Does the Relationship Between Natriuretic Hormones and Diastolic Function Differ by Race?

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Abstract: *Introduction:* Heart failure develops earlier and is more prevalent in blacks than whites because of their higher incidence of hypertension and diabetes and likely subsequent diastolic dysfunction. Natriuretic peptides (NP) prevent cardiac malfunction through pressure, natriuresis action. However, whether race affects the relationships of NP action with cardiac function is unknown. *Methods:* To assess this, 55 (21 whites and 27 males) normotensive adults underwent a 2-hour protocol of 40 minutes rest, video game stressor and recovery. Mitral inflow and myocardial velocities (tissue Doppler) were recorded every 20 minutes. Blood pressure and heart rate were obtained at 10-minute intervals. Blood samples for pro-atrial NP and pro-brain NP (pro-BNP) were collected every 40 minutes. *Results:* There were differences in the association between (1) the changes from rest to stress for E/A ratio and double product (whites, $r = -0.42$; blacks, $r = 0.10$; $P = 0.034$ for difference between correlations); (2) stress E_m and pro-atrial NP (whites, $r = 0.59$; blacks, $r = -0.25$; $P = 0.025$); (3) rest E_m and BNP (whites, $r = 0.83$; blacks $r = -0.17$; $P = 000$); (4) rest E_m/A_m and pro-BNP (whites, $r = 0.70$; blacks, $r = -0.42$; $P = 0.003$); (5) rest E/E_m and pro-BNP (whites, $r = -0.61$; blacks, $r = 0.31$; $P = 0.015$) and (6) stress E and pro-BNP (whites, $r = 0.56$; blacks, $r = -0.18$; $P = 0.043$). *Conclusion:* The higher correlations between levels of NP and diastolic function indices both at rest and stress suggest that NP protective action is more pronounced in whites than in blacks.

Key Indexing Terms: Natriuretic hormones; Mental stress; Diastolic function; Race. **[Am J Med Sci 2012;344(2):96–99.]**

Epidemiologic studies have established that blacks have higher prevalence of adverse patterns of cardiac structure, geometry and function.[1–3] Consequently, congestive heart failure (CHF) develops earlier and is more prevalent and faster progressing in blacks than in whites because of clustering of cardiovascular risk factors in blacks, including hypertension, obesity and diabetes.[4,5] Blacks have 2 to 3 times greater mortality as a result of CHF than whites.[6,7] This rate is still high when adjusting for covariates (eg, age, sex and cause of ventricular dysfunction). The underpinning mechanisms for ethnic differences in cardiac function of healthy individuals have not been fully elucidated.

Natriuretic peptides, including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), are major defense mechanisms against the effects of excess pressure and/or volume loads.[8,9] Natriuretic peptides cause natriuresis and vasodilatation through renal action (ie, increased glomerular filtration rate) and through inhibition of the sympathetic nervous system, the renin-angiotensin-aldosterone system and endo-thelial regulation.[10–15] We hypothesize that there are racial differences in cardioprotective factors such that blacks might experience ineffective cardioprotective effects of natriuretic hormones.

The purpose of this study was to determine the influence of race on the relationship between the effects of natriuretic peptides and indices of heart function at rest and during mental stress stimulation.

METHODS

Study Population

The subjects were 55 healthy normotensive adults aged 30 to 50 years. There were 22 whites and 33 blacks. Descriptive statistics of study participants are shown in Table 1. The protocol was approved by the Human Assurance Committee of the Medical College of Georgia. Written informed subject consent was obtained before testing.

Laboratory Evaluation

Participants were placed on a controlled, normal sodium (4000 ± 200 mg/d) diet for 3 days before testing. On the 4th day, the participants were brought to the laboratory. During the 40-minute pretest period, the subjects watched movies. The movies were limited to PG-rated films that are nonviolent. Subjects' interest was held so that they did not fall asleep. During the stress visit, this was followed by a 40-minute stress period during which the subjects played a competitive video game task for a monetary reward (car driving; Sony Corp, Foster City, CA). During the control visit, the protocol was the same except that during the stress period, subjects watched movies. Finally, there was a 40-minute post-test recovery period that was the same as the pre-test period.

Hemodynamic measurements were obtained during the 2 hours at 10-minute intervals using the Dinamap monitor (Di-namap Compact Monitor, Tampa, FL) for blood pressure (BP) and heart rate (HR). Simultaneous with Dinamap measurements, a 40-second continuous sample of impedance waveforms was recorded using impedance cardiography (Cardiodynamics BioZ; Cardiodynamic, San Diego, CA) for stroke volume. The electrocardiography R-R intervals in this 40-second sample interval were assessed and converted into HR statements (ie, beats per minute). Stroke volume was multiplied by HR to generate cardiac output (CO) values. Total peripheral resistance was calculated by dividing mean arterial pressure with CO. The ensemble averaging procedure improves signal sampling capabilities, and filtering respiratory and movement artifact, thereby optimizing the validity and reliability of impedance CO measurement.[16]

Doppler Evaluations of Global and Regional Diastolic Function

Mitral Inflow

For diastolic function, pulsed Doppler Echocardiography was used to record the mitral inflow to derive indices of left

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TABLE 1. Descriptive statistics

Variable	Blacks (n = 33)	Whites (n = 22)	P (2-tailed)
Sex (male/female)	17/16	10/12	0.66
Age (yrs)	40.9 ± 5.9	42.6 ± 4.4	0.21
Height (cm)	169.2 ± 10.1	172.1 ± 7.4	0.22
Weight (kg)	85.7 ± 21.1	79.0 ± 12.4	0.10
BMI (kg/m^2)	29.9 ± 6.6	26.3 ± 3.8	0.02
SBP (mmHg)	121.1 ± 13.8	116.1 ± 14.1	0.20
DBP (mmHg)	76 ± 8.5	73.9 ± 9.0	0.40
HR (beats/min)	70.6 ± 9.2	69.6 ± 8.2	0.71

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

ventricular filling. The sample volume was placed at the tips of mitral leaflets to record the highest velocity of diastolic inflow. The tracing of 5 consecutive cardiac cycles having the highest velocity in early filling were analyzed as previously described.[17] The following parameters were examined: peak velocity of early filling *(E);* the acceleration (Acc.T) and deceleration (Dec.T) times, peak velocity of late filling *(A)* and the ratio of early to late filling peak velocities *(E/A).*

Tissue Doppler

Tissue Doppler was obtained using an apical 4-chamber view for evaluating the mitral valve annulus. The sample volume was placed at the basal portion of the referred walls. The lowest possible wall filter setting and the minimum optimal gain were used as recommended by the manufacturer. Peak spectral longitudinal contraction (S_m), initial (E_m) and final (A_m) diastolic velocities for 5 consecutive beats were analyzed, E/E_m and E_m/A_m ratio were calculated.

The reproducibility of both acquiring and measuring S_m, E_m and A_m was determined in recordings obtained from 10 subjects. The intraobserver and interobserver differences in parameter estimates were less than 10%.

Natriuretic Peptide

Pro-ANP and pro-BNP concentrations in plasma samples were determined using commercially available kits purchased from Biomedica-Gruppe (American Research Products, Belmont, MA). Two hundred microliters of standards, controls and diluted samples (1:2 in assay buffer) and 100 μL of detection antibody were added to a 96-well microtiter plate and incubated for 2.5 hours at 37°C. Contents of wells were discarded and washed. One hundred microliters of conjugate were added to each well, and samples were incubated for 1 hour at room temperature. Contents of wells were discarded again and washed. One hundred microliters of substrate will be added to all wells, and samples were incubated for 20 minutes at room temperature in the dark; at which point, 50 μL of stop solution were added to each well. Concentrations of pro-ANP and pro-BNP in samples were determined by measuring absorbance at 450 nm and comparing with a calibration curve generated from the standards.

Statistical Analyses

Comparisons of mean values of the variables shown in Table 1 were made with *t* tests. Covariance analyses were used to control for age, body mass index (BMI), BP and systolic function when comparing blacks and whites on mean levels of pro-BNP and pro-ANP.

Pearson correlation coefficients were computed to assess the degree of linear association among the hemodynamic variables, Doppler measurements and natriuretic peptide levels for the pretest resting period, stress period and the change from rest to stress. Spearman correlations were also computed to check for the effect of possible outliers on the Pearson correlations. SPSS version 19 (SPSS, an IBM company) was used to perform most calculations. Comparisons of correlation coefficients were made using *z* tests after *r* to *z* transformations.

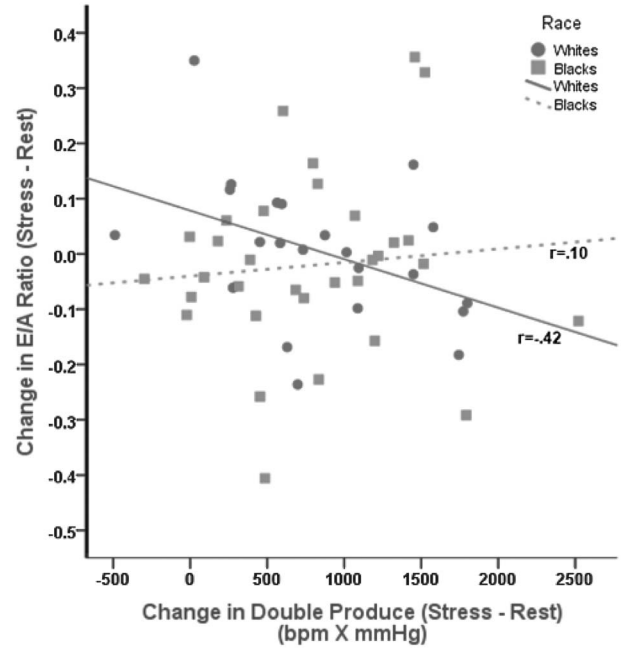

FIGURE 1. Relationship between changes in E/A ratio and double product by race. *E/A*: ratio of early (*E*) to late *(A)* filling velocities.

RESULTS

Black and white participants were similar with regard to age, sex distribution, height, BP and HR. The average BMI was higher in blacks than whites (Table 1).

Comparison of Cardiac Structure and Function

All individuals had normal left ventricular mass and geometry. Left ventricular systolic function was also normal for all individuals.

Impact of Race on the Association Between Diastolic Function and Natriuretic Hormones

Whites and blacks had normal diastolic function. A decrease in mean *E/A* ratio was observed during videogame stress. E_m increased in whites, whereas it increased in blacks. E/E_m decreased in whites, whereas it increased in blacks (all P values <0.01).

The association of change from rest to stress of *EIA* with double product (ie, SBP × HR) was greater in whites than blacks (whites, $r = -0.42$; blacks, $r = 0.10$; $P = 0.034$ for difference between correlations) (Figure 1). The association of stress E_m with ANP differed by race (whites, $r = 0.59$; blacks, $r = -0.25$; $P = 0.025$) (Figure 2).

Whites compared with blacks showed a greater association between pro-BNP and E_m (whites, $r = 0.83$; blacks, $r = -0.18$, $P = 0.03$) (Figure 3) and E_m/A_m (whites, $r = 0.72$; blacks, $r = -0.47$; $P = 0.002$) (Figure 4). The difference in the association between pro-BNP and *E/E'* (whites, $r = -0.50$; blacks, $r = 0.15$; $P = 0.13$) did not reach statistical