Cardiovascular Characteristics in American Youth With Prehypertension

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Background: Cardiovascular structure and function in youth with prehypertension have been incompletely investigated.

Methods: Casual and ambulatory blood pressure (BP) measurement, arterial stiffness, noninvasive hemodynamic profiles, and cardiac structure were studied in a twin cohort of American black and white youth (n = 942; mean age, 17.6 ± 3.3 years SD). A family history of essential hypertension was used as a proxy to study genetic susceptibility to prehypertension.

Results: The occurrence of prehypertension was approximately 12% in the entire sample. Body mass index and waist circumference were significantly greater in prehypertensive subjects than in normotensive subjects. The 24-h ambulatory systolic BP (SBP), 24-h ambulatory diastolic BP (DBP), nighttime ambulatory SBP, and nighttime ambulatory DBP were significantly elevated in prehypertensive subjects compared with normotensive subjects. In whites, prehypertensive subjects compared with normotensives showed increased radial (6.8 ± 0.1 vs 6.2 ± 0.1 m/sec, P < .001) and foot pulse-wave velocity (PWV) (7.4 ± 0.1 vs 7.0 ± 0.1 m/sec, P = .001).


Key Words: Prehypertension, youth, arterial stiffness, hemodynamics, left-ventricular structure and function, ambulatory blood pressure.

Current estimates suggest that 70 million Americans aged ≥20 years have prehypertension. The Framingham Heart Study showed that prehypertensive subjects were more likely to progress to hypertension than individuals with optimum blood pressure (BP). Several studies in adults further reported that prehypertension is associated with cardiovascular disease.

Prehypertension includes a sizable population of children and adolescents. The research on cardiovascular phenotypes of prehypertension, however, is incomplete in the pediatric literature. In particular, there is a paucity of phenotypic variation regarding the absolute or relative risks of cardiovascular disease in cardiovascular disease-free youth with this condition. As such, this cross-sectional study aimed at comprehensively investigating the cardiovascular structure and function characterized by prehypertension. The phenotypes included ambulatory BP measurement, arterial stiffness measured by pulse-wave velocity (PWV), hemodynamic profiles measured by noninvasive impedance cardiography, and cardiac structure measured by echocardiography in American black and white youth. In addition, we hypothesized that, as seen in hypertension, cardiovascular characteristics of prehypertension might vary with race. A family history of cardio-

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vascular disease is a proxy for genetic influence. Normotensive offspring of hypertensive subjects were found to be at higher risk for the development of essential hypertension.4 As such, a family history of essential hypertension was collected to study genetic susceptibility to prehypertension.

Twin studies provide an efficient research design for investigating the genetic and environmental influences underlying complex traits. The general quantitative phenotypes in twins were demonstrated to be normally distributed, and similar to those in the age-matched general population.5,6 As such, twins are representative of singleton populations. In particular, studies of twins have been a valid epidemiologic tool for hypertension.5,6 A large twin cohort of the Georgia Cardiovascular Twin Study was examined here.

Methods

Study Population

Data for this study were available for 942 twins (44.5% blacks) from the Georgia Cardiovascular Twin Study, including 232 monozygotic (MZ) and 253 dizygotic (DZ) pairs of same-sex as well as opposite-sex twins (mean age, 17.6 ± 3.3 years SD). Subject recruitment, zygosity, and determination of race were described previously.7 Body weight, height, and waist circumference were evaluated by using established protocols.8 All subjects were apparently healthy, based on parental report of the child’s medical history. Informed consent was provided by all subjects, and by parents if participants were aged <18 years. This study was approved by the Institutional Review Board at the Medical College of Georgia.

Smoking status was determined by self-report, using a questionnaire-based survey (http://www.cdc.gov/mmwr/). Smokers were defined as those who reported smoking any cigarettes in the past 30 days; heavy smokers were defined as those who reported smoking ≥10 cigarettes/day; light smokers were defined as those who reported smoking <10 cigarettes/day; and nonsmokers were defined as those who reported smoking 0 cigarettes/day. A positive family history of essential hypertension was defined as the occurrence of hypertension in one or both biological parents.

Casual BP and Hemodynamic Measurements

Casual BP and hemodynamics were automatically measured in supine position over a 15-min resting period. The testing procedure was described previously.9 Briefly, hemodynamics and heart rate (HR) were measured using a Dinamap 1846 SX (Criticon, Inc., Tampa, FL). Stroke volume (SV) and cardiac output (CO) were obtained by bioimpedance cardiography (NCCOM-3, BoMeD Medical Manufacturing, Ltd, Big Lake, MN). Cardiac output was indexed by body surface area (ie, cardiac index, CI). The total peripheral resistance index (TPX) was calculated as mean arterial pressure/CI. Measurements were taken at 11, 13, and 15 min, during a 15-min period in which subjects were instructed to relax as completely as possible while lying supine on a hospital bed with their heads resting on a pillow. The average of three measurements was used to represent hemodynamic data.

Ambulatory BP Measurement

Our procedures for ambulatory BP recordings were previously described in detail.10 Briefly, the ambulatory BP monitor was fitted to the nondominant arm (model 90207, SpaceLabs, Redmond, WA). Measures were obtained every 20 min during the day (8 AM to 10 PM) and every 30 min at night (12 midnight to 6 AM). Transitional periods from 6 AM to 8 AM and 10 PM to midnight were not included in analyses. The adequacy of recordings was based on acceptable readings using previously established criteria10 for ≥14 readings over the 14 h designated as daytime and ≥6 readings over the 6 h designated as nighttime, as suggested by the European Society of Hypertension Working Group on Blood Pressure Monitoring.11

PWV Measurements

Carotid-radial (radial) PWV and carotid-dorsalis-pedis (foot) PWV were measured noninvasively with application tonometry (Millar Instrument, Inc., Houston, TX) and commercially available acquisition and analysis software (SphygmoCor, AtCor Medical, Sydney, Australia). Pressure waves were recorded at the common carotid and radial arteries for radial PWV, and at the common carotid and dorsalis-pedis arteries for foot PWV. The PWV was then automatically calculated from measurements of pulse transit time and the distance traveled by the pulse between the two recording sites: PWV = Distance (meters)/Transit time (seconds).

Echocardiographic Measurements

Two-dimensional directed M-mode echocardiograms were performed using a Sonos 1500 echocardiograph (Hewlett-Packard, Andover, MA). Left-ventricular posterior wall thickness in diastole (LVPWD), interventricular septal thickness in diastole, and left-ventricular internal dimension in diastole (LVIDd) were measured according to the American Society of Echocardiography Convention.12 Left-ventricular mass (LVM) was derived using the formula of Devereux et al,13 which was validated for use in individuals with normal cardiac function. Based on the recommendation of de Simone et al,14 LVM was divided by height2.7 to adjust for normal growth (LVM). Relative wall thickness (RWT) was calculated as: RWT = (LVPWD + IVD)/LVIDd.

Definition of Prehypertension

Casual BP measurements were used to define normotensive and prehypertensive subjects. For individuals aged
Ages 18 years, according to age, sex, and height, prehypertension was defined as an average BP/DBP ≥90th and ≤95th percentile of SBP or DBP, or SBP/DBP ≥120/80 mm Hg. Height percentiles were determined by the Standard Height Charts of the 2000 Center for Disease Control Growth Charts (http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm). For subjects aged ≥18 years, those with SBP/DBP 120 to 139/80 to 89 mm Hg were considered prehypertensive.

#### Statistical Analyses

Statistical analyses were performed with STATA 8.0 (Stata Corp., College Station, TX). The sex ratio among normotensive subjects and prehypertensive subjects was compared by χ² test in blacks and whites separately. Values for continuous variables are presented as adjusted mean ± standard error (SE). Log-transformation was performed to obtain an approximation of normal distribution when necessary. Age among normotensive and prehypertensive subjects was compared by one-way ANOVA. Differences in continuous variables between normotensive and prehypertensive subjects were compared by generalized estimating equations (GEE), a regression technique that allows for the relatedness between twins, and yields unbiased SEs and P values. The differences among normotensive and prehypertensive subjects were compared in blacks and whites separately. All analyses were adjusted for possible confounders, including age, sex, and body mass index (BMI). The interactions between race and BP categories were also tested. P < .05 was deemed statistically significant.

### Results

#### General Characteristics

The presence of prehypertension was slightly more common in blacks than in whites, at 13% vs 11% (P > .05), respectively. Regardless of race, prehypertensive subjects were older than normotensive subjects, and prehypertension was more common in males than in females (Table 1). In blacks and whites, prehypertensive subjects had a greater BMI and waist circumference than normotensive subjects. Furthermore, there were greater percentages of smokers and heavy smokers in prehypertensive than normotensive subjects, especially among blacks.

#### Family History of Essential Hypertension

Prehypertensive subjects were more likely to have a positive family history of essential hypertension than normotensive subjects, although the difference was only statistically significant in blacks.

#### Ambulatory BP

In 432 subjects with valid ambulatory BP measurement, all ambulatory BP measures, including 24-h, daytime, and nighttime BP, were significantly elevated in prehypertensive subjects compared with normotensive subjects in both racial groups (Table 2).

#### Hemodynamics

In whites, TPX was significantly elevated in prehypertensive subjects compared with normotensive subjects (Table 3). In whites, mean HR was elevated in prehypertensive subjects compared with normotensive subjects. In blacks,

### Table 1. General characteristics and blood pressure of NTs and PHTs

| Phenotypes | Whites | | | Blacks | | | Overall | | | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | NTs | PHTs | Overall | NTs | PHTs | Overall |
| N | 474 | 58 | 532 | 353 | 57 | 410 |
| Age (y) | 17.6 (3.1) | 20.4 (3.6)† | 17.9 (3.3) | 16.8 (2.8) | 20.2 (3.8)† | 17.3 (3.2) | .003 |
| Male/female | 218/256 | 47/11† | 265/267 | 148/205 | 33/24† | 181/229 | .098 |
| BMI (kg/m²)* | 22.9 (0.3) | 25.0 (0.5)† | 23.0 (0.3) | 24.3 (0.4) | 25.7 (0.5)† | 24.6 (0.3) | <.001 |
| Waist (cm)* | 78.7 (0.7) | 84.6 (1.3)† | 79.0 (0.8) | 78.2 (0.8) | 81.4 (0.1)† | 79.0 (0.8) | .853 |
| Casual SBP (mm Hg)* | 108 (0.4) | 124 (1.0)† | 110 (0.5) | 111 (0.4) | 126 (1.0)† | 113 (0.5) | <.001 |
| Casual DBP (mm Hg)* | 57 (0.3) | 64 (0.8)† | 58 (0.3) | 60 (0.4) | 65 (0.8)† | 61 (0.4) | <.001 |
| Family history of hypertension (%) | 31.3 | 48.0 | 32.2 | 35.5 | 58.3 | 39.0 | .143 |
| Smoker (%) | 20.3 | 22.4 | 20.6 | 8.8 | 21.1† | 10.2 | <.001 |
| Heavy smoker (%) | 5.7 | 12.1 | 6.5 | 2.0 | 7.0† | 2.5 | .004 |

Mean ages (SD) between groups were compared by t test.
Analyses of differences in anthropometric variables between groups were adjusted for age and sex. Age, sex, and body mass index (BMI) were adjusted in comparisons of casual systolic blood pressure (SBP) and diastolic blood pressure (DBP). Data were adjusted mean (SE), unless indicated otherwise.

NTs = normotensive subjects; PHTs = prehypertensive subjects.
* P values were based on log-transformed data. P values are based on the difference between blacks and whites.
† P < .05 for the difference between NTs and PHTs.
but not in whites, both CO and CI were greater in prehypertensive than in normotensive subjects, respectively.

Cardiovascular Structure and PWV

As seen in Table 4, in blacks, there were no statistical differences in radial and foot PWV between normotensive and prehypertensive subjects. In whites, there was a significant elevation of both radial PWV and foot PWV from normotensive to prehypertensive subjects. After adjustment for SBP and DBP, in whites, radial PWV still remained higher in prehypertensive than in normotensive subjects (6.6 ± 0.2 m/sec vs. 6.2 ± 0.1 m/sec, P = .025). The LVMI was significantly greater in black prehypertensive subjects than in black normotensive subjects (33.0 ± 0.9 vs. 31.3 ± 0.4, respectively; P = .03), although the significance disappeared after adjustment for age, sex, and BMI.

Discussion

This study attempted to evaluate the cardiovascular risk profile in prehypertension compared with normotension in American youth. The rate of prehypertension was approximately 12% in this young cohort. Data indicate that essential hypertension is prevalent in adult residents in the southeastern United States. In the present study, a positive family history of essential hypertension occurred more commonly in prehypertensive than in normotensive youth, especially in black youth. This suggests that prehypertensive subjects may have a preexisting genetic predisposition to BP elevation.

Self-reported smoking status and heavy smoking status were associated with the presence of prehypertension, although statistical significance was found only in blacks. The impact of smoking, including environmental tobacco smoke exposure, on the development of prehypertension in youth deserves further evaluation, using physiological measures such as carbon monoxide and cotinine.

Prehypertensive subjects had increased BMI and waist circumference compared with normotensive subjects in both racial groups. In a recent study of 560,588 individuals aged 16.5 to 19 years, a substantial number of prehypertensive adolescents exhibited a BMI greater than normal. Our data support the contention that prehypertension dur-

### Table 2. Ambulatory blood pressure between NTs and PHTs in blacks and whites

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>NTs</th>
<th>PHTs</th>
<th>NTs</th>
<th>PHTs</th>
<th>P (Race * BP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>209</td>
<td>26</td>
<td>156</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>24-h SBP (mm Hg)*</td>
<td>113 (0.4)</td>
<td>120 (1.0)†</td>
<td>114 (0.4)</td>
<td>120 (1.1)†</td>
<td>.048</td>
</tr>
<tr>
<td>Daytime SBP (mm Hg)*</td>
<td>117 (0.5)</td>
<td>124 (1.2)†</td>
<td>118 (0.5)</td>
<td>124 (1.1)†</td>
<td>.077</td>
</tr>
<tr>
<td>Nighttime SBP (mm Hg)*</td>
<td>107 (0.5)</td>
<td>113 (0.8)†</td>
<td>107 (0.5)</td>
<td>113 (0.8)†</td>
<td>.320</td>
</tr>
<tr>
<td>24-h DBP (mm Hg)*</td>
<td>66 (0.3)</td>
<td>69 (0.8)†</td>
<td>65 (0.3)</td>
<td>69 (0.8)†</td>
<td>.135</td>
</tr>
<tr>
<td>Daytime DBP (mm Hg)*</td>
<td>70 (0.4)</td>
<td>73 (0.9)†</td>
<td>69 (0.4)</td>
<td>73 (0.9)†</td>
<td>.179</td>
</tr>
<tr>
<td>Nighttime DBP (mm Hg)*</td>
<td>58 (0.4)</td>
<td>61 (0.7)†</td>
<td>58 (0.4)</td>
<td>61 (0.6)†</td>
<td>.612</td>
</tr>
</tbody>
</table>

Data were adjusted means (SE) after adjustment for age, sex, and body mass index.
NTs = normotensive subjects; PHTs = prehypertensive subjects; SBP = systolic blood pressure; DBP = diastolic blood pressure.
Race * BP indicates interaction between race and blood pressure categories.
* P values were based on log-transformed data.
† P < .05 for the difference between NTs and PHTs.
Cardiovascular structure and pulse-wave velocity between NTs and PHTs in blacks and whites after adjustment for age, sex and body mass index

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Whites</th>
<th></th>
<th>Blacks</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NTs</td>
<td>PHTs</td>
<td>NTs</td>
<td>PHTs</td>
<td>(Race * BP)</td>
</tr>
<tr>
<td>Radial PWV (m/sec)*</td>
<td>6.2 (0.1)</td>
<td>6.8 (0.1)†</td>
<td>6.7 (0.1)</td>
<td>6.7 (0.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Foot PWV (m/sec)*</td>
<td>7.0 (0.1)</td>
<td>7.4 (0.1)†</td>
<td>7.2 (0.1)</td>
<td>7.2 (0.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>LVMI*</td>
<td>31.1 (0.3)</td>
<td>31.4 (0.9)</td>
<td>31.4 (0.4)</td>
<td>32.6 (0.8)</td>
<td>0.458</td>
</tr>
<tr>
<td>IVSD (cm)*</td>
<td>0.8 (0.0)</td>
<td>0.8 (0.0)</td>
<td>0.8 (0.0)</td>
<td>0.8 (0.0)</td>
<td>0.634</td>
</tr>
<tr>
<td>LVIdD (cm)*</td>
<td>4.8 (0.0)</td>
<td>4.7 (0.1)</td>
<td>4.7 (0.0)</td>
<td>4.7 (0.1)</td>
<td>0.181</td>
</tr>
<tr>
<td>LVPWD (cm)*</td>
<td>0.8 (0.0)</td>
<td>0.8 (0.0)</td>
<td>0.8 (0.0)</td>
<td>0.8 (0.0)</td>
<td>0.615</td>
</tr>
<tr>
<td>RWT*</td>
<td>0.3 (0.0)</td>
<td>0.4 (0.0)</td>
<td>0.4 (0.0)</td>
<td>0.4 (0.0)</td>
<td>0.162</td>
</tr>
</tbody>
</table>

Data were adjusted means (SE) after adjustment for age, sex, and body mass index. NTs = normotensive subjects; PHTs = prehypertensive subjects; LMVI = left-ventricular mass/height²; IVSD = interventricular septal thickness in diastole; LVIdD = left-ventricular internal dimension in diastole; LVPWD = left-ventricular posterior wall thickness in diastole; PWV = pulse-wave velocity; RWT = relative wall thickness.

Race * BP indicates interaction between race and blood pressure categories.

* P values were based on log-transformed data.
† P < .05 for the difference between NTs and PHTs.

Consistent with previous findings, we observed that TPR, TPX, and HR, but not CO or CI, were elevated in white prehypertensive subjects compared with white normotensive subjects. These findings indicate that prehypertension in young whites may be neurogenic, largely driven by excessive sympathetic tone. This was supported by our findings of higher HR in prehypertensive white youth. In another Atherosclerosis Risk in Communities study consisting of 3275 subjects aged 45 to 64 years, King et al demonstrated that elevated HR contributes to increased coronary heart-disease risk in subjects with prehypertension. Heart rate in prehypertensive subjects was thought to possess a long-term prognostic value for coronary heart disease. The observation that CO was increased from black normotensive subjects to black prehypertensive subjects implies the contribution of extracellular volume expansion. Prehypertension in black youth might be associated with salt sensitivity and sodium retention, which is driven by excessive activity of the renin-angiotensin aldosterone system as BP elevation progresses. These observations of race-related differences in the hemodynamic characteristics of prehypertension need to be verified in future studies, including biomarkers such as plasma renin activity. In addition, there were no statistical differences in the parameters of left-ventricular structure between normotensive and prehypertensive subjects. This suggests that prehypertension in youth might occur at an early stage of the adaptations and alterations in ventricular structure.

Ambulatory BP measurement is considered to provide more accurate BP measurement, and to predict cardiovascular risk more accurately than casual BP measurement. Ambulatory BP measurement offers advantages over casual BP readings, such as tracking circadian BP patterns, and excluding white-coat effect and masked BP elevation. However, only a few studies of prehypertension measured ambulatory BP levels, and even fewer studies are available in youth. In the subjects available for ambulatory BP analyses, both in blacks and whites, prehypertensive compared with normotensive subjects had greater ambulatory SBP and DBP values, including daytime and nighttime. Thus individuals with prehypertension, as defined by casual BP readings, may have a consistent elevation of BP throughout the 24-h period.

This study was limited by its cross-sectional design. Longitudinal analyses with repeated measures would provide the dynamic changes of cardiovascular structure and function in the development of prehypertension. Our association observations cannot answer the chicken-and-egg question, namely, whether prehypertension is a cause or a consequence of the unfavorable cardiovascular phen-
types in these young individuals. We speculate that prehypertension plays an important role in the development of cardiovascular disease in their adulthood. There are additional limitations in the present study. First, the use of the dorsalis-pedis (foot) as an alternative to the femoral measurement site was considered less sensitive, although it was more readily accepted by the young subjects. Foot PWV represents a mixture of both proximal elastic arteries and distal muscular arteries. Some discrepancies with other reports that typically measured carotid-femoral PWV are thus expected. However, our previous findings revealed that foot PWV, as a combination of central and peripheral measures, was more strongly correlated with age than was radial PWV. Foot PWV is comparable with the characteristics of carotid-femoral PWV. Second, according to the guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the classification of prehypertension requires two or more office visits. In this study, prehypertension was classified during a single office visit, although BP was taken with caution, and the average of three measures was used. Moreover, the casual BP data were supported by the ambulatory BP data. Third, the use of Dinamap to measure BP has been criticized. However, BP measurements performed with the use of Dinamap were also shown to be highly reproducible. Because BP measurements were performed with the same device throughout the entire study, the use of Dinamap could not have caused the observed differences in BP between the two racial groups. Moreover, as discussed above, the casual BP data collected by the Dinamap were in agreement with the ambulatory BP data among the three BP groups. Third, there is concern about the accuracy of hemodynamic assessments such as CO by impedance cardiography. Nevertheless, this technique is noninvasive, and thus feasible for studies with large populations. Fourth, the phenotypic differences between the two racial groups should be interpreted with caution, and are in need of independent replication in other cohorts.

In conclusion, our data show that prehypertension compared with normotension exhibited unfavorable cardiovascular phenotypes. Although there is certainly a continuum of cardiovascular risk across levels of BP, the new term “prehypertension,” a higher-than-normal BP, would help to differentiate levels of risk, reinforce preventative approaches, and define treatment thresholds. 

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