Heritability of Blood Pressure and Hemodynamics in African- and European-American Youth

Harold Snieder, Gregory A. Harshfield, Frank A. Treiber

Abstract—Hypertension prevalence is much higher in African-Americans (AAs) than in European-Americans (EAs). It is unknown whether this difference is related to potential ethnic differences in the relative contribution of genes and environment to population variation in blood pressure and underlying hemodynamics. We studied 308 EA and 226 AA twin pairs, including monozygotic and dizygotic twins, of the same as well as the opposite sex (mean±SD age, 14.7±3.1 years). Supine resting systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure, and heart rate (HR) were measured by a Dinamap instrument and hemodynamics (stroke volume, cardiac index, and total peripheral resistance [TPR] index) by impedance cardiography. Ethnic and sex effects on genetic and environmental contributions to resting blood pressure and hemodynamics were estimated by genetic model fitting. For most measures, the best-fitting model showed no differences in heritability between AAs and EAs or between males and females, with heritabilities of 0.50 for cardiac index, of 0.64 for HR, and of SBP, pulse pressure, and stroke volume in between. Heritability of DBP was 0.45 in EAs and 0.58 in AAs with no effect of sex. For TPR index in EAs, 46% of the variance could be attributed to familial effects, but no significant distinction could be made between shared environmental and genetic factors. Heritability of TPR index in AAs was 0.51. Adjustment for obesity yielded virtually identical heritabilities. In summary, relative influences of genetic and environmental factors on blood pressure and hemodynamics in AA and EA youth are similar and independent of (genes for) obesity. (Hypertension. 2003;41:1196-1201.)

Key Words: blood pressure • hemodynamics • genetics • twins • blacks

The prevalence of essential hypertension in African-Americans (AAs) is more than twice that of European-Americans (EAs). Longitudinal studies show that ethnic differences in blood pressure (BP) levels are already present in childhood, but possible causes of this difference remain to be elucidated. Some researchers have proposed a major role for environmental factors. Anderson’s contextual model of stress-induced hypertension, for example, hypothesizes that the greater prevalence of hypertension in AAs is principally due to differential exposure to chronic social and environmental stressors in AAs compared with EAs. Others have put forward genetic explanations for higher BP in AAs, such as the slavery hypothesis, which states that selection pressures occurring during the trans-Atlantic slave trade and New World slavery itself favored those genetically best equipped to retain sodium and water. Recent studies in black Londoners of Caribbean and West African origin reported that allelic variants responsible for increased BP in the G protein β3 subunit and the β-subunit of the epithelial sodium channel showed a much higher frequency in blacks compared with whites. Findings such as these might indicate that genetic polymorphic variation underlying BP variance might be more important within black populations compared with white populations.

The question whether the relative influence of genetic and environmental factors on individual differences in BP within the black population is different from that in the white population is most efficiently addressed by a classic twin study including both ethnic groups living in the same area. Previous twin studies have found heritabilities around 50% for both systolic (SBP) and diastolic (DBP) BP but have mostly involved white twins and, with 1 exception, did not include measures of BP hemodynamics.

The main aim of our study was, therefore, to estimate and compare the relative influence of genetic and environmental factors on BP and underlying hemodynamics in a large sample of young EA and AA twins from the southeastern United States. We further investigated to what extent heritable influences on BP hemodynamics might be due to obesity, an important covariate of BP hemodynamics that might explain part of its familial aggregation.

Methods

Study Population
Subjects were 308 EA and 226 AA twin pairs, including monozygotic (MZ) and dizygotic (DZ) pairs of the same as well as the opposite sex (mean±SD age, 14.7±3.1 years; range, 10.0 to 25.9
years). Zygosity determinations and recruitment of twin pairs into the Georgia Cardiovascular Twin Study have been described previously, as have been the criteria to classify subjects as AA or EA. Self-identification of ethnicity, as used here, was strongly advocated for purposes of human categorization in biomedical and genetic research in a recent publication.

All subjects were apparently healthy, based on (parental) report of the child’s medical history. Three twin pairs were excluded because 1 twin of each pair had an SBP \( \geq 160 \text{ mm Hg} \) or a DBP \( > 90 \text{ mm Hg} \). None of the subjects used any antihypertensive medication.

### Measures

After arrival in the laboratory, anthropometric data were evaluated by using established protocols. Next, participants were instrumented for the recording of BP and heart rate (HR) by Dinamap (model 1864 SX) and of stroke volume and cardiac output by bi impedance cardiography (NCCOM-3, BoMed Medical Manufacturing Ltd). Pulse pressure was calculated (SBP – DBP) as a proxy for arterial stiffness. The NCCOM-3 yields reliable and valid measures of cardiac output when compared with simultaneous thermodilution and Fick-derived measures of cardiac output obtained from supine individuals. Cardiac output was indexed by body surface area (ie, cardiac index). Total peripheral resistance (TPR) index was calculated as mean arterial pressure/cardiac index. Bioimpedance measures were not available for 8 subjects because of equipment failure. As a result, 8 twin pairs were excluded from the analyses of these variables. Measurements were taken at 11, 13, and 15 minutes while the subjects lay (supine) on a hospital bed. The average of the 3 measurements was used.

### Analytical Approach

The main aim of our analyses was to estimate the relative influence of genetic and environmental factors on individual differences in resting BP and hemodynamics and to test for their dependence on ethnicity and sex. First, we conducted model-fitting analyses for AA and EA twins separately to estimate ethnicity-specific genetic and environmental variance components and investigate sex differences. Eventually we combined both ethnic groups into 1 model to test for potential differences in AAs and EAs. Because obesity is an important covariate of BP hemodynamics and might explain part of its familial aggregation, we performed all model-fitting analyses before and after adjustment for body mass index (BMI). A path diagram of the applied twin model is shown in the Figure; \( k \) is the scalar factor that indicates that the total variance of the phenotype might differ between males and females.

SBP, DBP, pulse pressure, and TPR index were logarithmically transformed before analysis to obtain normal distributions. Standard hierarchical \( \chi^2 \) tests were used to select the best-fitting models in combination with Akaike’s information criterion (AIC = \( \chi^2 - 2 \text{ df} \)).

Ethnic and sex effects on mean values of resting BP and hemodynamics were tested in regression models that included ethnicity, sex, and their interaction by generalized estimating equations, which take the nonindependence of twin data into account and yield unbiased probability values. Genetic modeling was carried out with MX.

### Results

Table 1 shows mean values of general characteristics and hemodynamics for EA and AA males and females in the twin sample. As shown in Table 1, age, height, weight, and BMI were very similar for AAs and EAs. In this sample of youth with a mean age of 14.7 years, AAs already show significantly higher SBP, DBP, and TPR index and significantly lower cardiac index compared with EAs. Pulse pressure, HR, and stroke volume did not differ. Males were taller and heavier and showed higher SBP, pulse pressure, and TPR index but lower DBP, HR, and cardiac index than females.

Table 2 shows the twin correlations for each sex-by-zygosity group in EAs and AAs before and after adjustment for BMI. MZ correlations show consistently higher values than do DZ correlations, indicating an important contribution of genetic factors. The only exception is TPR index in EAs, where MZ and (same-sex) DZ correlations were similar, pointing to a shared environmental effect. Adjusting for BMI only had a minimal effect on the twin correlations. Separate model-fitting analyses in AA and EA twins allowed us to estimate ethnicity-specific genetic and environmental variance components and investigate sex differences. These results are not shown but helped guide our eventual model fitting in which we included both ethnic groups into 1 model. Within this model, including all 10 sex-by-ethnicity-by-zygosity groups, we tested for potential differences in AA and EA variance components and selected the best-fitting overall model for each variable. Parameter estimates and 95% confidence intervals (CIs) of these best-fitting models are presented in Table 3. For most measures (SBP, pulse pressure, HR, stroke volume, and cardiac index), the best-fitting model showed no differences in heritability between AAs and EAs or between males and females, with heritabilities of 0.50 for cardiac index and 0.64 for HR and intermediate heritability estimates for SBP (0.57), pulse pressure (0.54), and stroke volume (0.56). For SBP, a significant scalar effect for ethnicity was found, indicating that AAs show larger variability in SBP than do EAs. For cardiac index, males showed smaller variability than females. The best-fitting model for DBP yielded different heritability estimates for AAs and EAs, but these differences were not statistically significant, as shown by the overlap in 95% CIs. DBP heritabilities in this model were 0.45 in EAs and 0.58 in AAs, with no effect of sex. However, there was a sex effect on the total variance of DBP, with males showing larger variability in EAs.
smaller variability in AAs. For TPR index in EAs, no statistically significant distinction could be made between a model that attributed familial resemblance solely to shared environmental or genetic factors, and a model that included both components (ACE model) is reported in Table 3. No contribution of shared environment was found in AAs, with the best-fitting model showing a heritability estimate of 0.51. Just as for DBP, male TPR variability was larger than female variability in EAs but smaller in AAs.

Table 4 shows parameter estimates and 95% CIs of the best-fitting models after all variables were adjusted for BMI. Comparison with Table 3 shows that in general, heritability estimates become somewhat smaller after BMI adjustment, but only very slightly so.

**Discussion**

We estimated and compared the influence of genetic and environmental factors on BP and underlying hemodynamics...
in a large sample of young EA and AA twins from the southeastern United States. Relative contributions of genetic and environmental factors to BP variability in AA youth were similar to those in EA youth, the same in males and females, and consistent with heritability estimates for BP in white twins. 10-11

Previous twin studies have found heritabilities of ≈ 50% to 60% for both SBP and DBP but have almost exclusively involved white twins, 11 and only 1 small study included measures of BP hemodynamics. 9 Here we show that heritabilities for pulse pressure, HR, stroke volume, cardiac index, and TPR index (in blacks) are similar to those for BP and, except for TPR index, these estimates do not show any significant differences between AAs and EAs. The clear genetic basis of these hemodynamic variables underlying BP regulation merits inclusion in studies designed to identify specific genetic determinants for BP and hypertension. Heritability estimates were virtually identical after adjustment for BMI, supporting the conclusion that our findings in this sample of young subjects are largely independent of obesity.

Heritability estimates were somewhat higher than in our study for stroke volume (0.78), cardiac index (0.64), and TPR (0.78). Excess sib-pair similarity is likely to have been induced by the selection of affected sib pairs in this study (both sibs needed to be hypertensive and hyperlipidemic). Bielen et al 9 used Doppler echocardiography to measure stroke volume, cardiac output, and TPR in a small (32 MZ and 21 DZ pairs) sample of male white twins between 18 and 31 years and reported heritabilities of 0.69, 0.36, and 0.66, respectively.

To the best of our knowledge, this is the first twin study to directly compare and test differences in the relative influence of genetic and environmental factors on BP and hemodynamics in AAs and EAs. Most twin studies were conducted in white populations, and some studies combined twins from different ethnic groups without reporting separate heritability estimates. 11 An early study by Havlik and colleagues 24 in 7-year-old twins is the only 1 that did report BP heritabilities in blacks and whites separately, but no formal tests of ethnic differences were conducted. Weinberg et al 25 estimated hereditary and environmental influences on BP in black and white children in the Bogalusa Heart Study. However, the derivation of genetic and environmental estimates was based on a comparison of full sibs with half sibs, which severely limited the power of their study and yielded unreliable estimates of heritabilities.

### Table 3: Parameter Estimates and 95% CIs of Best-Fitting Models

<table>
<thead>
<tr>
<th>Measure</th>
<th>European Americans</th>
<th>African Americans</th>
<th>Scalar Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>h² (95% CI)</td>
<td>c² (95% CI)</td>
<td>e² (95% CI)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>0.57 (0.49–0.63)</td>
<td>0.43 (0.37–0.51)</td>
<td>0.57 (0.49–0.63)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>0.45 (0.34–0.56)</td>
<td>0.55 (0.44–0.66)</td>
<td>0.58 (0.45–0.68)</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>0.54 (0.47–0.61)</td>
<td>0.46 (0.39–0.54)</td>
<td>0.54 (0.47–0.61)</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>0.64 (0.58–0.70)</td>
<td>0.36 (0.30–0.42)</td>
<td>0.64 (0.58–0.70)</td>
</tr>
<tr>
<td>Stroke volume, mL/beat</td>
<td>0.56 (0.48–0.62)</td>
<td>0.45 (0.38–0.52)</td>
<td>0.56 (0.48–0.62)</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>0.50 (0.41–0.57)</td>
<td>0.50 (0.43–0.59)</td>
<td>0.50 (0.41–0.57)</td>
</tr>
<tr>
<td>TPR index, mm Hg/L/min/m²</td>
<td>0.18 (0.00–0.54)</td>
<td>0.28 (0.00–0.50)</td>
<td>0.54 (0.43–0.66)</td>
</tr>
</tbody>
</table>

Mean values of all variables were adjusted for age, ethnicity, sex, and their interactions.
estimates. For example, heritability estimates for SBP showed impossible values of 1.37 in whites and −0.26 in blacks. More recently, heterogeneity in familial resemblance was tested in black and white families as part of the HERITAGE study. In contrast to our findings, noticeably higher heritabilities for BP were found in the black sample (68% for SBP, 56% for DBP) than in the white sample (43% for SBP, 24% for DBP). However, the authors acknowledged that ‘heritability’ estimates from their family study represent both genetic and familial (ie, shared) environmental factors. These 2 sources of familial resemblance cannot be efficiently discriminated in nontwin family data, because there is no differential sharing of genotype among first-degree relatives. Both parent-offspring and sibling pairs share, on average, 50% of their genetic material.

We observed higher mean values for SBP, DBP, and TPR index and a lower cardiac index in AAs compared with EAs for this sample of youth with a mean age of 14.7 years, thereby confirming observations from our longitudinal studies and those of others that ethnic differences in BP are already present in childhood. The classic twin study is established as the ideal study design to estimate the relative importance of genetic and environmental factors to the variance of traits and diseases in human populations, but without actual measurement of specific genes or environments, it cannot attribute the ethnic difference in mean values to either of these factors. However, our study does show that the observed difference in mean values did not translate to many differences in genetic and environmental variability within each ethnic group. The magnitude of trait heritability is an important determinant of power for quantitative trait locus detection in whole-genome linkage scans, and the results of our study render it unlikely that quantitative trait locus detection is more likely to be successful in AAs compared with EAs as a result of any heritability differences. The fact that a similar amount of BP variation is explained by genetic factors within different ethnic groups does not exclude the possibility, however, that the actual genes (or their number) responsible for this heritability differ between ethnic groups. For example, genes for sodium handling might be more important for BP regulation in blacks and conversely, vasodilation-related genes might be more important in whites.

Our young, healthy, normotensive twin cohort was not selected on the basis of family history of cardiovascular disease and were unlikely to have developed any significant target-organ damage. Results are therefore unconfounded by pathological changes and are likely to be representative of the general (nontwin) population.

For the TPR index in EAs, 46% of the variance could be attributed to familial effects, but no statistically significant distinction could be made between shared environment or genes, and a model including both components showed a small heritability estimate of 0.18. This small heritability is somewhat unexpected, and continued follow-up of this twin cohort will provide additional power and show whether the majority of the familial effect is truly due to shared environment. A recent study in a subsample of the same twin cohort illustrates the importance of heritable variation in TPR index for EAs; we observed a significant effect of the Gln27Glu locus of the β2-adrenergic receptor gene on TPR index in EAs but not in AAs.

**Perspectives**

Our study shows that contributions of genetic and environmental factors to individual differences in resting BP and hemodynamics in AA youth are similar to those in EA youth and consistent with heritability estimates for BP in previous research of white twins. Future studies pinpointing the specific genetic and environmental factors responsible for individual differences within each ethnic group are likely to also provide clues as to which factors are responsible for the higher BP in AA youth that eventually results in increased prevalence of adult hypertension. Our findings suggest that genes for obesity will play only a minor role in this respect. Resting BP and its underlying hemodynamics are phenotypes with moderate to high heritability in both ethnic groups, as such heritability estimates of this study provide a yardstick against which relative contributions of specific candidate genes to these phenotypes can be assessed in future studies of both AAs and EAs.

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**References**


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