Association of Parental Hypertension With Concentrations of Select Biomarkers in Nonhypertensive Offspring


Abstract—Children of parents with hypertension are at increased risk of developing high blood pressure. We hypothesize that circulating concentrations of putative biomarkers (that may play a role in development of high blood pressure) are higher in nonhypertensive offspring of parents with hypertension. We compared concentrations of 4 different biomarkers (urinary albumin:creatinine ratio, circulating C-reactive protein, aldosterone:renin ratio, and plasminogen activator inhibitor-1) in nonhypertensive Framingham offspring study participants with none (n = 233), 1 (n = 474), or both (n = 322) parents with hypertension. Parental hypertension was defined as onset before age 60 years, based on longitudinal observations of the original Framingham cohort. Serum C-reactive protein concentrations were higher in nonhypertensive offspring with 1 (median: 1.7; Q1 to Q3: 0.8 to 3.6 mg/L) or both parents with hypertension (median: 1.8; Q1 to Q3: 0.7 to 3.6 mg/L) compared with offspring without parental hypertension (median: 1.4; Q1 to Q3: 0.7 to 3.2 mg/L). In multivariable analyses, parental hypertension was associated with higher serum C-reactive protein concentration in offspring (15% increase per parent with hypertension; P = 0.004). Prospectively, the relation of parental hypertension to longitudinal changes in blood pressure in the nonhypertensive offspring was attenuated on adjustment for C-reactive protein (P = 0.04 for attenuation). The levels of the other biomarkers evaluated did not significantly differ in offspring according to parental hypertension status. In conclusion, serum C-reactive protein concentrations are higher in nonhypertensive offspring of parents with hypertension. These data suggest that inflammation may partly mediate the familial influences on hypertension risk. (Hypertension. 2008;52:381-386.)

Key Words: hypertension ■ offspring ■ biomarkers ■ C-reactive protein

Elevated blood pressure (BP) is an important vascular risk factor associated with increased cardiovascular morbidity and mortality. Hypertension (HTN) is a condition with an enormous public health burden, affecting almost one third of all adults in the United States and is associated with substantial health care expenditure. Consequently, prevention of HTN is a public health priority. The underlying pathophysiology of elevated BP, however, is incompletely understood. BP is considered a complex trait influenced by several environmental and genetic factors, with approximately 30% to 60% of the interindividual variation in BP being attributed to additive genetic factors. It is well established that HTN clusters in families and that a positive family history represents a major risk factor for future HTN in nonhypertensive offspring.

Recent studies have indicated that circulating concentrations of several biomarkers that represent distinct biological pathways are correlated with BP levels cross-sectionally and are associated with a greater incidence of HTN prospectively. For instance, a recent investigation from the Framingham Heart Study demonstrated that circulating concentrations of C-reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1), and the urinary albumin:creatinine ratio (UACR) predict incident HTN in nonhypertensive individuals during short-term follow-up. Framingham investigators have also reported that serum aldosterone concentrations and the aldosterone:renin ratio (ARR) predict incident HTN. Furthermore, there is evidence that these biomarker levels are heritable traits like BP, raising the possibility that genetic influences on HTN risk may be mediated in part via these putative biomarkers. One approach for evaluating this premise is to examine whether concentrations of candidate biomarkers (known to be associated with the risk of developing HTN) are higher in offspring of parents with HTN. Indeed, a recent study reported that nonhypertensive children of parents with HTN had higher circulating concentrations of
CRP compared with children of parents without HTN. Other investigators have focused on circulating components of the renin-angiotensin-aldosterone system and urinary albumin excretion in offspring of parents with HTN, but the results have been conflicting. Previous studies were limited by the evaluation of only single biomarkers and by relatively small samples. To our knowledge, concentrations of multiple biomarkers have not yet been investigated systematically in nonhypertensive offspring of parents with HTN in a large community-based sample.

We hypothesized that, cross-sectionally, nonhypertensive offspring of parents with HTN will have higher levels of select biomarkers (that have been associated with HTN risk) compared with children of parents without HTN. We further postulate that the association of parental HTN with longitudinal BP tracking in the offspring is attenuated on adjustment for biomarkers that are related to parental HTN in the cross-sectional analysis.

Methods

Study Sample
The Framingham Heart Study was initiated in 1948 to investigate risk factors for cardiovascular disease in the community. Starting in 1971, the Framingham offspring study enrolled 5124 offspring of the original cohort and the spouses of the offspring. Participants of the Framingham offspring study cohort are examined at the heart study clinic approximately every 4 years. During these visits, participants undergo a targeted medical history and physical examination, including BP measurements (see below), and laboratory assessment of cardiovascular risk factors. The study protocols were approved by the Boston University Medical Center Institutional Review Board, and all of the participants gave written informed consent.

Offspring study participants who were nonhypertensive (BP <140/90 mm Hg and not on antihypertensive medications) and free of prevalent cardiovascular disease at the sixth examination cycle (1995–1998) were eligible for the present investigation if they had both parents in the original cohort (n = 1057) and nonmissing marker values (n = 1029). A total of 1804 participants with both parents in the original cohort attended examination 6 (77% of offspring cohort participants with both parents in the original cohort who were alive in 1995). A total of 1582 of those who attended examination 6 were free of cardiovascular disease and had nonmissing marker values. Of these, 1029 were nonhypertensive and included in the present analyses. These 1029 individuals belong to 662 families, with an average of 1.6 (range: 1.0 to 6.0) offspring per family. Parental HTN was defined as a BP ≥140/90 mm Hg or antihypertensive treatment at any time in life before the age of 60 years; we chose to define parental HTN before age 60 years, because the lifetime risk of HTN is the highest at any time in life before the age of 60 years; we chose to define parental HTN before age 60 years, because the lifetime risk of developing HTN is very high (90%);22 as such, few offspring will have parents who do not eventually develop HTN.

BP Measurement
During the visits at the Framingham Heart Study clinic, BP is measured by a physician on the participants’ left arm using a mercury column sphygmomanometer and a cuff of appropriate size after the individual has been seated in a chair for ≥5 minutes. After another 5 minutes, a second BP reading is obtained using the same protocol. The mean of both measurements is considered the examination BP.

Biomarker Measurements
At the sixth examination cycle, blood was drawn in the morning after an overnight fast with the participant in a supine position for ~5 to 10 minutes. Samples were immediately centrifuged, and plasma and serum were stored at −80°C until the biomarkers were measured. Of biomarkers measured at examination cycle 6, UACR, CRP, ARR, and PAI-1 have been associated with HTN incidence in this cohort. So, the present investigation focused on these biomarkers.

The UACR was measured on a spot urine sample obtained in the morning. Urine albumin was assessed quantitatively using an immunoturbidimetric test (Tinaquant Albumin assay, Roche Diagnostics), and urinary creatinine was determined with a modified Jaffe method. Interassay coefficients of variation for urinary albumin and urinary creatinine assays were 7.2% and 2.3%, respectively. High-sensitivity CRP was measured using a nephelometer (Dade Behring BN100) with an average interassay coefficient of variance of 2.2%. Serum aldosterone was measured using a radioimmunoassay (Quest Diagnostics) with an average interassay variation coefficient of 4.0% for high concentrations and 9.8% for low concentrations. Plasma renin was measured using an immunoenzymometric assay (Nichols assay, Quest Diagnostics) with an average coefficient of variation of 2.0% for high concentrations and 10.0% for low concentrations. Plasma levels of PAI-1 were measured with a commercially available ELISA, as described previously (TintEliza PAI-1, Biopool AB). The coefficient of interassay variation was 7.7%.

Statistical Analyses
Biomarkers with skewed distributions were natural logarithmically transformed before analyses. Clinical characteristics were descriptively compared between offspring with none, 1, or 2 parents with HTN using general estimating equations to account for correlations within families. A general estimating equation was also used to compare biomarker concentrations among offspring with 1 and 2 parents with HTN with levels in offspring of nonhypertensive parents adjusting for relevant covariates (model 1: age and sex; model 2: age, sex, body mass index [BMI], systolic and diastolic BP, total/high-density lipoprotein [HDL] cholesterol ratio, triglycerides, lipid lowering treatment, hormone replacement therapy, and smoking) that have been previously related to biomarker levels in our cohort. We used a trend test that models parental HTN as a 0, 1, and 2 variable because it maximizes statistical power and because previous Framingham data indicate a linear trend for increasing HTN incidence according to the number of parents with HTN.

To test the hypothesis that the higher risk of HTN in offspring with parental HTN was mediated by higher levels of a biomarker, we conducted additional analyses. First, we related parental HTN to change in systolic BP (SBP) during follow-up (ΔSBP; from examination cycle 6 to examination cycle 7) in the offspring who attended examination cycle 7 (n = 963) using censored normal regression models, adjusting for age, sex, BMI, systolic and diastolic BP, total/HDL cholesterol ratio, triglycerides, lipid-lowering treatment, hormone replacement therapy, and smoking at baseline. The approach proposed by Levy et al24 and Tobin et al25 was used to account for antihypertensive treatment on follow-up in some individuals. We evaluated the change in SBP alone (as opposed to systolic and diastolic BP), because systolic HTN is the most common form of HTN in the community in middle-aged-to-elderly adults (such as in our sample). Next, we adjusted for the biomarkers that were associated with parental HTN in the principal cross-sectional analyses detailed above. We evaluated whether the regression coefficient for parental HTN (for predicting longitudinal change in offspring SBP on follow-up) was attenuated by adjustment for the putative biomarkers. Significance level of the attenuation was tested using a nonparametric bootstrap with 4999 replications, as described in detail elsewhere.

Results

Baseline Characteristics
The clinical characteristics, as well as biomarker concentrations, of the study sample stratified by parental HTN status are displayed in Tables 1 and 2. Although all of the offspring had BP levels within the nonhypertensive range (by definition), offspring who had both parents with HTN displayed slightly higher levels for systolic and diastolic BPs compared...
Table 1. Clinical Characteristics Stratified by Parental HTN Status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No Parental HTN (n=233)</th>
<th>1 Parent With HTN (n=474)</th>
<th>2 Parents With HTN (n=322)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>58.2 (9.1)</td>
<td>53.9 (8.7)</td>
<td>52.3 (7.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Women, %</td>
<td>59.7</td>
<td>51.9</td>
<td>54.0</td>
<td>0.30</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>117 (12)</td>
<td>117 (11)</td>
<td>120 (11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>71 (8)</td>
<td>73 (8)</td>
<td>75 (7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.0 (4.7)</td>
<td>26.9 (4.7)</td>
<td>27.1 (4.5)</td>
<td>0.73</td>
</tr>
<tr>
<td>BMI ≥30 kg/m², %</td>
<td>21.5</td>
<td>20.3</td>
<td>23.7</td>
<td>0.66</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>212 (60)</td>
<td>206 (38)</td>
<td>206 (40)</td>
<td>0.88</td>
</tr>
<tr>
<td>Total:HDL cholesterol ratio</td>
<td>4.6 (3.6)</td>
<td>4.3 (1.5)</td>
<td>4.2 (1.5)</td>
<td>0.16</td>
</tr>
<tr>
<td>Triglycerides, mg/dL, median (Q1, Q3)</td>
<td>111 (75, 158)</td>
<td>106 (73, 146)</td>
<td>106 (75, 161)</td>
<td>0.70</td>
</tr>
<tr>
<td>Lipid-lowering treatment, %</td>
<td>2.6</td>
<td>4.6</td>
<td>5.0</td>
<td>0.014</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>13.7</td>
<td>15.4</td>
<td>19.3</td>
<td>0.24</td>
</tr>
<tr>
<td>Hormone replacement therapy, %</td>
<td>20.9</td>
<td>27.2</td>
<td>20.7</td>
<td>0.92</td>
</tr>
<tr>
<td>Blood sugar, mg/dL</td>
<td>98 (15)</td>
<td>98 (15)</td>
<td>98 (24)</td>
<td>0.69</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>3.0</td>
<td>4.2</td>
<td>4.3</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Values for clinical features are means (SD) or percentages.

*Data show the P value for trend in the number of patients with HTN adjusted for age and sex (except for age and sex characteristics).

with offspring of whom both parents were nonhypertensive. Furthermore, the mean age of nonhypertensive offspring participants decreased as the number of parents with HTN increased. Specifically, offspring with no parental HTN were, on average, 58.2 years old (range: 33 to 75 years); offspring with 1 or 2 hypertensive parents had a mean age of 53.9 years (range: 33 to 78 years) and 52.3 years (range: 35 to 71 years), respectively. Offspring mean levels of BMI, total cholesterol, and blood sugar and the offspring prevalence of obesity (BMI: ≥30 kg/m²), current smoking, and diabetes did not differ by parental HTN status (Table 1).

### Association of Parental HTN With Offspring Biomarker Levels

Mean CRP concentrations were higher in offspring with 1 or 2 parents with HTN compared with offspring of parents without HTN (Table 2). Regression analyses revealed a 15% increase in adjusted mean CRP concentrations per parent with premature HTN (P=0.004 for trend in a multivariant model adjusting for age, sex, BMI, systolic and diastolic BP, total:HDL cholesterol ratio, triglycerides, lipid-lowering treatment, hormone replacement therapy, and smoking; Table 3). Median and interquartile range for offspring ARR did not differ by parental HTN status (Table 2). However, regression analyses demonstrated a borderline significant 7% increase in offspring log-ARR levels per parent with HTN (Table 3). By contrast, concentrations of PAI-1 and UACR did not differ among the offspring according to parental HTN status (Tables 2 and 3). The power to detect a contribution to model R² of the magnitude observed for CRP was as follows: 90% for PAI-1, 82% for ARR, and 74% for UACR.

### Attenuation of Relation of Parental HTN to Longitudinal Change in Offspring BP on Adjustment for CRP

In the Framingham Offspring Study, parental HTN predicts incident HTN in the offspring. Consistent with this finding, we demonstrated in the present analyses that parental HTN was related to the change in SBP in the offspring (Table 4, model A). The mean increase in SBP during follow-up was 3.6 mm Hg (95% CI: 2.0 to 5.3 mm Hg), 2.0 mm Hg (95% CI: 0.8 to 3.1 mm Hg), and 4.7 mm Hg (95% CI: 3.3 to 6.0 mm Hg) in offspring with 0, 1, or 2 parents with HTN, respectively, after adjustments for baseline BP levels and antihypertensive treatment at examination cycle 7 (end of follow-up). Likewise, CRP at baseline was positively associated with ΔSBP during follow-up in the offspring (Table 4, model B). Importantly, the relation of parental HTN to ΔSBP in the offspring was attenuated on adjustment for CRP (Table 4, model C; P for attenuation=0.042).

### Discussion

**Principal Findings**

We evaluated the association of parental HTN status with circulating biomarker concentrations in nonhypertensive offspring in a large, community-based sample. Compared with nonhypertensive offspring of parents without HTN, offspring with 1 or 2 parents with HTN (before the age of 60 years) had higher mean CRP concentrations. This association remained
Table 3. Association of Parental HTN With Offspring Biomarkers

<table>
<thead>
<tr>
<th>Log Biomarker</th>
<th>Multivariable-Adjusted Model: Fold-Increase in Marker When Parental HTN Present*</th>
<th>P</th>
<th>Multivariable-Adjusted Model: Fold-Increase in Marker When Parental HTN Present*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein</td>
<td>1.13 (1.01 to 1.26)</td>
<td>0.03</td>
<td>1.15 (1.04 to 1.26)</td>
<td>0.004</td>
</tr>
<tr>
<td>PAI-1</td>
<td>1.00 (0.94 to 1.06)</td>
<td>0.98</td>
<td>1.00 (0.95 to 1.05)</td>
<td>0.97</td>
</tr>
<tr>
<td>Aldosterone/renin ratio</td>
<td>1.08 (1.00 to 1.15)</td>
<td>0.04</td>
<td>1.07 (1.00 to 1.15)</td>
<td>0.06</td>
</tr>
<tr>
<td>UACR</td>
<td>0.91 (0.77 to 1.07)</td>
<td>0.25</td>
<td>0.86 (0.72 to 1.02)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

The values in the parentheses are the 95% CI of the exponentiated regression coefficient. Multivariable model is adjusted for age, sex, BMI, SBP, diastolic BP, total:HDL cholesterol ratio, triglycerides, lipid-lowering treatment, hormone replacement therapy, and smoking.

*Data indicate the fold-increase in biomarker level per parent with HTN.

Comparison With Previous Findings

**CRP and HTN**

Our findings regarding the association of offspring mean CRP concentrations with parental HTN status are consistent with results of a much smaller study in children (n=120) reported by Diaz et al.15 The latter study evaluated adolescents (mean age: ≈18 years) from families recruited through hypertensive parents and did not analyze levels according to the number of parents with HTN. We confirm this association in a larger community-based sample of middle-aged men and women. Furthermore, we extend these findings by demonstrating that the mean CRP concentrations in nonhypertensive offspring increase with the number of parents with HTN.

We have reported previously that parental HTN predicts incident HTN.6 Consistent with these findings, we demonstrate that parental HTN predicts change in offspring SBP during follow-up. Of note, the association of parental HTN with change in SBP during follow-up was attenuated when CRP was incorporated into the multivariable model. This is consistent with the notion that the risk of an increase in offspring SBP on follow-up conferred by parental HTN may be mediated in part by the association of parental HTN with mean CRP concentrations in the offspring.

In previous cross-sectional and longitudinal studies, CRP concentrations have been shown to strongly correlate with BP levels27 and the incidence7 of HTN. Recently, using a multimarker approach to predict new-onset HTN, Wang et al12 demonstrated that CRP, UACR, and PAI-1 concentrations were significant correlates of incident HTN of a panel of biomarkers tested. In addition to being a marker of HTN risk, a causal role for CRP in the pathogenesis of high BP is supported by experimental studies.28 For instance, CRP has been shown to reduce the expression and bioactivity of the endothelial NO synthase and release of prostacyclin in human aortic endothelial cells.29,30 Endothelial NO synthase catalyzes endothelial synthesis of NO, which is a potent vasodilator.31 Furthermore, CRP leads to increased PAI-1 expression and activity in human aortic endothelial cells.32 In addition, CRP upregulates angiotensin type 1 receptors in vascular smooth muscle cells in vivo and in vitro.33 Importantly, the BP-modulating effects of the renin-angiotensin-aldosterone system are mediated through this receptor.34

The increased CRP concentrations in nonhypertensive offspring of parents with HTN suggest that CRP might be an important heritable intermediate phenotype for HTN. This is further supported by twin and population-based studies providing heritability estimates for CRP ranging from 20% to 52%.35,36

**Albuminuria and HTN**

Recent studies have demonstrated that UACR concentrations are positively associated with BP progression and the incidence of HTN in nonhypertensive individuals without diabetes in the community.11 In nonhypertensive offspring of parents with HTN, urinary albumin excretion has been found to be increased in some18 but not in other studies.19 In the present analyses, UACR measured in a spot urine was not related to the parental HTN status. This finding does not exclude the possibility that UACR may be a valuable marker of HTN risk.

**Renin-Angiotensin-Aldosterone-System and HTN**

Framingham investigators have shown previously that serum aldosterone concentrations and the ARR predict incident HTN8,9 and that the ARR has a substantial heritable component (h²=0.40). Data on plasma concentrations of circulating components of the renin-angiotensin-aldosterone system in offspring of hypertensive parents are sparse and have yielded...
inconsistent results.\textsuperscript{16,17} We observed a borderline statistically significant association of offspring ARR with parental HTN. However, considering the number of biomarkers tested and the level of significance, these findings have to be interpreted with caution.

**PAI-1 and HTN**

Framingham investigators and others have reported that PAI-1 concentrations also correlate positively with SBP cross-sectionally\textsuperscript{10,37} and are associated with incident HTN prospectively.\textsuperscript{12} In the present investigation, concentrations of PAI-1 in offspring did not vary according to parental HTN status. However, this finding does not exclude an important role for PAI-1 in the development of HTN.

**Strengths and Limitations**

The strengths of the present study include the large community-based design, the availability of a panel of biomarkers, and the standardized assessment of BP and clinical covariates. However, some limitations should be noted. We focused on biomarkers that have been associated previously with incident HTN in the Framingham offspring sample. Therefore, several other biomarkers linked to HTN in other samples (eg, fibrinogen\textsuperscript{58}) were not included in the present analyses, because these biomarkers were not associated with incident HTN or with BP progression in our sample.\textsuperscript{10,12} Furthermore, several other biomarkers that have previously been associated with parental HTN status in smaller studies (eg, leptin\textsuperscript{59}) were not measured in our cohort. In addition, all of the biomarkers were measured only on a single occasion, raising the possibility of misclassification. We did not have information regarding the presence of systemic inflammatory conditions in our participants at the baseline examination 6. Although such conditions can potentially alter biomarker concentrations, it is unlikely that the prevalence of these conditions will vary according to parental HTN status. Therefore, we would expect that a lack of adjustment for inflammatory conditions would result in non-differential misclassification, biasing the results toward a null hypothesis of no association of parental HTN with offspring CRP levels.

The UACR was measured in a spot urine sample and not in a 24-hour urine collection. However, urinary albumin excretion from spot urine has been shown to serve as an excellent predictive marker in previous studies.\textsuperscript{40} Good correlation between urinary albumin excretion measured in a 24-hour urine collection and in a spot urine have been reported.\textsuperscript{41} Lastly, our sample was composed of white individuals of European descent; the generalizability of our findings to other races and/or ethnicities is unknown.

**Perspectives**

Given the public health burden posed by high BP, it is important to identify nonhypertensive individuals who are at greatest risk of developing the condition and to elucidate biological mechanisms that underlie disease susceptibility. Circulating biomarkers offer a potential approach in this regard. Given the substantial heritability of HTN, we investigated whether offspring of individuals with high BP have an altered biomarker profile antedating the development of high BP. We examined the cross-sectional association of concentrations of 4 biomarkers, associated previously with incident HTN, in nonhypertensive offspring according to their parental HTN status. Compared with offspring without parental HTN, offspring with parental HTN had higher CRP concentrations. These data are consistent with the notion that inflammation may mediate, in part, the familial influences on HTN risk. Additional studies are warranted to confirm our findings and to investigate a larger panel of biomarkers in individuals with and without parental HTN.

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**Disclosures**

None.

**References**

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