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Does the relationship between natriuretic hormones and diastolic function differ by race?

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Abstract

Background—Heart failure develops earlier and is more prevalent in Blacks (B) than Whites (W) due to their higher incidence of hypertension and diabetes and likely subsequent diastolic dysfunction. Natriuretic hormones (NP) prevent cardiac malfunction through pressure–natriuresis action. However, whether race affects the relationships of NP action with cardiac function is unknown.

Method—To assess this, fifty-five (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 (BP) and heart rate were obtained at 10 minute intervals. Blood samples for pro-atrial and pro-brain natriuretic peptides (pro-ANP and 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 (W $r=-.42$, B $r=.10$; $p=.034$ for difference between correlations), (2) Stress Em and pro-ANP (W $r=.59$, B $r=-.25$, $p=.025$), (3) rest Em and BNP (W $r=.83$, B $r=-.17$, $p=.000$), (4) rest Em/Am and pro-BNP (W $r=.70$, B $r=-.42$, $p=.003$), (5) rest E/Em and pro-BNP (W $r=-.61$, B $r=.31$, $p=.015$), (6) Stress E and pro-BNP (W $r=.56$, B $r=-.18$, $p=.043$).

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.

Keywords

Natriuretic Hormones; Mental Stress; Diastolic Function; Race

Introduction

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 due to clustering of cardiovascular risk factors in Blacks including among other hypertension, obesity and diabetes^{4,5}. Blacks have two to three times greater mortality due

to CHF than Whites^{6,7}. This rate is still high when adjusting for co-variates (e.g., 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 (i.e., increased glomerular filtration rate) and through inhibition of the sympathetic nervous system, the renin-angiotensin-aldosterone system and endothelial 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-old. 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 prior to testing.

Laboratory Evaluation

Participants were placed on a controlled, normal sodium (4000±200 mg/day) diet for 3 days prior to testing. On the fourth day, the participants were brought to the laboratory. During the 40 minutes pre-test period the subjects watched movies. The movies were limited to PG rated films which are nonviolent. Subjects' interest was held so that they did not fall asleep. During the stress visit, this was followed by a 40 minutes 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 minutes post-test "recovery" period that was the same as the pre-test period.

Hemodynamic measurements were obtained during the two hours at 10 minute intervals using the Dinamap monitor (Dinamap 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, CardiodynamiDiego, CA) for stroke volume (SV). The electrocardiography R-R intervals in this 40-second sample interval were assessed and converted into heart rate statements (i.e., beats per minute). Stroke volume was multiplied by heart rate to generate cardiac output (CO) values. Total peripheral resistance (TPR) was calculated using the equation $TPR = \text{mean arterial pressure (MAP)}/CO$. The ensemble averaging procedure improves signal sampling capabilities, as well as filtering respiratory and movement artifact, thereby optimizing the validity and reliability of impedance CO measurement¹⁶.

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 ventricular filling. The sample volume was placed at the tips of mitral leaflets to record the highest velocity of diastolic inflow. The tracing of

five consecutive cardiac cycles having the highest velocity in early filling were analyzed as previously described¹⁷. 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—TD was obtained by 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 (Sm), initial (Em), and final (Am) diastolic velocities for 5 consecutive beats were analyzed, E/Em and Em/Am ratio were calculated.

The reproducibility of both acquiring and measuring Sm, Em and Am were determined in recordings obtained from 10 subjects. The intra observer and inter observer differences in parameter estimates were less than 10%.

Natriuretic Peptide—Pro-ANP and Pro-BNP concentrations in plasma samples will be determined using commercially available kits purchased from Biomedica-Gruppe (American Research Products, Belmont, MA). 200 μ L of standards, controls, and diluted samples (1:2 in assay buffer) and 100 μ L of detection antibody will be added to a 96 well microtiter plate and incubated for 2.5 hours at 37 °C. Contents of wells will be discarded and washed. 100 μ L of conjugate will be added to each well and samples will be incubated for one hour at room temperature. Contents of wells will be discarded again and washed. 100 μ L of substrate will be added to all wells and samples will be incubated for 20 minutes at room temperature in the dark, at which point 50 μ L of stop solution will be added to each well. Concentrations of pro-ANP and pro-BNP in samples will be determined by measuring absorbance at 450 nm and comparing to 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, bmi, blood pressure, 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 pre-test resting period, stress period, and the change from rest to stress. Spearman correlations were also computed in order to check for the effect of possible outliers on the Pearson correlations. SPSS version 19 (SPSS Inc, an IBM company) was used to perform most calculations. Comparisons of correlation coefficients were made using z-tests after r to z transformations.

Results

Black and White participants were similar with regard to age, sex distribution, height, blood pressure and heart rate. The average BMI was higher in Blacks than Whites (see 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. Em increased in Whites while it decreased in Blacks. E/Em decreased in Whites while it increased in Blacks (all p s <.01).

The association of change from rest to stress of E/A with double product (i.e., SBP X HR) was greater in Whites than Blacks (W $r = -.42$, B $r = .10$; $p = .034$ for difference between correlations) (see Figure 1). The association of Stress Em with ANP differed by race (W $r = .59$, B $r = -.25$, $p = .025$) (Figure 2).

Whites compared to Blacks showed a greater association between pro-BNP and Em (W $r = .83$, B $r = -.18$, $p = .003$) (see Figure 3) and Em/Am (W $r = .72$, B $r = -.47$, $p = .002$) (see Figure 4). The difference in the association between pro-BNP and E/E' (W $r = -.50$, B $r = .15$, $p = .13$) did not reach statistical difference.

The Spearman correlations were quite similar to those obtained with the Pearson formula.

Discussion

Our major finding is that there is a race difference in the relationship between natriuretic hormones and heart function. This difference is independent of body size. In Whites, not in Blacks, higher blood levels of pro-BNP are associated with lower cardiac load, increased myocardial relaxation, and lower filling pressure. This suggests a race difference in the susceptibility to the cardioprotective effect of natriuretic hormones.

Left ventricular relaxation as reflected by Em is a preload independent marker of congestive heart failure¹⁸. To the best of our knowledge, this is the only study that has concomitantly examined the relationship between natriuretic hormones and myocardial relaxation in healthy humans and in a laboratory paradigm. The analyses were carried out in the entire sample and in each group separately to observe potential race specific effects. We found that greater Em was associated with increased pro-BNP only in Whites. The mechanisms of greater and beneficial associations in Whites are unclear from our study of healthy individuals. Also, the association between natriuretic hormones and diastolic function indices were evident in early diastole rather than late diastole suggesting that these hormones have greater influence on early phase relaxation than on compliance per se.

The modulating effect of race on blood levels of pro-BNP is controversial. Some^{19,20} but not all²¹ studies have shown race related differences in blood levels of pro-BNP. In the present study, blood levels of natriuretic hormones were not different between the two studied groups despite the greater BMI in Blacks and the well established negative association between BMI and pro-BNP^{22,23}. No difference was found after taking into account covariates (e.g., blood pressure, age, cardiac structure and systolic function).

In a previous study using a similar protocol we have shown that race differences in pressure natriuresis is a mechanism of race related differences in heart structure and function²⁴. The present study expands this concept to propose difference in sensitivity to natriuretic hormones as a mechanism that may explain race disparity in heart function. Our data suggest that Whites but not Blacks show the positive effect of natriuretic hormones on diastolic function.

Blood levels of natriuretic peptide did not differ by race. In both groups stress induced increase in blood pressure and heart rate whereas natriuretic blood levels were unaffected suggesting either that NP basal levels were enough to regulate stress induced changes in hemodynamics or that NP response to stress was delayed. Another possibility is that

behavioral stress was not enough to affect natriuretic hormone release factors including increased body mass index, sex, age, ventricular wall tension, ventricular dysfunction, and subclinical myocardial injury and/or ischemia^{25–27}.

Kim et al.²⁸ demonstrated that progression of left ventricular hypertrophy in end-stage renal disease patients is associated with rising filling pressure that parallels increasing blood levels of Nt-ProBNP. The findings in our study evoke a possible race difference in the beneficial effect of BNP and ANP. The associations between pro-ANP and pro-BNP and indices of diastolic function were moderately stronger in Whites than in Blacks. However, combining the standardized values of pro-ANP and pro-BNP to create a single index yielded an even stronger association, suggesting that biomarkers have stronger predictive value in White than in Blacks. The paradox of lack of association between diastolic function and natriuretic hormones in Blacks suggest that cardiac posttranslational process of natriuretic hormone precursors has ethnic variability and warrant myocardial characterization to further understand the influence of race on myocyte biology, receptor affinity and endopeptidase activity.

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Perspective

Existing studies have focused on natriuretic hormones as markers of cardiac dysfunction in patient populations but have not explored their homeostatic role in healthy individuals. Our study demonstrates that, within the normal range, levels of NP may be used to identify individuals at risk of developing cardiovascular disease. A longitudinal study will tie the observed race differences into concrete cardiovascular outcomes.

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.

Figure 2. Relationship Between Em and pro-ANP by Race

Em: myocardial relaxation

Pro-ANP: pro-Atrial Natriuretic Peptide

Figure 3. Relationship Between Resting Myocardial Relaxation and pro-BNP by Race

Em: myocardial relaxation

Pro-BNP: pro-Brain Natriuretic Peptide

Figure 4. Relationship Between Resting Mitral Annulus EM/AM and pro-BNP by Race
 Em/Am: ratio of early to late myocardial relaxation
 Pro-BNP: pro-Brain Natriuretic Peptide

Table 1

Descriptive Statistics

Variable	Blacks n=33	Whites n=22	p (2-tailed)
Sex	17M, 16F	10M, 12F	0.66
Age	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	29.9 ± 6.6	26.3 ± 3.8	0.02
SBP	121.1 ± 13.8	116.1 ± 14.1	0.20
DBP	76 ± 8.5	73.9 ± 9.0	0.40
HR	70.6 ± 9.2	69.6 ± 8.2	0.71