Risk</th>
<th>Subjects With Increase of BP by ≥1 JNC VI BP Category, %</th>
<th>Subjects Developing Hypertension, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 1</td>
<td>4</td>
<td>360</td>
<td>34.7</td>
<td>16.1</td>
</tr>
<tr>
<td>C 2</td>
<td>5.42 (4.1–7.1)</td>
<td>135</td>
<td>25.9</td>
<td>9.6</td>
</tr>
<tr>
<td>C 3</td>
<td>9.67 (7.2–13.3)</td>
<td>136</td>
<td>44.9</td>
<td>21.3</td>
</tr>
<tr>
<td>C 4</td>
<td>25.11 (13.4–106)</td>
<td>135</td>
<td>41.5</td>
<td>19.3</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 1</td>
<td>4</td>
<td>292</td>
<td>32.5</td>
<td>13.7</td>
</tr>
<tr>
<td>C 2</td>
<td>6.51 (4.1–9.1)</td>
<td>249</td>
<td>31.7</td>
<td>13.3</td>
</tr>
<tr>
<td>C 3</td>
<td>13.07 (9.2–18.1)</td>
<td>245</td>
<td>35.1</td>
<td>18.0</td>
</tr>
<tr>
<td>C 4</td>
<td>30.89 (18.2–117.0)</td>
<td>249</td>
<td>33.3</td>
<td>17.3</td>
</tr>
</tbody>
</table>


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**TABLE 3. Risk of Progression by One or More JNC VI Blood Pressure Stage According to Plasma BNP Levels at Baseline**

<table>
<thead>
<tr>
<th>Plasma BNP Category</th>
<th>Men OR (95% Confidence Limits)</th>
<th>Women OR (95% Confidence Limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C 1 (referent)</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>C 2</td>
<td>0.68 (0.43–1.07)</td>
<td>0.98 (0.67–1.44)</td>
</tr>
<tr>
<td>C 3</td>
<td>1.51 (0.99–2.28)</td>
<td>1.09 (0.75–1.60)</td>
</tr>
<tr>
<td>C 4</td>
<td>1.37 (0.89–2.12)</td>
<td>0.92 (0.61–1.36)</td>
</tr>
<tr>
<td>Trend across categories</td>
<td>1.15 (1.00–1.32)</td>
<td>0.99 (0.87–1.12)</td>
</tr>
</tbody>
</table>

OR indicates odds ratio. Data are adjusted for age, smoking, diabetes, body mass index, baseline blood pressure category, systolic blood pressure, diastolic blood pressure.
disease at baseline, the association of plasma BNP with blood pressure progression in men was maintained.

**Statistical Power to Assess Risk of Blood Pressure Outcomes**

Given that change in blood pressure category was related to plasma BNP levels in men but not women and that incidence of hypertension was not significantly related to plasma BNP levels in either gender, we assessed our statistical power to detect these associations. In women, we had >80% power to detect an odds ratio of 1.20 for increase in blood pressure category on follow-up across plasma BNP groups at an α level of 0.05 (an effect size similar to that noted in men). However, we had limited statistical power to detect modest effects (odds ratio of 1.30 or less for trend across plasma BNP categories) of plasma BNP levels on hypertension incidence in both men and women. Statistical power to detect an increasing trend for hypertension incidence across plasma BNP categories (at an α level of 0.05) varied from: in men, 0.79 for an odds ratio of 1.30 but 0.48 for an odds ratio of 1.20; in women, 0.81 for an odds ratio of 1.30 but 0.51 for an odds ratio of 1.20.

**Discussion**

A large body of evidence supports a key role for natriuretic peptides in blood pressure regulation, yet clinical studies of natriuretic peptides and blood pressure have yielded conflicting results. In most reports, hypertensive individuals tend to have higher plasma BNP levels relative to their nonhypertensive counterparts. However, some investigators have reported that hypertensive individuals (especially the obese) may have low plasma natriuretic peptide levels, that is, they have a “natriuretic handicap.” Still others have reported no relations of plasma natriuretic peptide levels to blood pressure. A potential reason for these conflicting results is that prior studies were cross-sectional and limited by selection bias (examination of hypertensive patients with varying durations and degrees of blood pressure elevation and confounded by treatment effects) and small samples. We sought to examine the relations of plasma BNP levels to longitudinal blood pressure tracking in a large community-based sample of nonhypertensive individuals.

**Principal Findings**

In our investigation, increased baseline plasma BNP levels were significantly associated with higher odds of blood pressure progression on follow-up in men but not in women. We did not observe any effect modification by BMI, and the results were not attenuated by adjustment for echocardiographic LV mass.

There was no significant association of plasma BNP levels with incidence of hypertension in either gender. The lack of association with hypertension incidence (in contrast to the significant findings for BP progression in men) must be interpreted with caution. Our investigation had limited statistical power to detect modest influences of plasma BNP levels on the incidence of hypertension in either gender.

**Plasma BNP and Blood Pressure Tracking: Potential Mechanisms and Gender Differences**

It is important to consider potential explanations for the observed relations of higher plasma BNP levels to greater blood pressure progression in men. In experimental studies, underexpression of the BNP gene (or the natriuretic peptide receptor-A) is associated with hypertension, whereas overexpression of BNP or the administration of NP (or inhibitors of neutral endopeptidase that degrades NP) results in lowering of blood pressure. However, the natriuretic peptides have a vital counterregulatory role in clinical settings. Elevations of blood pressure and increased ventricular and vascular wall stress typically trigger an upregulation of BNP gene expression. We speculate that increased plasma BNP levels are a marker of elevated ventricular wall stress and/or of increased vascular stiffness that may antedate or be closely related to subsequent blood pressure increase.

The lack of association of plasma BNP and blood pressure progression in women, in contrast to the significant relations observed in men, merits comment. It is important to note that we had more women than men in our sample, and our investigation had reasonable statistical power to detect modest associations of plasma BNP with blood pressure progression in women. Perhaps gender-related differences in BNP responses to hemodynamic stress may contribute to this observation. Luchner et al have recently demonstrated that women have a lesser degree of plasma BNP elevation compared with men for the same level of LV dysfunction or hypertrophy.

**Strengths and Limitations**

The large community-based sample of nonhypertensive individuals, standardized assessment of blood pressure at baseline and on follow-up, and the multivariable analyses adjusting for factors known to influence both BNP levels and blood pressure progression strengthen the present investigation. Several limitations of our study should be acknowledged. As noted above, we had limited statistical power to examine relations of plasma BNP to hypertension incidence. Possibly, the elapsed time of 4 years between the 2 examinations was long enough to note a significant effect of plasma BNP levels on blood pressure progression but too short to observe any influence on hypertension incidence (blood pressure progression being a more common occurrence). Additional analyses...
over longer periods of time, or of larger samples will be necessary to assess the association of plasma BNP and incidence of hypertension more definitively. The lower detection limit of the BNP assay was 4 pg/mL in this study and a considerable proportion of subjects (47% of men and 28% of women) had values at this level. Therefore, potential effects of lower plasma BNP levels on blood pressure changes might have been underestimated in this group. The truncation of plasma BNP levels and the large number of variables that influence both plasma BNP and blood pressure could have hampered our investigation of possible U-shaped relations of plasma BNP to blood pressure.

Perspectives

It is well known that individuals with normal and high normal blood pressure progress to hypertension. However, there is considerable interindividual variability in the rates of such progression. It would be useful to have a biomarker that could serve as a reliable indicator of risk of blood pressure progression above and beyond other clinical determinants. Such a biomarker should be inexpensive and easily assayed, have narrow intrindividual physiological variation, be a good indicator of the likelihood of blood pressure progression, and serve as a reliable correlate of target organ damage or clinical outcome. If such a biomarker were to exist, it could be used to risk-stratify individuals with normal and high normal blood pressure who could be targeted for aggressive nonpharmacological treatment. Plasma BNP is a candidate biomarker based on cross-sectional associations with blood pressure measures. The next step is to examine whether blood levels for the marker are associated with longitudinal blood pressure progression. In our investigation, the association of BNP with blood pressure progression, although statistically significant, was weak and restricted to men. Additional larger, adequately powered studies are needed to confirm this association, to examine the basis of the gender-differences in findings, and further assess the relations of BNP to incidence of hypertension and target organ damage.

Conclusions

In our community-based sample, elevated plasma BNP levels at baseline were significantly associated with increase in blood pressure category (progression) on follow-up in men but not in women. These observations raise the possibility that elevated plasma BNP may indicate a greater likelihood of future blood pressure increase in men. Additional studies are warranted to confirm our findings.

Acknowledgments

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