Plasma Homocysteine Concentration and Blood Pressure in Young Adult African Americans

Rajani Dinavahi, Nicole Cossrow, Harvey Kushner, and Bonita Falkner

Background: An association of plasma homocysteine concentration ([Hcy]) with cardiovascular events has been described, but the role of [Hcy] in the early phase of cardiovascular disease is uncertain. The purpose of this study was to determine whether [Hcy] is related to blood pressure (BP) or other risk factors in African Americans, a population at high risk for cardiovascular disease.

Methods: This cross-sectional study was conducted on a sample of premenopausal African American women (N = 119) and men (N = 56), 30 to 40 years of age. Each subject was classified as normotensive or hypertensive. Fasting blood samples were obtained for serum lipids, insulin, glucose, Hcy, folate, and B-12, followed by an oral glucose tolerance test.

Results: Mean [Hcy] was higher in hypertensives compared to normotensives, but the difference was statistically significant only in women (10.5 ± 5.3 vs 8.2 ± 2.3; P < .01). In women, the simple correlation analysis revealed a statistically significant relationship of [Hcy] with systolic BP (r = 0.22, P = .02) and diastolic BP (r = 0.240, P = .01). However, after adjusting for age and body mass index (BMI), the correlations were attenuated and no longer significant. There was a significant inverse relationship of [Hcy] with plasma folate (r = −0.35, P < .001) and B-12 (r = −0.29, P < .01) in women.

Conclusions: Although the simple correlation coefficient suggests a significant relationship of [Hcy] with BP in women, this relationship was no longer statistically significant after adjustment for age and BMI. The significant inverse relationship of plasma folate and B-12 with [Hcy] suggest that diet factors may affect the crude [Hcy]–BP relationship identified in this sample. Am J Hypertens 2003;16:767–770 © 2003 American Journal of Hypertension, Ltd.

Key Words: Blood pressure, hypertension, homocysteine, folate, African American.

Cardiovascular diseases and stroke are the leading causes of morbidity and mortality.1 These disorders occur at disproportionately greater rates in African Americans compared to whites, especially in African American women compared to white women.2 Yet, there is little data to explain the excess prevalence and morbidity in this minority group.

Elevated plasma homocysteine concentration ([Hcy]) has been considered a possible risk factor for cardiovascular disease. In humans, the range for normal [Hcy] is between 5 and 15 μmol/L. Mild or moderate hyperhomocysteinemia and severe hyperhomocysteinemia are defined as 16 to 100 μmol/L, and >100 μmol/L, respectively.3 Several observational studies reported higher [Hcy] in patients with established vascular disease compared to controls.4 Hyperhomocysteinemia has been linked with histopathologic features of vessel injury, including proliferation of vascular smooth muscle cells, inhibition of fibrinolysis, and hemostatic changes suggestive of a prothrombotic state.3

Results of clinical investigations demonstrate an association of [Hcy] with cardiovascular endpoints including stroke, myocardial infarction, and peripheral vascular diseases.5,6 Epidemiologic investigations have identified an increasing relative risk for cardiovascular disease with increments in [Hcy].7,8 Data on white populations indicate that [Hcy] may be more predictive for cardiovascular disease in women.9,10 Recently, Kahleova et al11 reported higher [Hcy] in adolescents and young adults with hypertension compared to age-matched normotensives. These investigators also reported a statistically significant direct correlation of [Hcy] with systolic blood pressure (BP), suggesting that [Hcy] may have a role in the early stages of hypertension. There is a paucity of data on the relationship of [Hcy] with BP or other cardiovascular disease risk factors in African Americans. The purpose of this study...
was to determine whether there is a relationship of \([\text{Hcy}]\) with BP and other cardiovascular disease risk factors, including body mass index (BMI), glucose, insulin, lipids, and smoking status, in a young adult African American population.

**Methods**

**Population**

Participants in this study were African American men and premenopausal women, aged 30 to 40 years. Written informed consent was obtained from each participant at the time of enrollment on an institutionally approved consent form. Participants with known hypertension and who were taking antihypertensive medications were not withdrawn from their medication. Participants were excluded if they were diabetics or taking medications known to affect plasma [\(\text{Hcy}\)] including vitamin supplements.

**Procedures**

Each participant was questioned about his or her health status and current health behaviors, including smoking. Height and weight were obtained and BMI was calculated. The BP measurements were obtained from the subject after a 10-min rest period in a seated position using auscultation with a mercury column sphygmomanometer. The average of two determinations of systolic (first phase) and diastolic (fifth phase) were used as systolic BP and diastolic BP, respectively. An oral glucose tolerance test (OGTT) was conducted after a 12-h overnight fast. Diet history obtained on enrollment indicated that the usual carbohydrate intake was approximately 50% of total intake. Therefore, no dietary changes were made before OGTT. A fasting blood sample for serum lipids, insulin, homocysteine, folate, B-12, and glucose was obtained, followed by ingestion of 75 g of glucose. Blood samples were obtained at 30, 60, 90, and 120 min after ingestion and were assayed for glucose and insulin concentrations.

A fasting serum sample was sent to the Lipid Research Laboratory where total cholesterol, HDL cholesterol, and total triglycerides were analyzed with standard enzymatic methods. Low-density lipoprotein cholesterol was calculated by the Friedewald equation. Plasma glucose concentration was analyzed with the glucose oxidase technique (YS Model 27; Glucostat, Yellow Springs, OH). Plasma insulin, folic acid, and B-12 concentrations were determined by radioimmunoassay (DPC, Los Angeles, CA). Samples were assayed for [\(\text{Hcy}\)] by HPLC according to the methods of Jacobsen et al.

**Data Analysis**

Participants were stratified by sex and classified according to BP status as normotensive or hypertensive (systolic BP >140 mm Hg or diastolic BP >90 mm Hg or if the participant was taking antihypertensives). Sex-specific one-way analysis of variance (ANOVA) was used to compare mean values between hypertensives and normotensives. According to self-report on current smoking, cases were classified as smokers or nonsmokers. A sex-specific one-way ANOVA was also applied to mean [\(\text{Hcy}\)] values according to smoking status. To examine the relationship between parameters as continuous variables, a Pearson correlation coefficient was examined. To assess the influence of confounders, simple correlation coefficients were subsequently adjusted for the cofactors of age and BMI. For all statistical tests, a \(P\) value of < .05 was considered statistically significant.

**Results**

Data are presented on 175 participants (119 women and 56 men). Table 1 provides the sex-specific mean values of age, BMI, [\(\text{Hcy}\)], folate, and B-12 for hypertensives and normotensives. Mean age was higher in hypertensive compared to normotensive participants in both men \((P = .016)\) and women \((P < .001)\). The mean BMI for women and for hypertensive men was >30 kg/m².

Within each gender, the mean [\(\text{Hcy}\)] was higher in the hypertensives compared to the normotensives; however, this difference was statistically significant only in women \((P < .01)\). There was no significant difference in plasma folate or plasma B-12 between normotensives and hypertensives. Folate intake computed from diet history in a sample of cases \((N = 63)\) indicated a moderately lower

### Table 1. Mean values according to gender and blood pressure group

<table>
<thead>
<tr>
<th></th>
<th>Women (119)</th>
<th></th>
<th>Men (56)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (88)</td>
<td>H (31)</td>
<td>N (37)</td>
<td>H (19)</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>34.4 ± 5.7</td>
<td>39.4 ± 9.4</td>
<td>34.5 ± 5.4</td>
<td>37.7 ± 4.3</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>31.7 ± 7.5</td>
<td>34.6 ± 7.8</td>
<td>27.5 ± 5.9</td>
<td>30.3 ± 8.2</td>
</tr>
<tr>
<td><strong>SBP (mm Hg)</strong></td>
<td>115 ± 10</td>
<td>140 ± 15</td>
<td>121 ± 10</td>
<td>148 ± 15</td>
</tr>
<tr>
<td><strong>DBP (mm Hg)</strong></td>
<td>70 ± 7.3</td>
<td>90 ± 8</td>
<td>72 ± 7</td>
<td>94 ± 16</td>
</tr>
<tr>
<td><strong>Hcy (µmol/L)</strong></td>
<td>8.2 ± 2.3</td>
<td>10.5 ± 5.3</td>
<td>10.2 ± 1.9</td>
<td>11.4 ± 4.2</td>
</tr>
<tr>
<td>**Folate (ng/mL)</td>
<td>18.8 ± 7.3</td>
<td>17.5 ± 10.6</td>
<td>20.9 ± 9.5</td>
<td>20.4 ± 7.6</td>
</tr>
<tr>
<td><strong>B-12 (pg/mL)</strong></td>
<td>453 ± 222</td>
<td>436 ± 190</td>
<td>438 ± 190</td>
<td>461 ± 13</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation

\(N\) = normotensive; \(H\) = hypertensive; \(SBP\) = systolic blood pressure; \(DBP\) = diastolic blood pressure; \(Hcy\) = homocysteine.
folic acid intake in hypertensives compared to normotensives ($P = .05$). The [Hcy] was also compared between smokers ($N = 79$) and nonsmokers ($N = 96$). Among men, there was no significant difference in mean [Hcy] between smokers (10.4 ± 3.7) and nonsmokers (10.7 ± 2.2). Among women, the mean [Hcy] was significantly higher in smokers than nonsmokers (9.6 ± 4.3 vs 8.1 ± 2.3, $P < .02$).

To examine further the difference in [Hcy] between hypertensive and normotensive women, the sex-specific correlation coefficients of [Hcy] with the other parameters as continuous variables were examined. In African American women, [Hcy] was significantly correlated with both the systolic BP ($r = 0.22$, $P = .02$) and diastolic BP ($r = 0.24$, $P = .01$). There was no significant correlation in their male counterparts (systolic BP, $r = 0.05$, $P = .71$; diastolic BP, $r = 0.03$, $P = .83$). For women, when BMI and age were added as cofactors, the correlation coefficients for [Hcy] with systolic and diastolic BP were no longer statistically significant ($r = 0.152$ for systolic BP and $r = 0.094$ for diastolic BP). Because folate and B-12 are cofactors in homocysteine metabolism, correlation analyses were performed to determine whether [Hcy] was related to plasma folate or B-12 concentration. The correlation coefficients for folate and B-12 with [Hcy] in women and men were all negative, indicating an inverse relationship of [Hcy] with folate and B-12. In women, the correlation coefficients were statistically significant for folate ($r = -0.348$, $P < .001$) and B-12 ($r = -0.286$, $P = .002$). In men, the $r$ value was only marginally significant for folate ($r = -0.254$, $P = .057$).

Pearson’s correlation coefficients were also examined for [Hcy] with other risk factor parameters, including BMI, plasma lipids, glucose, and insulin. In men, the only modestly statistically significant (unadjusted) correlation coefficient for [Hcy] was plasma triglyceride ($r = 0.29$, $P = .05$). In women, there was a significant unadjusted correlation of [Hcy] with BMI ($r = 0.254$, $P = .005$) and triglycerides ($r = 0.258$, $P = .001$).

**Discussion**

Data on this sample of young, adult African Americans demonstrate a significant direct correlation of [Hcy] with systolic and diastolic BP in premenopausal women but not in men. However, when the correlation was adjusted for age and BMI in women, the relationship of [Hcy] with BP was no longer statistically significant. We detected some effect of smoking status on plasma homocysteine concentration among women, but not men. With the exception of a weak unadjusted relationship with plasma triglycerides, there were no other metabolic risk factors that were significant correlates of [Hcy] in this cohort. An inverse relationship of [Hcy] with plasma folate and B-12 was present and the correlation coefficients were highly significant in women, suggesting a possible dietary effect on [Hcy].

There were no cases of severe homocysteinemia in our sample of young African Americans, and with the exception of only two cases having mild elevation, all [Hcy] were in the normal range. The unadjusted relationship of [Hcy] with BP in women occurred within the normal range of plasma homocysteine. Other investigations have detected a positive relationship between homocysteine and BP.8,10 The Hordaland Homocysteine Study, which examined homocysteine and cardiovascular risk factors in over 12,000 Scandinavians detected a weakly positive association of homocysteine with systolic and diastolic BP, which was stronger in the elderly subjects.9 This is the first study to report on the relationship of homocysteine with BP in young adult African Americans. Although we detected a significant simple correlation coefficient of [Hcy] with BP in young adult women, this relationship was no longer significant after applying an adjustment for age and BMI in the analysis.

The relationship (unadjusted) between [Hcy] and BP in women but not men, may be consistent with data from several epidemiologic studies on white populations that report a stronger relationship of plasma [Hcy] with cardiovascular risk factors in women than in men.9,10 The gender difference in the relationship between [Hcy] and BP was also detected in an analysis of data from the Third National Health and Nutrition Examination Survey (1988–1994) by Lim and Cassano.14 These investigators reported that [Hcy] had an independent positive association with BP after adjusting for cardiovascular risk factors. They also found that a 1 SD increase in Hcy was associated with increases in systolic and diastolic BP of 0.5 and 0.7 mm Hg, respectively, in men, and of 0.7 and 1.2 mm Hg in women. It is proposed that Hcy may reduce the bioavailability of nitric oxide (NO), thereby decreasing endothelial-dependent vasodilation.15 This concept is supported by a study by Chambers et al,16 who demonstrated a marked reduction in endothelial-dependent vasodilation after elevation of [Hcy] by a methionine load. Experimental work in rodents has shown that both NO synthase activity and NO release in response to acetylcholine infusion are higher in women than in men.17 The sex difference in response may be because estrogen stimulates NO production. Thus, it is theoretically plausible that premenopausal women could express greater vascular sensitivity to variations in NO bioavailability, which may be modulated to some extent by [Hcy]. However, because we found that the relationship between [Hcy] and BP was no longer significant after adjusting for the covariates of age and BMI, this explanation has little support from our data.

Our data demonstrate the expected inverse relationship between [Hcy] and the B vitamins, folic acid, and B-12, which are cofactors in methionine metabolism. Dietary information from our sample suggested that the hypertensive women had a lower dietary intake of folic acid. The data from this study support an additional dietary explanation for the unadjusted positive relationship detected between [Hcy] and BP in the African American women.
The Dietary Approach to Stop Hypertension (DASH) study demonstrated the BP reduction effect of a diet that was high in multiple nutrients achieved by high intakes of fruits, vegetables, and low fat dairy foods. In the DASH study, the diet effect on lowering BP was greatest among the sample of African Americans with mild hypertension.\(^{18}\) Therefore, it is possible that the association of higher BP with higher [Hcy] that was detected in our sample of young adult African American women was a consequence of lower dietary intakes of vitamins critical in Hcy metabolism as well as other nutrients that have a beneficial effect on BP.

Our data do not demonstrate an independent effect of plasma [Hcy] on BP in young adult African Americans. The relationship of [Hcy] with BP that co-segregates with plasma [Hcy] on BP in young adult African Americans. Data from this study support the potential benefit of efforts to improve dietary intake of multiple nutrients along with smoking cessation as preventive measures in this high-risk population.

References