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Brain Natriuretic Hormone Predicts Stress Induced Alterations in Diastolic Function

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Abstract

Background—Mental stress (MS) reduces diastolic function (DF) and may lead to congestive heart failure with preserved systolic function. Whether brain natriuretic hormone (BNP) mediates the relationship of MS with DF is unknown.

Method and Results—160 individuals aged 30 to 50 years underwent 2 hour protocol of 40 minutes rest, videogame stressor and recovery. Hemodynamics, pro-BNP samples and DF indices were obtained throughout the protocol. Separate regression analyses were conducted using rest and stress E/A, E' and E/E' as dependent variables. Predictor variables were entered into the stepwise regression models in a hierarchical fashion. At the first level age, sex, race, height, BMI, pro-BNP, and LVM were permitted to enter the models. The second level consisted of SBP, DBP and HR. The final level contained cross-product terms of race by SBP, DBP and HR. E/A ratio was lower during stress compared to rest, and recovery ($p<0.01$). Resting E/A ratio was predicted by a regression model of age (−.31), pro-BNP (.16), HR (−.40) and DBP (−.23) with an $R^2 = .33$. Stress E/A ratio was predicted by age (−.24), pro-BNP (.08), HR (−.38), and SBP (−.21), total R2 = .22. Resting E' model consisted of age (−.22), pro-BNP (.26), DBP (−.27) and LVM (−.15) with an $R^2 = .29$. Stress E' was predicted by age (−.18), pro-BNP (.35) and LVM (−.18) with an $R^2 = .18$. Resting E/E' was predicted by race (.17, B>W) and DBP (.24) with an $R^2 = .10$. Stress E/E' consisted of pro-BNP (−.36), height (−.26) and HR (−.21) with $R^2 = .15$.

Conclusion—pro-BNP predicts both resting and stress DF suggesting that lower BNP during MS may be a maker of diastolic dysfunction in apparently healthy individuals.

Keywords

Brain Natriuretic Hormone; Mental Stress; Diastolic Function

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INTRODUCTION

Mental stress (MS) induces cardiac malfunction due to increased cardiac load deriving from hemodynamics arousal expressed as increased blood pressure, heart rate and total peripheral resistance[1–8]. This MS stimulation of the cardiovascular system may translate into increased vascular tone, reduced myocardial perfusion, decreased ratio of early to late filling (E/A) velocities and reduced myocardial relaxation (E')[3,6,7]. The reduction of diastolic function in response to MS suggests that repetitive biobehavioral stress of modern life may induce diastolic dysfunction in at risk individuals such as blacks and women who are more likely to develop premature congestive heart failure than whites and males[9,10].

Pump function deterioration is associated with increased blood levels of BNP which plays an important role in body fluids (i.e., salt handling) and vascular tone regulation[11–13]. As diastolic dysfunction is also a putative mechanism of congestive heart failure, it becomes necessary to determine whether MS induced alteration in diastolic function is linked to secretion of cardioprotective hormone such as brain natriuretic (BNP)[14,15]. BNP is a marker of wall tension which is determined by chamber size and pressure. In general, increased blood levels of BNP are observed in reduced systolic function of hypertensive and coronary artery disease patients, but not in normotensive individuals[16–18]. This raises the concern of whether BNP levels may represent changes in diastolic function of healthy individuals.

We hypothesize that pro-BNP which is a precursor of BNP would be a predictor for DF in healthy subjects especially during stressful circumstances. To address this, we conduct this study to probe the predictive value of pro-BNP on DF at rest and during stress.

METHOD

Study Population

The subjects were 80 Blacks (B) (40 males) and 80 White (W) (40 females) healthy normotensive adults aged 30 to 50 years old (mean ± SD = 39.5 ± 5.9), not on any medications and without a history of any medical diagnosis.

Inclusion criteria: normal blood pressure (systolic <140 mm Hg and diastolic <90 mm Hg), no history of CAD, no chest pain syndrome, a normal resting ECG, normal ejection fraction, normal kidney function (creatinine< 1mg/l, no microalbuminuria), no hypercholesterolemia (total cholesterol ≤250 mg/dL and LDL cholesterol ≤160 mg/dL), no food allergies by self-report, ability to complete the necessary protocols and questionnaires.

Exclusion criteria: pregnancy, smoking, endocrine systemic disease (e.g., thyroid disorders, diabetes mellitus), chronic pulmonary disease, abnormal echocardiography findings (EF<50%, regional wall-motion abnormalities, peripheral vascular disease, anything that would impede the subject from complying with the diet.

The protocol was approved by the Human Assurance Committee of the Georgia Health Sciences University. Written informed 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 and given breakfast. Blood samples were then drawn and urine collected. During the 40 minute pre-test "rest" phase the subjects watched movies of their own choosing from our video library. During the experimental visit, this was followed by a 40 minute stress phase during which the subjects played a competitive video game task for a monetary reward (Snowboard, Sony Corp, Foster City, CA). Subjects improving their scores in the final stages of the game were given an additional $20. Finally, there was a 40 minute post-test, "recovery" phase that was the same as the pre-test phase. During each of the 40 minute phases subjects consumed one 12-oz. bottle of water and after each phase blood and urine samples were taken. Hemodynamic measurements were obtained during the two hours at 5 minute intervals using the Dinamap monitor (Dinamap Compact Monitor, Tampa FLA) for SBP and diastolic blood pressure (DBP) and heart rate (HR).

For diastolic function, pulsed Doppler Echocardiography (Hewlett-Packard Sono 7500; Andover, MA) 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 described[19,20]. A number of parameters were examined including the following: peak velocity of early filling (E), peak velocity of late filling (A) and the ratio of early to late filling peak velocities (E/A).

Tissue Doppler

Tissue Doppler measurements were obtained by using apical 4-chamber view for evaluating the septum portion of the mitral valve annulus. The sample volume was placed at the basal portion of the referred walls. The lowest possible wall filter settings and the minimum optimal gain were used as recommended by the manufacturer. Initial (E'), and final (A') diastolic velocities for 5 consecutive beats were analyzed; the E/E' ratio was calculated.

The reproducibility of both acquiring and measuring E' and A' were determined in recordings obtained from 10 subjects. The intra observer and inter observer differences in parameter estimates were less than 10%. Doppler measurements were obtained at 20 and 40 minutes in each of the three phases.

Brain Natriuretic Peptide

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 were 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-BNP in samples were determined by measuring absorbance at 450 nm and comparing with a calibration curve generated from the standards.

Pro-BNP and LVM

For 39 subjects, we were unable to obtain values for pro-BNP and/or LVM. We compared those 39 subjects with the 121 for which we had complete data on the variables shown in Table 1. There were no significant differences for any of those variables (i.e., all p's >0.05). Additionally, the groups did not differ significantly by race or sex (Fisher's exact test p-values = 0.27 and 1.00, respectively).

Statistical Analyses

The distribution of pro-BNP and BMI was skewed, so we used log values of pro-BNP and BMI. Initially repeated measures analyses of variance (RmANOVA) were conducted to test if the stress protocol produced changes in E, A, E/A, E', A' and E/E'. Protocol phase (rest, stress, recovery) were used as the trial effects in these analyses. Following the RmANOVA's, separate regression analyses were conducted using the E/A ratio, E', E/E' during the rest phase and during the stress phase as dependent variables. The predictor variables were entered into the stepwise regression models in a hierarchical fashion. At the first level age, sex, race, height, BMI, pro-BNP, and LVM were permitted to enter the models. The second level consisted of SBP, DBP and HR. The third (final) level contained cross-product terms of race by SBP, DBP and HR.

RESULTS

Descriptive statistics of study participants are shown in Table 1. BMI and pro-BNP were transformed via natural log to correct for skew in the distribution of the original variables. All individuals had normal blood pressure, left ventricular mass and geometry and **ejection fraction**. As shown in Table 1, there were sex differences in height, blood pressure and heart rate and race differences in systolic blood pressure (SBP). In addition there was a significant race by sex interaction for BMI with W females having lower values and B females having higher values than males.

Stress and Diastolic Function

For E, there was a greater decrease from the rest phase to the stress phase and an increase from the stress phase to the recovery phase (rest = 55.4 cm/sec, stress = 53.9 cm/sec, recovery = 54.9 cm/sec). For A, there was an increase from rest to stress followed by a decrease from stress to recovery (rest = 43.7 cm/sec, stress = 44.2 cm/sec, recovery = 42.8 cm/sec). Subsequently, E/A ratio was lower during stress compared to rest, and recovery ($p<0.01$).

For E' the phase effect was not significant (p's>.59). For A' the phase effect was statistically significant ($p<.001$) with the pattern showing mean decreases from rest to stress to recovery (rest= 6.05 cm/sec, stress = 6.00 cm/sec, recovery = 5.79 cm/sec). The phase effect in E/E' were not statistically significant.

Diastolic Function Correlates at rest and during stress

In order to allow a more complete examination of the relationships between the dependent and independent variables than is usually possible by examining only the results of the regression analyses, we have given the zero-order correlations (and their associated two-tailed p-values) between the variables in these sets in Table 2.

Prediction of Diastolic Function

The E/A ratio during the rest phase was predicted by a stepwise model of age (−.31), pro-BNP (.16), HR (−.40) and DBP (−.23) with an R^2 = .33. (The numbers in parentheses are the beta weights, sometimes referred to as the standardized regression weights; the absolute value of the beta weight can be used to interpret the relative importance of each of the variable within the regression models). During the stress phase, the E/A ratio regression had an R^2 = .22 and consisted of age (−.24), pro-BNP (.08), HR (−.38), and SBP (−.21).

The regression model for E' during the rest phase consisted of age (−.22), pro-BNP (.26), DBP (−.27) and LVM (−.15) with an R^2 = .29. E' during the stress phase was predicted by age (−.18), pro-BNP (.35) and LVM (−.18) with an R^2 = .18.

During the rest phase the E/E' was predicted by race (.17) and DBP (.24) with an R^2 = .10. The beta weight for race indicates that B's were higher than W's since B's were coded as "2" and W's were coded as "1". During the stress phase, the regression model for E/E' consisted of pro-BNP (−.36), height (−.26) and HR (−.21) with R^2 = .15.

DISCUSSION

We demonstrate that pro-BNP consistently predicts DF (i.e., E/A, E' and E/E') among healthy normotensive individuals. Higher blood levels of pro-BNP were associated with higher E/A ratio, E' and lower E/E' suggesting an enhancement of DF. Also, B's and males have lower pro-BNP compared to W and females.

The association between higher pro-BNP and higher diastolic indices (i.e., E/A, E') represents the normal direction of the pro-BNP and diastolic function interaction. Within the normal range (BNP <100 pg/mL) increasing levels of BNP reflects a compensatory mechanism to buffer the hemodynamic burden in healthy individuals. Our findings of an association between lower E/E' and higher pro-BNP lends support to the assumption of lower BNP being predictive of reduced diastolic function during stress. The situation is different in pathological circumstances (BNP >100 pg/mL) where the elevated tension within ventricular wall elicits greater and persistent secretion of BNP coupled to systolic and/ or diastolic dysfunction meaning in essence that BNP levels are no longer able to counter cardiac malfunction. Our work raises the potential of using BNP combined to biobehavioral stress in primordial and primary prevention of congestive heart failure.

Plasma levels of natriuretic peptides are higher in hypertensive patients compared to normotensive individuals[16–18]. However, the natriuretic hormone profile is not completely understood in normotensives. Montorsi et al. and Sagnella et al. [16,18] did not observe an association between BP and natriuretic peptides in normotensives. While Wang et al [21]

showed a negative association between DBP and natriuretic peptides in normotensives. This discrepancy was attributed to the use of newer assays and a difference in sample sizes.

To our knowledge, this is the first study to concomitantly explore the effect of MS on blood pressure, heart rate and DF after controlling for the possible effect of salt intake in healthy normotensive adults. Consistent with previous studies[2–4,6,22–25] we found that MS induced reduction of DF was paralleled with increased SBP, DBP and HR suggesting activation of sympathetic system.

In our study there was no significant increase in blood levels of pro-BNP during MS in contrast to increase in pro-BNP seen with post strenuous endurance exercises[26]. The likely explanation is that exercise causes increase in venous return leading to atrial stretch causing increase release of natriuretic peptides. Other determinant factors of pro-BNP include age, left ventricular hypertrophy, ventricular dysfunction (i.e., decreased ejection fraction and/or increased left ventricular end diastolic pressure) and subclinical myocardial injury and ischemia[21,27–29].

Consistent with previous studies there was a sex and race effect on pro-BNP[21,30,31]. Pro-BNP at baseline was higher in females and whites compared to males and blacks. We and other have shown negative correlation of BMI and pro-BNP[32–36]. In general, females had lower BMI compared to their male counterpart which translates in females having higher pro-BNP levels at baseline. However, B females had both higher BMI and pro-BNP compared to B males counterpart. The reason for this exception is unclear. In Dallas Heart Study[32], the negative correlation between BMI and pro-BNP was found to be dependent on lean body mass than the fat mass. We previously demonstrated that although females have higher BMI their lean body mass is lower than males[37]. This raises the possibility that B females could have higher BMI and lower lean mass.

We found a race difference in E/E’ which is a hallmark of DF reflecting of LV end filling pressure. B showed higher E/E’ compared to W counterpart suggesting that blacks compared to white have higher filling pressures at rest. The underpinning mechanisms for ethnic differences in cardiac function of healthy individuals are not completely understood.

Our finding of a predictive value of pro-BNP on diastolic function of healthy individuals is clinically relevant suggesting that BNP could be used as both marker of systolic and diastolic function as well. It implies that blacks are at higher risk of developing cardiac malfunction given their lower levels of pro-BNP along with the well reported cluster of cardiovascular risk factors. This is in keeping with the general observation that compared to whites, B experience early onset and rapid progression of congestive heart failure[38–40]. This race difference remains after taking in account confounders.

Despite the remarkable power of Doppler echocardiography to assess diastolic function, it should be noted that the noninvasive nature of this study prevents us from measuring left and right ventricles end-diastolic pressures which are landmarks of DF. Also, we couldn’t completely exclude the presence of subclinical myocardial ischemia that has been shown to alter filling profile. Although we could not perform invasive techniques, we chose to include only healthy individuals with no symptoms or signs of cardiac disease.

We have consistently found that videogame challenge induces hemodynamic arousal after a period of PG-13 movie viewing. This is probably not due to excitement from the nature of the game but to the competitive aspect of the video game protocol. Indeed, after the protocol we also asked subjects questions regarding their perceived anxiety, nervousness, and how relaxed they felt at each phase of the protocol. Sixty-seven percent of subjects claim to be trying hard to win the game (i.e., improve the score).

CONCLUSION

These findings demonstrate the cardioprotective effect of BNP in healthy individuals suggesting that lower BNP during MS may lead to diastolic dysfunction in at risk individuals. Further studies are needed to explore the repercussion of race differences in BNP and its possible implications in congestive heart failure prevention.

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ABBREVIATIONS

A	Late filling velocity peak
A’	late velocity of myocardial relaxation
AA	African American
B	Black
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
DBP	Diastolic Blood Pressure
DF	Diastolic Function
E’	early velocity peak of myocardial relaxation
E/A	ratio of early to late filling peaks
E/E’	ratio of early inflow peak to early myocardial relaxation
EA	European American
HR	Heart Rate
LVM	Left Ventricular Mass
MS	Mental Stress
SBP	Systolic Blood Pressure
W	White

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Table 1

Demographic, hemodynamic and ultrasound characteristics

Variable	Male EA	Male AA	Female EA	Female AA	Significant Differences†
Age	39.5± 6.3	39.8± 5.8	40.8± 5.2	40.4± 6.1	
Height (cm)	178.5± 8.0	177.3± 5.8	165.8± 6.0	163.3± 6.0	M > F
BMI (ln)	3.31± .15	3.33± .22	3.28± .18	3.42± .20	F AA> M AA, M EA, F EA
Pro-BNP (ln)	2.73± .69	2.36± 1.03	3.37± .56	2.89± .78	F > M; EA > AA
SBP (mmHg)	118.9± 11.2	126.4± 14.3	109.0± 12.3	114.9± 12.5	M > F; AA > EA
DBP (mmHg)	75.9± 6.5	77.7± 7.6	69.2± 8.1	71.6± 8.1	M > F
HR (bpm)	70.5± 10.7	67.9± 7.9	74.2± 6.5	75.4± 8.2	F > M
LVM (g/ht($^{m2.7}$))	27.7± 6.3	29.4± 6.7	23.7± 5.1	28.2± 6.5	M > F; AA > EA

† $p<0.05$

Cell entries contain mean +SD. The significance column uses results from ANOVA for main effects and Tukey's hsd (honestly significant difference) post hoc test for interaction effects.

AA: African American, EA: European American, BMI: body mass index, BNP: Brain natriuretic peptide, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, LVM: left ventricular mass

Table 2

Diastolic function correlates

	E/A rest	E' rest	E/E' rest	E/A stress	E' stress	E/E' stress
Age	r = −.28 (p<.001)	r = −.25 (p<.001)	r = .12 (p>.14)	r = −.19 (p<.02)	r = −.19 (p<.02)	r = .06 (p>.43)
Height	r = −.04 (p>.61)	r = −.08 (p>.32)	r = −.10 (p>.19)	r = −.05 (p>.57)	r = −.05 (p>.54)	r = −.07 (p>.35)
BMI	r = −.18 (p<.03)	r = −.21 (p<.01)	r = .04 (p>.35)	r = −.12 (p>.14)	r = −.19 (p<.02)	r = .09 (p>.24)
Pro-BNP	r = .20 (p<.02)	r = .32 (p<.001)	r = −.12 (p>.18)	r = .16 (p>.07)	r = .33 (p<.001)	r = −.26 (p<.01)
LVM	r = −.10 (p>.25)	r = −.19 (p<.03)	r = .16 (p>.06)	r = −.08 (p>.37)	r = −.19 (p<.03)	r = .15 (p>.06)
SBP (rest)	r = −.16 (p<.04)	r = −.28 (p<.001)	r = .26 (p<.001)	r = −.14 (p>.06)	r = −.16 (p<.03)	r = .15 (p>.06)
DBP (rest)	r = −.28 (p<.001)	r = −.34 (p<.001)	r = .21 p(<.01)	r = −.18 (p<.03)	r = −.25 (p<.01)	r = .16 (p<.05)
HR (rest)	r = −.30 (p<.001)	r = .00 (p>.98)	r = −.08 (p>.33)	r = −.27 (p<.001)	r = .03 (p<.70)	r = −.12 (p>.13)
SBP (stress)	r = −.18 (p<.03)	r = −.29 (p<.001)	r = .22 (p<.01)	r = −.14 (p>.07)	r = −.17 (p<.04)	r = .15 (p>.05)
DBP (stress)	r = −.27 (p<.001)	r = −.34 (p<.001)	r = .16 (p<.04)	r = −.19 (p<.02)	r = −.24 (p<.01)	r = .17 (p<.04)
HR (stress)	r = −.22 (p<.01)	r = .07 (p>.23)	r = −.07 (p>.37)	r = −.22 (p<.01)	r = .10 (p>.20)	r = −.07 (p>.37)

BMI: body mass index, BNP: brain natriuretic peptide, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, LVM: left ventricular mass, E/A: ratio of early to late filling, E': early velocity of myocardial relaxation, E/E': ratio of early inflow to early myocardial relaxation.