Association of Plasma B-Type Natriuretic Peptide Concentrations With Longitudinal Blood Pressure Tracking in African Americans
Findings From the Jackson Heart Study


Abstract—Water and sodium retention precedes the development of high blood pressure (BP) and explains a compensatory rise in B-type natriuretic peptide (BNP) concentrations. It is unclear whether BNP concentrations antedate the BP progression. We hypothesized that higher BNP concentrations in our African American cohort will be associated with longitudinal increases in BP, progression of BP stage, and incident hypertension. Our study sample consisted of 888 normotensive (based on BP at examination 1 [2000–2004]) participants of the Jackson Heart Study (mean age, 47±12 years; 61% women). We examined the relation of BNP concentrations at the baseline examination to change in systolic and diastolic BPs, BP progression (an increase by 1 BP stage as defined by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) and incident hypertension by examination 2 (2005–2008) adjusting for baseline BP stages, systolic and diastolic BPS, traditional risk factors, and echocardiographic left ventricular mass. Over a median follow-up period of 5.0±0.8 years, 36.9% progressed to a higher BP stage and 19.3% developed hypertension. In multivariable regression models, higher log-BNP concentrations at examination 1 were significantly and positively associated with changes in systolic and diastolic BPs (P<0.05 for both). Baseline log-BNP was significantly associated with BP progression (P=0.046). Every SD increase in baseline log BNP was associated with a 12% increased risk of BP progression. Log-BNP was not significantly associated with incident hypertension (P=0.12). In our community-based sample of African Americans, higher BNP concentrations predicted a longitudinal increase in systolic and diastolic BPs and progression of BP stage. 

Key Words: blood pressure ■ b-type natriuretic peptide ■ African Americans

B-type natriuretic peptide (BNP) is a peptide hormone released by the cardiac myocytes in response to myocardial stretch during pressure and volume overload states. The peptide has known systemic effects, including vasodilatation, increase in urinary output, and sodium excretion, as well as inhibition of the sympathetic nervous system and the renin–angiotensin–aldosterone system. BNP maintains hemodynamic and neurohormonal equilibrium by counterbalancing the vasoconstriction and retentive effects of sustained neurohormonal secretion. Although it acts as a compensating mechanism to reduce preload and afterload, the increase in endogenous BNP is not sufficient to compensate for pressure and volume overload in disease states such as hypertension and heart failure.

Animal studies suggest that BNP expression antedates the development of hypertension. Although circulating plasma BNP concentrations have been associated with blood pressure (BP) in cross-sectional human studies, there is limited information on the relations of BNP to longitudinal changes in BP and incident hypertension, specifically in African Americans. The Jackson Heart Study (JHS) provides a unique opportunity to pursue this research question. We hypothesized that higher BNP concentrations will be associated positively with longitudinal changes in systolic and diastolic BPs and progression of BP stage.

Methods

The JHS is a longitudinal, observational cohort established in 2000 in part to prospectively investigate the role of environmental and genetic factors in the development of cardiovascular risk factors in an African American population. The base population was derived from a tri-county area that encompasses Jackson, MS (Hinds County, Madison County, and Scott County). The JHS participants were selected to ensure a community-based sample from which to derive a final sample of African Americans.

Received April 29, 2012; first decision May 17, 2012; revision accepted October 7, 2012.
From the University of Mississippi Medical Center, Jackson, MS (E.R.F., S.K.M., H.S.N., T.E.S., H.A.T.); Texas Tech University Health Sciences Center, Lubbock, TX (P.S.); Morehouse School of Medicine, Atlanta, GA (A.B.); University of Minnesota, Minneapolis, MN (M.W.S.); Massachusetts General Hospital, Harvard Medical School, Boston, MA (T.J.W.); and Boston University School of Medicine, Boston, MA (R.S.V.).

*Dr Fox and Dr Musani are joint first authors.
Correspondence to Ervin Fox, Department of Medicine, Division of Cardiovascular Diseases, University of Mississippi Medical Center, 2500 North State St, Jackson, MS 34216. E-mail efox@umc.edu

Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.112.197657
Three sets of analyses were performed to determine the association of plasma BNP with longitudinal changes in BP over time. In the first analysis, we investigated the relations of circulating natural logarithmically transformed BNP to changes in systolic and diastolic BP using generalized additive models implemented in SAS version 9.2 (SAS Inc, Cary, NC). Penalized regression splines were used to demonstrate the overall shape of the relation between log-transformed BNP and continuous BP changes.

In the second analysis, we investigated the relation of circulating log-transformed BNP (continuous) or categorical (quartiles) to BP progression defined as an increase by ≥1 JNC VI category. In the third analysis, we investigated the relation of circulating log-transformed BNP to incident hypertension. For participants taking BP medications, BP values were imputed by adding 10 mm Hg to the systolic BP and 5 mm Hg to the diastolic BP. We performed Poisson regression with robust error variance for both the second and third analyses.

In all 3 of the analyses, we adjusted for covariates known to influence circulating serum BNP, as well as BP and BP changes over time, including age, sex, BP categories, systolic and diastolic BPs, BMI, diabetes mellitus, smoking, heart rate, estimated glomerular filtration rate, and LV mass (fully adjusted model). LV mass was placed in the model because plasma BNP is associated positively with LV mass, and increased LV mass has been associated with elevated BP. Specific for BP progression and incident hypertension analyses, we used multiple models with progressive degrees of adjustment (model 1, age-sex adjusted; model 2, fully adjusted without SBP or DBP; model 3, fully adjustment without SBP but with DBP; and model 4, fully adjusted).

Because previous investigators have reported low plasma BNP concentrations in obese hypertensive subjects, we examined statistical models incorporating interaction terms (BNP×BMI) to assess effect modification by BMI. In a secondary analysis, we used JNC VII categories (as opposed to JNC VI categories used in the primary analysis) to further investigate the relation of BNP to incident hypertension in those with prehypertension at the baseline examination.

Results

The study sample consisted of 888 participants (mean age, 47±12 years; 61% women). The median follow-up period was 5.0±0.8 years. The main characteristics (clinical, biochemical features, BP categories, estimated glomerular filtration rate, and echocardiography) are summarized in Table 1.

Figures 1 and 2 show plots relating change in systolic BP and change in diastolic BP to baseline log-BNP concentrations after multivariable adjustment, respectively. Test of deviation from linearity showed that plasma BNP was linearly related to both systolic \((P=0.01)\) and diastolic \((P=0.032)\) BP changes. The spline term (3 degrees of freedom) revealed lack of a nonlinear relation between log plasma BNP with systolic \((P=0.20)\) and diastolic \((P=0.59)\) BP changes. Overall, log BNP was linearly related to changes in systolic and diastolic BPs; thus, Poisson regression models were deemed appropriate to estimate the relative risk (RR) of BP progression and incident hypertension described by plasma BNP concentrations.

Overall, 36.9% of the participants (36.2% men and 38.0% women) progressed to a higher BP stage, and 19.3% (18.2% men and 21.1% in women) developed incident hypertension. The clinical characteristics of those who had BP progression compared with those who did not have BP progression are presented in Table 2. There were no differences in the mean of baseline clinical characteristics or in estimated glomerular filtration rate; however, there was a significant difference in the median of BNP concentration. The median of BNP was significantly higher in those with BP progression \((P=0.0042)\) than in those without BP progression. In Table 3, the relations of log-BNP to change in BP outcomes over the 5-year follow-up period are shown for all 4 models with increasing levels of adjustment. In the fully adjusted
model, baseline log-BNP ($P=0.046$) was significantly associated with BP progression. Every SD increase in baseline log-BNP was associated with a 12% increased RR of BP progression. Baseline log-BNP, as a continuous variable, however, was not significantly associated with incident hypertension ($P=0.12$; Table 3). Level of adjustment did not affect the significance of the relation between BP progression and log-BNP or between incident hypertension and log-BNP.

Table 4 shows the association of BP outcomes with BNP where BNP concentrations are in quartile ranges. In the fully adjusted model, elevated plasma BNP concentrations (highest quartile) were significantly ($P=0.008$) associated with increased RR of BP progression. Baseline log-BNP, as a continuous variable, however, was not significantly associated with incident hypertension ($P=0.12$; Table 3). Level of adjustment did not affect the significance of the relation between BP progression and log-BNP or between incident hypertension and log-BNP.

In a secondary analysis, we used JNC VII categories to evaluate the relation of BNP to incident hypertension with a specific interest to look at those with prehypertension at baseline. Similar to our finding with JNC VI, there was no significant relation between BNP concentrations and incident hypertension in either the group with optimal BP or the group with prehypertension at the baseline examination.

### Discussion

**Principal Findings**

Our results indicate a compelling and graded positive association between BNP concentrations and both longitudinal change in systolic and diastolic BPs and BP progression. In a comparison of clinical risk factors and BNP concentrations in individuals with and without BP progression over the 5-year follow-up, BNP was significantly associated with BP changes seen. Our findings suggest that plasma BNP may be a precursor of or a response to the development of vascular changes that lead to higher BP and hypertension. BNP has been established as a regulator of cardiovascular hemodynamics since it was first identified in 1981 by de Bold et al.20 Long-standing hypertension is associated with LV hypertrophy, fibrosis, and subsequent onset of LV systolic and diastolic dysfunction.21 Because the main stimulus for BNP production is myocyte stretch, it is not surprising that elevated BNP concentrations are typically seen in hypertensive patients.22,23 Our investigation extends the literature on this biomarker to include its potential value as a predictor of future progression of BP.

### BNP Relation to Longitudinal BP

We observed a significant association of BNP concentration with increase in both systolic and diastolic BPs and with progression of BP category over an ≈5-year follow-up. There is...
BNP concentrations in individuals who were hypertensive but reported no association and others that have reported lower related to high BP.6,24 There have been some studies that have conflicting evidence for whether higher BNP concentrations are between baseline and exam 2. $P_{\text{linearity}} = 0.01$

![Figure 1](image1.png)

Figure 1. Change in systolic blood pressure (BP; SBP) by baseline log B-type natriuretic peptide (BNP) concentrations after multivariable adjustment. $\Delta$SBP is defined as the change in SBP between baseline and exam 2. $P_{\text{linearity}}$ represents the $P$ value from the test of linearity in the relation between log-BNP concentration and change in SBP after adjusting for age, sex, baseline systolic and diastolic BPs, body mass index (BMI), diabetes mellitus status, current smoking, heart rate, estimated glomerular filtration rate (eGFR), and left ventricular mass. Results suggest a significant linear relation between log-BNP concentration and change in SBP.

There have been some studies that have reported no association and others that have reported lower BNP concentrations in individuals who were hypertensive but also obese.19,25 Framingham investigators recently identified a relation of BNP concentrations to longitudinal BP tracking in men in their cohort, supporting findings in this investigation.26 They did not find such an association in women. To our knowledge, this is the first study to investigate the relation of BNP to longitudinal changes in BP and to BP progression in a large community-based group of African Americans.

One theory that explains the relation of BNP to BP progression is that increased vascular resistance and cardiac stress may lead to an increase in the circulating plasma BNP concentrations antedating the development of the disease state itself.2 Early in the development of hypertension, there is an increase in vascular stiffness. Arterial stiffness is associated with increased LV afterload, which may lead to BP progression and eventual development of hypertension.27,28 BNP is known to lower vascular resistance by a variety of actions including the following: (1) vasodilatation, (2) decrease of the sympathetic tone, and (3) reduction in cardiac preload by shifting the intravascular volume into an extravascular compartment.2 Natriuretic peptides reduce the sympathetic tone in the peripheral vasculature by inhibiting the release of catecholamines from autonomic nerve endings and suppression of sympathetic outflow from the central nervous system, thereby suppressing the reflex tachycardia and vasoconstriction that accompany the reduction in preload and promoting the lowering of arterial BP.3,29,30 Through suppression of the renin–angiotensin–aldosterone system and alteration of salt appetite and water intake, natriuretic peptides are also involved in reducing the extracellular fluid volume.4 Some experts suggest that, through these multiple hemodynamic mechanisms (in response to increased vascular resistance and pressure overload), there is potential for a rise in circulating plasma BNP concentrations that precedes an increase in BP and the development of hypertension.

Our finding that BNP concentrations are related to longitudinal change in BP (in particular, progression of systolic and diastolic BPs and BP class) has clinical importance. Individuals in a higher BP class are at a higher risk of developing hypertension.31 In the Framingham Heart Study, investigators found that, compared with those with optimal BP (<120/80 mm Hg), those with systolic BP 120 to 129 mm Hg and diastolic BP 80 to 84 mm Hg had a greater incidence of hypertension (5% vs 17%, respectively). Accordingly, those with systolic BP 130 to 139 mm Hg and diastolic 85 to 90 mm Hg had yet a higher risk (37%) compared with those with optimal BP.31 Studies have shown that those with prehypertension have as high as a 2-fold higher risk of adverse cardiovascular disease outcomes compared to those with optimal BP.32 Relevant to our study involving African Americans, in the Reasons for Geographic and Racial Differences in Stroke study, this population had higher rates of prehypertension, and prehypertension was significantly related to microalbuminuria and chronic kidney disease, in addition to cardiovascular disease.33 For the study sample in the current study, the rates of cardiovascular outcomes were too low over the 5-year follow-up to determine the RR of outcome in those with BP progression compared with those without BP progression (n=7, n=5, and n=5 for CHD, stroke, and congestive heart failure, respectively).

In this investigation, there was no significant relation between BNP and incident hypertension. Current literature supports the notion that NP concentration varies in occult hypertension.5,26 In
Table 2. Characteristics of the Study Population by Evidence of Blood Pressure Progression Between the Baseline and Second Examination

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Those Without Blood Pressure Progression (n=560)</th>
<th>Those With Blood Pressure Progression (n=328)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>46.5±12.0</td>
<td>47.8±11.0</td>
<td>0.0931</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>61.3</td>
<td>59.5</td>
<td>0.6533</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>11.8</td>
<td>12.5</td>
<td>0.6807</td>
</tr>
<tr>
<td>Blood pressure category, %</td>
<td></td>
<td></td>
<td>0.0158</td>
</tr>
<tr>
<td>Optimal</td>
<td>47.7</td>
<td>52.4</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>37.9</td>
<td>39.3</td>
<td></td>
</tr>
<tr>
<td>High-normal</td>
<td>14.4</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>5.4</td>
<td>5.5</td>
<td>0.9934</td>
</tr>
<tr>
<td>Baseline systolic blood pressure, mmHg</td>
<td>114.8±11.7</td>
<td>116.3±9.6</td>
<td>0.0636</td>
</tr>
<tr>
<td>Baseline diastolic blood pressure, mmHg</td>
<td>75.4±7.9</td>
<td>75.7±7.3</td>
<td>0.6121</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.8±5.3</td>
<td>29.5±5.4</td>
<td>0.3592</td>
</tr>
<tr>
<td>Left ventricular mass, g</td>
<td>135.6±32.5</td>
<td>136.5±30.2</td>
<td>0.7095</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>92.7±15.5</td>
<td>92.0±13.0</td>
<td>0.7117</td>
</tr>
<tr>
<td>B-type natriuretic peptide, median±75th percentile, pg/mL</td>
<td>7.9±9.0</td>
<td>9.8±10.8</td>
<td>0.0042</td>
</tr>
</tbody>
</table>

Values are mean±SD unless otherwise indicated. eGFR indicates estimated glomerular filtration rate.

1 study that evaluated concentrations of circulating molecular forms of BNP (BNP32 and N-terminal proBNP) in individuals with mild, moderate, and severe hypertension. Investigators found that compared with those with normal BP, concentrations of molecular forms of BNP were either not elevated or lower than those of age- and sex-matched controls with mild hypertension. However, in those with moderate and severe hypertension, BNP concentrations were higher. One explanation for potential lower concentrations with mild hypertension could be impairment of the natriuretic peptide system in the early phase of hypertension and a need for a particular threshold to be met early on in hypertension before activation of the natriuretic peptide system occurs in the early phase of the disease.

Limitations and Strengths

One limitation of the current investigation is that change in BP was assessed by comparing BP at 2 single visits (at the baseline examination and time of the second examination). It is unclear how serial BP assessments between the examinations may affect our results. Another limitation is that BNP was measured only at baseline; BNP concentration at follow-up was unknown. Thus, investigators could not account for the change in BNP in assessing the relation of BNP to change in BP. We excluded those with hypertension at baseline; therefore, at baseline none of the participants in the study sample were on BP medication; however, at follow-up, a portion of those with hypertension were on BP medication, and imputation was used to adjust for the effect of BP medication. Tobin et al tested multiple analytical models to adjust for the use of BP medication. Investigators showed that imputing the systolic BP and diastolic BP by a sensible constant was among the better models to offset the influence of medication with the technique, performing well both in simulated and real data sets.

Table 3. Relation of Log-B-Type Natriuretic Peptide to Blood Pressure Progression and Incident Hypertension Using Multivariable Regression

<table>
<thead>
<tr>
<th>Model</th>
<th>Blood Pressure Progression</th>
<th>Incident Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Risks (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age- and sex-adjusted</td>
<td>1.13 (1.01–1.26)</td>
<td>0.039</td>
</tr>
<tr>
<td>Full model without SBP and DBP</td>
<td>1.12 (1.00–1.26)</td>
<td>0.050</td>
</tr>
<tr>
<td>Full model with DBP</td>
<td>1.13 (1.01–1.28)</td>
<td>0.041</td>
</tr>
<tr>
<td>Full model with SBP and DBP</td>
<td>1.12 (1.00–1.26)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Relative risk for blood pressure progression represents the risks of progressing upward by ≥1 category of blood pressure based on Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines. Relative risk for incident hypertension represents the risk of developing hypertension based on blood pressure or interview in exam 2 after being normotensive at baseline. The full multivariable model includes the following covariates: age, sex, baseline systolic and diastolic blood pressures, body mass index, diabetes mellitus status, current smoking, heart rate, estimate glomerular filtration rate, and left ventricular mass.
In this investigation, the study sample was composed completely of African Americans, thus allowing for the assessment of a large, underrepresented population known to have higher rates of hypertension and hypertensive heart disease compared with other ethnic groups. Although the cohort used represents a strength of this study, the results may not be generalizable to other ethnic populations. A unique strength of this study is that data were prospectively collected using standardized methods for BNP measurement at baseline and assessment of BP and covariates data at baseline and follow-up examination.

**Perspectives**

The prevalence of hypertension in African Americans is among the highest in the world and is reported to be increasing. Between 1988–1994 and 1999–2002, the prevalence of hypertension in adults increased from 35.8% to 41.4% in African Americans. The prevalence among whites has also increased; however, the rates have been substantially lower than those in African Americans, thus allowing for the assessment of a large, underrepresented population known to have higher rates of hypertension and hypertensive heart disease compared with other ethnic groups. Although the cohort used represents a strength of this study, the results may not be generalizable to other ethnic populations. A unique strength of this study is that data were prospectively collected using standardized methods for BNP measurement at baseline and assessment of BP and covariates data at baseline and follow-up examination.

**Conclusions**

In this study of a community-based cohort of middle-aged African Americans, baseline circulating plasma BNP concentration predicted an increase in systolic BP, diastolic BP, and in the progression of BP category over a 5-year follow-up period. There was no significant relation of plasma BNP concentration to incident hypertension over the follow-up period.

**Sources of Funding**

The JHS is supported by National Institutes of Health contracts N01-HC-95170, N01-HC-95171, and N01-HC-95172, HL076784 provided by the National Heart, Lung, and Blood Institute and the National Center for Minority Health and Health Disparities, and AG028321 provided by the National Institute of Aging. This study was partially supported by Public Health Service Award UL1 RR025008 from the Clinical and Translational Science Award program, National Institutes of Health, National Center for Research Resources to A. Bidulescu.

**Disclosures**

None.

**References**


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Hypertension. 2013;61:48-54; originally published online November 26, 2012; doi: 10.1161/HYPERTENSIONAHA.112.197657
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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