Hemodynamic and Echocardiographic Profiles in African American Compared With White Offspring of Hypertensive Parents: The HyperGEN Study

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BACKGROUND
Alterations in cardiovascular structure and function have been shown to precede the finding of elevated blood pressure.

METHODS
This study is part of the Hypertension Genetic Epidemiologic Network (HyperGEN) in which genetic and environmental determinants of hypertension were investigated in 5 geographical field centers. All nonhypertensive offspring (n = 1,035) were included from the entire HyperGEN study population that consists of 2,225 hypertensive patients and 1,380 nonhypertensive patients who had adequate echocardiographic left ventricular (LV) mass measurements. Participants were compared by self-declared race (African American and white).

RESULTS
Nonhypertensive African American offspring were younger (aged 31 years vs. 38 years), more likely to be female, and had a higher body mass index (BMI) and higher systolic blood pressure (SBP) than their white counterparts. After adjusting for age, sex, SBP, pulse pressure (PP), BMI, diabetes status, and family effects, we observed statistically significant and potentially pathophysiological differences (all with $P \leq 0.001$) with greater LV mass/height, relative wall thickness, and posterior wall thickness and with lesser midwall shortening, PP/stroke volume, and (PP/stroke volume)/fat-free body mass.

CONCLUSION
This study shows that ethnic differences in hemodynamic and echocardiographic profiles exist in a large, population-based cohort of nonhypertensive offspring of hypertensive parents.

Keywords: blood pressure; echocardiography hypertensive offspring; HyperGEN; hypertension; left ventricular mass.

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A higher prevalence of left ventricular hypertrophy (LVH) and LV dysfunction in African Americans may partially explain their greater incidence of cardiovascular disease compared with whites. Nkomo *et al.* evaluated the prevalence of LVH and its relation to systolic function in a population-based sample of African Americans from the Atherosclerosis Risk in Communities (ARIC) study (2,543 African Americans aged 51–70 years without clinically apparent heart disease).[1] They found that LVH was highly prevalent in the ARIC population and was associated with poorer LV function.[1]

Several studies suggest that changes in vascular and cardiac structure precede the development of elevated blood pressure with resultant hypertension that ultimately leads to clinical events.[2–4] Alterations in cardiovascular structure and function also have been shown to precede the finding of elevated blood pressure and include the occurrence of LVH in children and young adults of hypertensive parents.[5] Diastolic filling abnormalities also occur in normotensive individuals predisposed to hypertension, and endothelial dysfunction often occurs as a precursor to hypertension.[6,7] Increased arterial stiffness in normotensive subjects also predisposes them to develop hypertension.[8]

Since African Americans have a much greater prevalence of hypertension and higher blood pressure levels relative to whites,[9] we analyzed the Hypertension Genetic Epidemiologic Network (HyperGEN) cohort to determine whether subclinical abnormalities in LV structure and function exist more frequently in African American normotensive offspring of hypertensive parents compared with their white counterparts.

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METHODS

Study population

This study is part of HyperGEN in which genetic and environmental determinants of hypertension were investigated in the following 5 geographical field centers: Forsyth County, NC; Minneapolis, MN; Framingham, MA; Salt Lake City, UT; and Birmingham, AL. Detailed information on the HyperGEN study design and recruitment strategy is provided elsewhere.[10,11] Briefly, the HyperGEN study is a component of the Family Blood Pressure Program, funded by the National Heart, Lung, and Blood Institute, to assess the genetic contribution to hypertension in population-based samples. It is a family study based on a sib-pair design that recruited hypertensive members of sibships in which ≥2 siblings had onset of hypertension without known cause by age 60 years, were willing to enroll, and had at least 1 additional hypertensive sibling who could be enrolled in the study. Institutional review boards at each participating institution approved the research protocols, and all participants provided informed consent.

For this analysis, we included data from all nonhypertensive offspring (n = 1,035) from the entire HyperGEN study population that consists of 2,225 hypertensive patients and 1,380 nonhypertensive patients who had adequate echocardiographic LV mass measurements. Participants were divided by self-declared race (African American and white). The diagnosis of hypertension was defined as the use of 1 or more antihypertensive treatments or the average of 3 systolic blood pressure (SBP) measurements >140 or the average of 3 diastolic blood pressure (DBP) measurements >90 on 2 or more separate clinic visits.[12] We included only participants with complete blood pressure measurements obtained from both arms and who had adequate echocardiographic measurements (Table 1).

Blood pressure measurements

Six seated blood pressure measurements were taken, and the last 5 were averaged using an oscillometric blood pressure monitor (Dinamap 1846 SX/P, now manufactured by GE Healthcare Worldwide, United Kingdom) with the participant's elbow bent (cubital fossa) and positioned at the level of the heart. Cuff size was chosen for each individual's right and left arm according to his or her mid-arm circumference, and the appropriate cuff size was used for each arm. Before blood pressure measurements were taken, subjects were seated alone in a quiet room for 5 minutes of rest.

In addition to the blood pressure examination, an interview was conducted to obtain information about demographics, writing handedness, family and personal history of cardiovascular disease, hypertensive medication use, and risk factors for cardiovascular disease. Methods used to ascertain body mass index (BMI) and current use of prescription medications have been described elsewhere.[13] Fat-free body mass was derived using measures of bioelectrical impedance with the method described by Lukaski.[14]

Echocardiographic methods

Doppler and 2-dimensional (2D) echocardiograms were performed and recorded using protocols and methods adapted from those used in previously published studies[15–17] from the Weill Cornell Medical Center Echocardiography Laboratory (which served as the echocardiographic reading center for the HyperGEN study). Correct orientation of planes for 2D and Doppler echocardiographic imaging recordings was verified using standardized procedures.[18] Echocardiographic LV geometric measurements, including LV internal dimension and interventricular septal and posterior wall thicknesses, were measured on up to 3 echocardiographic cardiac cycles at end diastole and end systole (following American Society of Echocardiography recommendations).[19,20] Segmental LV motion was graded using the 14-segment Mayo Clinic model,[21] and scores for the motion of individual segments were summed to provide a geometry-independent estimate of LV ejection fraction (EF) as previously described.[22]

Table 1. Descriptive statistics for participants included in analysis

Characteristic	African American participants (n = 460)	White participants (n = 575)	*P* value
Age, years	31.0 (8.2), 18–51	37.7 (8.0), 18–65	<0.001
Female, %	60.0	48.9	<0.001
Weight, kg	86.7 (23.4), 43.5–182.3	81.2 (17.3), 41.3–153.3	<0.001
Height, cm	1.69 (0.10), 1.44–1.98	1.72 (0.09), 1.48–1.99	<0.001
Body mass index, kg/m^2	30.2 (7.6), 17.0–60.2	27.5 (5.3), 15.1–51.3	<0.001
Fat-free body mass, kg	57.9 (19.1), 31.3–148.8	55.9 (11.6), 37.8–93.1	0.045
SBP, mm Hg	115 (11.0), 90–140	112 (11.2), 80–140	<0.001
DBP, mm Hg	70 (8.1), 48–90	69 (7.7), 45–89.0	0.07
Pulse pressure (SBP – DBP), mm Hg	47 (9.2), 26–78	44 (8.3), 23–71	<0.001
Diabetes, %	5.2	3.6	0.22

Normotensive Hypertension Genetic Epidemiologic Network offspring with Echocardiographic (ECHO) and covariate data, n = 1,035. Mean (standard deviation), range. Test of differences between races: analysis of variance for continuous variables, χ^2 test for categorical variables.

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

Calculation of derived variables

LV mass was calculated using an anatomically validated formula (r = 0.90) with good interstudy reproducibility (r = 0.93).[23,24] LV mass was normalized by body surface area and by height.[18,24] Relative wall thickness (RWT), an estimate of LV geometric concentricity, was calculated as LV posterior wall thickness divided by LV diastolic internal radius. Systolic cardiac function indices were calculated using 3 echocardiographic methods. These included LV EF calculated with end-diastolic and end-systolic LV volumes by the Teichholz method.[25] To ensure that conclusions were not dependent on use of a specific geometric model to calculate LV volumes, EF was also calculated from stroke volume obtained by Doppler echocardiography, which is the product of LV outflow time-velocity integral and aortic annulus cross-sectional area measured by 2D echocardiography.[26] Scores for the motion of individual LV segments were summed to provide another geometry-independent estimate of LV EF.[22] LV myocardial function was evaluated by LV midwall shortening and stress-corrected midwall shortening.[27]

Statistical approach

All statistical analyses were performed using Stata version 10.1 (StataCorp, College Station, TX). To test for differences in baseline characteristics between the races (Table 1), we used analysis of variance for continuous variables and χ^2 tests for categorical variables. To test for differences in 16 hemodynamic and echocardiographic phenotypes between the races (Table 2), we first set all outlying values (> or < 3 standard deviations from the mean) to missing for each phenotype, which totaled between 2 and 11 values, depending on the variable. We then used the "LADDER" command in Stata to search for the best transformation to approximate a normal distribution for each phenotype. The results of these analyses are shown in the footnote of Table 2. To account for the correlation of phenotypes between family members, we used mixed linear models with the unique family ID number as the group variable. We conducted analyses that were only minimally adjusted for family membership, as well as fully adjusted analyses (additionally adjusted for age, sex, SBP, pulse pressure (PP), BMI, and diabetes status). Because we compared 16 measurements of cardiac and hemodynamic structure and function among the race groups, a strict Bonferroni correction for multiple comparisons would require $P < 0.003$ (0.05/16) to achieve statistical significance.

RESULTS

The descriptive variables for the 1,035 participants in this analysis, 460 (from 212 families) African American and 575 (from 174 families) white nonhypertensive offspring of hypertensive parents, are presented in Table 1. African American offspring were younger (aged 31 years vs. 38 years), more likely to be female, had a higher BMI, and had higher SBP and PP than their white counterparts.

Table 2 depicts the mean hemodynamic and echocardiographic phenotypes by race. After adjusting for age, sex, SBP, PP, BMI, diabetes status, and family effects and after correcting for multiple tests, we observed statistically significant and potentially pathophysiologic differences (all with $P \leq 0.001$) between African Americans and whites for LV mass/height, RWT, posterior wall thickness, midwall shortening, PP/stroke volume, and (PP/stroke volume)/fat-free body mass. Among normotensive participants, there was no difference between African Americans and whites in the mean ratio of interventricular septal to posterior LV wall thickness (both = 1.08, $P = 0.43$).

DISCUSSION

We found differences in echocardiographic indices of cardiac structure and function between African American and white nonhypertensive offspring of hypertensive parents. Specifically, African Americans demonstrated greater LV mass (even when corrected for body surface area and height), RWT, and posterior wall thickness, with lower LV EF, peripheral resistance, and percent midwall shortening. African Americans also had changes consistent with more impaired diastolic filling. The ratio of PP to stroke volume was greater in whites.

The paradigm of elevated blood pressure resulting in changes in vascular integrity is being challenged since studies have shown that abnormalities in vascular structure and function may occur in nonhypertensive children of hypertensive parents. African Americans develop high blood pressure at younger ages than other groups in the United States and are more likely to develop complications associated with high blood pressure. African Americans also demonstrate excess cardiovascular morbidity and mortality relative to whites.[28] Specifically, hypertension is the primary cause and an independent risk factor for cardiovascular disease, renal disease, stroke, and LVH.[29] African American women have a higher prevalence of coronary heart disease and higher cardiovascular disease mortality compared with white women,[1] and the higher prevalence and higher incidence of coronary heart disease are not explained by quality of care. In the REGARDS (REasons for Geographic And Racial Differences in Stroke) study, the incidence of nonfatal myocardial infarction for areas in the United States with high, medium, or low relative acute coronary heart disease mortality was much lower for African Americans than whites (44%, 78%, and 60 % for respective regions), despite the higher coronary heart disease mortality rates for African Americans than whites in each of these regions, suggesting that case fatality is a possible explanation.[30] However, it is also possible that other contributors affect these outcomes. In REGARDS, despite similar blood pressure treatment rates, there was evidence of lesser blood pressure control in the African Americans.[31] This lesser blood pressure control may result in greater incidence of LVH in African Americans than in whites that could lead to a greater mortality rate.

Table 2. Mean, standard deviation, and range of measures of cardiac structure and function by race

Hemodynamic/echocardiographic phenotype	African American participants	White participants	Minimally adjusted *P* value (family effects only)	Fully adjusted *P* value[a]
Left ventricular mass, g	140.3 (35.4), 51.4–283.1	136.4 (43.8), 60.7–745.1	0.04	0.05
Left ventricular mass/body surface area, g/m^2	71.1 (13.6), 28.0–129.6	70.5 (21.2), 37.5–391.2	0.10	0.01
Left ventricular mass/height$^{2.7}$, g/m$^{2.7}$)	33.7 (7.3), 19.2–57.7	31.5 (10.3), 1.86–178.0	<0.001	0.001
Relative wall thickness, cm	0.293 (0.039), 0.185–0.417	0.289 (0.064), 0.179–1.418	0.003	<0.001
Left ventricular ejection fraction, %	61.4 (5.4), 43.3–78.2	62.0 (5.9), 36.2–98.6	0.19	0.41
Posterior wall thickness, cm	0.75 (0.10), 0.5–1.0	0.74 (0.17), 0.5–3.9	0.007	0.001
Velocity of circumferential fiber shortening, circ/s	1.07 (0.16), 0.63–1.87	1.05 (0.20), 0.55–3.36	0.03	0.04
Midwall shortening, %	18.6 (1.8), 13.5–25.5	19.0 (1.8), 8.2–25.1	0.001	<0.001
Mitral valve peak atrial phase velocity, cm/s peak	52.8 (13.4), 4.8–95.3	54.8 (13.9), 23.4–108.8	0.07	0.48
Mitral valve early fill phase peak	85.0 (17.0), 44.1–144.0	79.1 (15.6), 30.2–142.1	<0.001	0.15
Cardiac output/body surface area, mL/m^2	2,452 (483), 1,184–4,640	2,483 (524), 1,030–4859	0.54	0.94
Cardiac output/fat-free body mass	87.4 (23.2), 25.6–193.9	89.0 (24.9), 34.2–294.0	0.50	0.36
Total peripheral resistance × body surface area, dyne·sec·cm^{-5}/m^2	3,106 (715), 1,632–6,551	2,997 (792), 1,524–9,164	0.009	0.08
Total peripheral resistance × fat-free body mass	90,253 (29,786), 39,063–295,782	86,634 (27,914), 35,834–276,247	0.17	0.07
Pulse pressure/stroke volume	0.62 (0.17), 0.20–1.50	0.65 (0.18), 0.22–2.01	0.004	<0.001
(Pulse pressure/stroke volume)/fat-free body mass	0.0115 (0.0042), 0.0031–0.0256	0.0122 (0.0040), 0.0036–0.0257	0.07	0.001

Mean (standard deviation), range. Mixed linear model used with unique family ID number as group variable; phenotypes < or > 3 standard deviations from mean set to missing; phenotypes transformed to normalize distribution as follows: sqrt(LV mass), log(LV mass/body surface area), log(LV mass/ht$^{2.7}$), log(relative wall thickness), sqrt(mean LV shortening), sqrt(mitral valve atrial fill phase peak), sqrt(mitral valve early fill phase peak), sqrt(cardiac output/bsa), sqrt(cardiac output/ffbm), log(total peripheral resistance × bsa), log(total peripheral resistance × ffbm), sqrt(pp/sv), sqrt((pp/sv)/ffbm).

Abbreviation: bsa, ffbm, LV, left ventricular; pp, sqrt, sv

[a]Adjusted for age, sex, systolic blood pressure, pulse pressure (not included in adjustment for pulse pressure/stroke volume variables), body mass index, diabetes status.

Whether LVH is defined echocardiographically or electrocardiographically, it has been a powerful independent risk factor for coronary heart disease among both men and women with or without known cardiovascular disease.[1] After adjusting for other cardiovascular disease risk factors, LVH is associated with a doubling of mortality in both white and African American cohorts.[32] Other than age and existent coronary heart disease, LVH is perhaps the most important risk factor for 3-year cardiovascular disease mortality.[33] This effect of LVH on morbidity and mortality from cardiovascular disease appears to be greater in women than in men.[34] We were unable to assess differences in LVH between the races because relatively few of these young, normotensive participants had LVH. However, cardiovascular disease risk occurs along a continuum of LVM. In the Framingham Heart Study, the relative risk of all-cause mortality was 1.5 in men and 2.0 in women for every 50 g/m^2 increment in LVM indexed to height.[1] LV mass is also related to a depressed LV EF. Variability in LV mass and its strength of association with risk factors can only be partially explained by blood pressure levels and other hemodynamic variables. Our study provides data that suggest that LV mass is higher in African Americans than in whites over the entire range of blood pressure (including normotension). Taken together with evidence that, even in individuals with normal blood pressure, increased LV mass is a risk factor for coronary events and all-cause mortality,[35,36] the present findings suggest that higher LV mass may contribute to higher cardiovascular event rates among nonhypertensive African Americans as compared with white adults. Some prospective studies indicate that reduced small artery elasticity may indicate earlier vascular disease in African Americans compared with whites.[37]

The strengths of this study include the large number of hypertension-prone individuals (offspring of hypertensive parents) and the well-characterized echocardiographic protocol with a central reading center. Limitations include the lack of long-term outcome data. We also did not explore the potential influence of gene polymorphisms. There was a considerable difference in mean age between the African American and white participants, with African Americans being younger. This would be expected to bias the data toward a more favorable hemodynamic and echocardiographic profile for the African Americans, whereas the opposite was observed. There were also more women in the African American group compared with the white group. However, many differences observed between the groups remained after adjustment for gender. An issue not addressed in our study is the homogeneity of LV wall thickness and whether the homogeneity of wall thickness is the same in whites and African Americans. The method by Devereux was used to calculate LV mass, septal wall thickness, posterior wall thickness, and LV end-diastolic dimension. The wall thickness measurements were made at a single point in the LV (septal wall thickness is measured in the anteroseptal wall, whereas posterior wall thickness is measured in the inferolateral wall). It is possible that some individuals, such as those with asymmetric hypertrophy, have nonhomogeneous wall thicknesses that vary by segment, although the Devereaux method takes some of this into account by including both the septal and posterior wall thicknesses. We feel that it is acceptable to use the Devereaux method in a large population-based study, where the expectation is that most study participants will have uniform wall thickness. Finally, while it is true that the differences between ethnic groups are of modest magnitude, when placed in the context of the larger body of knowledge regarding black/white differences in the long-term prevalence and outcomes of hypertensive heart disease, it suggests that these modest changes may have pathophysiological significance. Given the cross-sectional nature of the data collection, however, we can only speculate that these black/white differences are pathophysiologically relevant.[38]

In conclusion, this study shows that in a large, population-based cohort of nonhypertensive offspring of hypertensive parents, ethnic differences in hemodynamic and echocardiographic profiles exist. Nonhypertensive African American offspring have more abnormalities in LV function than their white counterparts. We postulate that these abnormalities may be a precursor of the observed earlier appearance of cardiovascular disease in African Americans compared with whites.

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DISCLOSURE

The authors declared no conflict of interest.

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