

THE ASSOCIATION OF RACE AND SEX TO THE PRESSURE NATRIURESIS RESPONSE TO STRESS

Objective: Sympathetic nervous system activation promoting sodium retention has long been recognized to play a significant role in the development and maintenance of salt-sensitive hypertension. The purpose of this study was to examine the influence of race and sex on the pressure natriuresis response to prolonged behavioral stress in youth.

Methods: The 190 subjects included 94 boys (41 African American, 53 Caucasian) and 96 girls (44 African American, 52 Caucasian) of similar age (17–19 years). The stress test was composed of a one hour competitive video game task preceded and followed by two-hour rest periods. Blood pressure (BP) was obtained at 15 minute intervals and sodium excretion ($U_{Na}V$) was measured hourly. The general linear model was used to model the effects of race, sex, and their interaction on the variables of interest.

Results: Caucasians, compared to African Americans, had a greater change in $U_{Na}V$ ($F[1,183]=5.28$, $P=.0227$), as did boys compared to girls ($F[1,183]=5.72$, $P=.0178$), with no interaction between race and sex. The race-by-sex interaction was significant for the change in systolic BP ($F[1,183]=5.66$, $P=.0184$), with Caucasian girls showing a smaller change than the other three race/sex groups.

Conclusion: African Americans have a reduced natriuretic response to stress, which may be a marker or mechanism for the development of salt-sensitive hypertension in this population. The race difference within girls is of interest and requires further investigation. (*Ethn Dis.* 2007;17:498–502)

Key Words: Stress, Sodium, Blood Pressure, Natriuresis, Hypertension, Race, Sex

From the Georgia Prevention Institute (GAH, GKK, YD, MEC, DAL), and the Departments of Pediatrics (GAH, CH, GKK, YD, MEC, DAL), Biostatistics (DAL) and Physiology (GAH), Medical College of Georgia; Augusta, Georgia.

Address correspondence and reprint requests to Gregory A. Harshfield, PhD; Georgia Prevention Institute; Medical College of Georgia; MCG Annex H.S. 1640, Augusta, GA 30912-4534; 706-721-1755; 706-721-7150 (fax); Gharshfi@mail.mcg.edu

Gregory A. Harshfield, PhD; Coral Hanevold, MD; Gaston K. Kapuku, MD, PhD; Yanbin Dong, MD, PhD; Martha E. Castles, MA; David A. Ludwig, PhD

INTRODUCTION

It is well-established that African Americans compared to Caucasians have a greater incidence and prevalence of essential hypertension (HTN).^{1–4} Studies, which reported changes in blood pressure (BP) in response to changes in sodium intake (ie, salt sensitivity), demonstrated that impaired sodium regulation in African Americans contributes to this difference.^{3,5–7}

We^{8,9} and others^{10–12} hypothesized that an impaired natriuretic response to behavioral/mental stress (ie, impaired stress-induced pressure natriuresis [SIPN]) is a potential mechanism through which impaired sodium regulation contributes to the increased prevalence of HTN in African Americans. Impaired SIPN differs from the traditional assessment of salt sensitivity in that the load is “delivered” by the increase in renal sympathetic nerve activity resulting from the stress rather than by a diet or infusion. Three lines of research support this hypothesis and include: 1) studies that demonstrated an important role of the sympathetic nervous system (SNS) in the development of salt-sensitive HTN^{13–17}; 2) animal studies that demonstrated behaviorally induced SNS activation results in salt-sensitive HTN by inducing sodium retention, which increases intravascular volume and therefore cardiac output and BP^{15,18,19}; and 3) previous data by Light¹⁰ on a small sample of adults (14 African American, 14 Caucasian), and our group⁹, in youth. Therefore, the purpose of this study was to confirm the race difference in SIPN and examine potential interactions between race and sex.

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METHOD

Study Population

The volunteer sample consisted of 190 unrelated subjects and included 94 boys (41 African American, 53 Caucasian) and 96 girls (44 African American, 52 Caucasian) of similar age (17–19 years) who participated in two separate studies (ie, two cohorts) that employed the same protocol. The studies were approved by the Human Assurance Committee of the Medical College of Georgia. Written informed consent (for those ≥ 18 years of age) or parental consent and subject assent (for those < 18 years of age) was obtained prior to testing. Table 1 provides the subject's baseline characteristics by race and sex for the outcome variables evaluated in this study. The subjects were all normotensive, healthy, not on any over-the-counter or prescription medications (except for acne), and without a history of any medical diagnosis. They were recruited from area schools and by word-of-mouth.

Protocol

Our protocol has been described in detail previously.^{9,20} Briefly, the subjects were placed on a controlled sodium

Table 1. Means and adjusted standard errors by race and sex

Variable	African American		Caucasian	
	Girls	Boys	Girls	Boys
N	44	41	52	53
BMI (kg/m ²)	25.4 (6.3)	24.7 (6.5)	22.6 (3.2)	23.5 (4.4)
SBP (mm Hg)	106.4 (8.4)	115.4 (9.6)	101.5 (6.6)	110 (10.3)
DBP (mm Hg)	57.3 (5.8)	59.6 (6.8)	54.7 (5.3)	54.9 (4.9)
TPR (dynes.s.cm ₋₅)	13.8 (2.5)	14.7 (2.1)	13.3 (2.0)	12.5 (1.8)
SV (mL/min)	73.7 (11.9)	84.4 (1.8)	74.2 (12.5)	92.1 (13.4)
HR (bpm)	76.1 (7.7)	65.9 (7.2)	75.4 (8.4)	66.5 (8.3)
U _{Na} V (mEq/hr)	13.9 (5.6)	11.5 (5.2)	10.8 (4.6)	11.7 (5.1)

Abbreviations: BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, TPR=total peripheral resistance, SV=stroke volume, HR=heart rate, U_{Na}V=urinary sodium excretion

diet of 4000 ± 200 mg/day for three days prior to testing. The stress protocol included a 2-hour baseline period during which the subjects watched movies. This was followed by a 1-hour stress period during which the subjects played a competitive video game for a monetary reward (Snowboard, Sony Corp, Foster City CA). Urine samples were obtained hourly for the measurement of U_{Na}V. Hemodynamic measurements were obtained at 15-minute intervals using a Dinamap monitor (Dinamap Compact Monitor, Tampa, Fla) for the measurement of BP and a Cardiodynamics BioZ (Cardiodynamics, San Diego, Calif.) for the measurement of heart rate (HR), stroke volume (SV) and cardiac output (CO), from which total peripheral resistance (TPR) was calculated. These values were averaged across the time periods to produce a single value for each time period. The subjects were required to drink 200 mL of water every hour to

ensure they remained hydrated and provided adequate urine samples.

Analyses

The general linear model was used to model the effects of race, sex, and their interaction on change in hemodynamic variables and U_{Na}V during the competitive video game task. Additional covariates in the model included body mass index (BMI), baseline values associated with each dependent effect, and study cohort. Study cohort was included in the model (ie, blocking factor) since the data came from two separate studies. Study cohort was also used as a means of replicating the results. Race and sex means were adjusted for all effects in the statistical model. Full model residuals were examined against full model predicted values to evaluate the assumptions associated with the parametric general linear model. The intercorrelation structure of the dependent variables (ie, change

scores during the competitive video game) was examined by calculating the partial correlations from the error sums of squares and cross-products matrix of the general linear model. Standard errors associated with race and sex means presented in the tables and figure are adjusted standard errors and reflect the variation specifically associated with the statistical tests. Exact *P* values were calculated and reflect the probability of the observed mean difference in a noise only system.

RESULTS

Changes in Sodium Excretion

Table 2 provides the adjusted race-by-sex means and associated standard errors for the changes from baseline to stress.

We found significant main effects for both race ($F[1,183]=5.28$, $P=.0227$) and sex ($F[1,183]=5.72$, $P=.0178$) for U_{Na}V, but there was no interaction. The main effects of race and sex each accounted for approximately 3% of the total model variation (full model R^2 which included the covariates=.17). Caucasian, compared to African American (4.8 mEq/hr vs 2.8 mEq/hr), and boys compared to girls (4.8 mEq/hr versus 2.7 mEq/hr), had greater changes in U_{Na}V. The direction of the effects replicated across cohorts with virtually the same means and effect size obtained for the combined cohorts.

Hemodynamic Changes

The changes for systolic and diastolic BP are presented in Figure 1.

Caucasian girls had a smaller change in systolic BP than the other three race/sex groups. This produced a statistical interaction between race and sex ($F[1,183]=5.66$, $P=.0184$) since the difference in the change in systolic BP between races was greater in girls (4.3 mm Hg) than in boys (0.5 mm Hg). The smaller change in systolic BP

Table 2. Mean differences and adjusted standard errors between pre- and post-competitive video game by race and sex

Dependent Variable	African American		Caucasian	
	Girls	Boys	Girls	Boys
SBP (mm Hg)	6.73 (1.05)	9.44 (1.14)	2.43 (1.02)	9.90 (.09)
DBP (mm Hg)	5.64 (1.01)	5.91 (1.11)	3.91 (.88)	6.63 (.84)
TPR (dynes.s.cm ₋₅)	0.743 (.25)	0.953 (.26)	0.610 (.23)	0.579 (.23)
SV (mL/min)	-6.03 (1.18)	-5.6 (1.12)	-6.94 (1.05)	-4.67 (1.11)
HR (bpm)	10.35 (1.28)	5.77 (1.28)	8.15 (1.17)	7.42 (1.14)
U _{Na} V (mEq/hr)	1.77 (.9)	3.73 (.91)	3.70 (.82)	5.80 (.8)

Abbreviations same as in Table 1

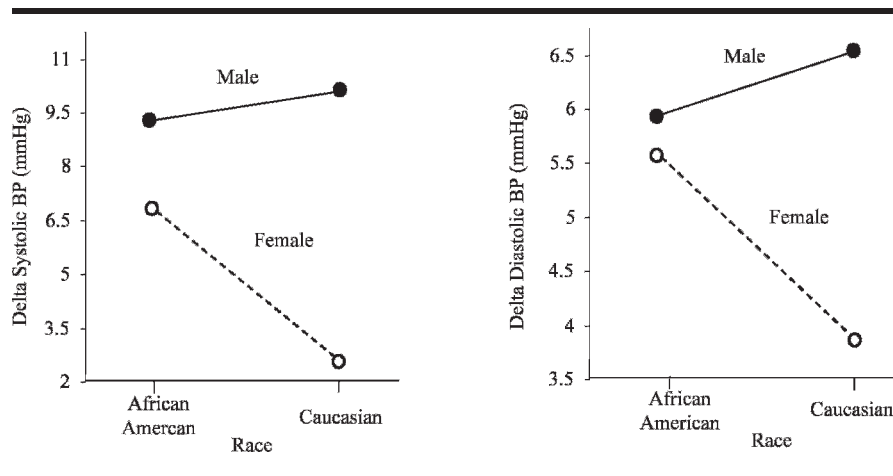


Fig 1. Pre- to post-competitive video game change in systolic and diastolic BP by race and sex

for Caucasian girls resulted in a main effect of sex ($F[1,183]=20.30, P=.0001$). The race main effect was marginal, resulting primarily from the disparity of the Caucasian girls as compared to the other three race/sex groups ($F[1,183]=3.44, P=.0652$). When the race/sex combinations were modeled as four separate groups rather than main effects and interactions (ie, factorial layout), the difference between Caucasian girls and the other three race/sex groups accounted for 86% of the difference between the four race/sex group combinations ($F[1,183]=25.8, P<.0001$). The full model R^2 was .19 with a partial R^2 of .10 associated with race/sex group differences. Race by sex means were generated separately for each study cohort to check the reproducibility of this result (ie, the large

difference due to Caucasian girls). For cohort 1 ($n=94$), Caucasian girls had a mean change in systolic BP of 2.19 mm Hg compared to an overall average of 10.43 mm Hg for the other three race/sex groups. For cohort 2 ($n=96$), the same pattern was observed. Caucasian girls had a mean difference in systolic BP of 2.50 mm Hg compared to an overall average of 7.03 mm Hg for the other three race/sex groups. The range of mean changes in systolic BP for all race/sex groups other than Caucasian girls was 12.2 mm Hg to 7.2 mm Hg for cohort 1, and 7.6 mm Hg to 6.2 mm Hg for cohort 2. The effect for change in diastolic BP, although not as strong, showed the same general pattern. For the change in diastolic BP, the lowest mean was associated with Caucasian girls. This produced a main

effect of sex ($F[1,183]=5.35, P=.0218$) and a slight race-by-sex interaction ($F[1,183]=3.57, P=.0605$) similar to that of change in systolic BP.

There were no main effects or interactions for the change in TPR or SV ($F_s[1,179] \leq 1.20, P_s \geq .2751$). There was only a slight sex main effect for change in HR ($F[1,179]=3.99, P=.0473$) with a greater change in heart rate for girls compared to boys.

The inter-correlation structure of the dependent measures was examined to evaluate the concordance between change scores during the competitive video game task. Table 3 presents the correlations of those variables that accounted for at least 2% shared variance. For purposes of replication, correlations were calculated separately for each cohort as well as the total sample. As might be expected, the hemodynamic variables correlate directly or indirectly with each other. The only hemodynamic measure that correlated with change in U_{NaV} was change in total peripheral resistance. All of the correlations replicated across cohort with the possible exception of HR and systolic BP.

DISCUSSION

The results of this study are consistent with the hypothesis that race differences in SIPN contribute to the development of salt-sensitive HTN in African Americans. Overall, African Americans compared to Caucasians showed a smaller natriuretic response to the prolonged stress period. A fourth of the increase in BP in Caucasian girls induced a similar natriuretic response to that observed in African American boys, indicating a far superior pressure natriuresis response for this group. The increase in BP was similar for the African American and Caucasian boys, but this was associated with more than a 2 mEq/hour greater increase in U_{NaV} for the Caucasian boys, suggesting

Table 3. Correlations between dependent variable change scores by cohort and by total sample

Variables	Cohort 1	Cohort 2	Combined
$\Delta SBP, \Delta DBP$.54	.56	.65
$\Delta SBP, \Delta HR$.18	.65	.44
$\Delta DBP, \Delta TPR$.53	.32	.46
$\Delta SV, \Delta TPR$.62	.45	.55
$\Delta TPR, \Delta HR$.38	.42	.39
$\Delta TPR, \Delta U_{NaV}$.18	.16	.16

Abbreviations same as in Table 1

Note: Delta is change from baseline to video game challenge. For all correlations in the combined sample, $P<.05$. Correlations not presented were $<2\%$ explained variance (ie, $R^2<.02$). Correlations were calculated from the full model error sums of squares and cross-products matrix (ie, corrected for race, sex, and covariates).

Overall, African American compared to Caucasians showed a smaller natriuretic response to the prolonged stress period.

a superior pressure natriuresis response for this group. The African American girls had the smallest change in $U_{Na}V$ relative to their change in BP, which was less than half the change for Caucasian girls despite more than twice the change in BP. This is consistent with a superior pressure natriuresis response for the Caucasian compared to the African American girls.

These findings are consistent with those reported by Light and her colleagues¹⁰ in the first study to report race differences in SIPN. They exposed 28 adults, including 14 African Americans and 14 Caucasians, to a series of mental stressors for one hour. The African American subjects showed a smaller stress-induced change in $U_{Na}V$ with a reduction in $U_{Na}V$ in 6 of the 14 African Americans compared to only 2 of the 14 Caucasian subjects. The results are also consistent with our initial study in youths⁹ that was performed on a cohort of 118 African Americans aged 15–18 years. We observed that approximately a third of these individuals retained rather than excreted sodium during a one hour competitive video game task. Sodium retention was associated with a volume-mediated increase in BP. In addition, the results are consistent with a previous study by our group,⁸ which examined changes in $U_{Na}V$ across a series of tasks (playing video game, ice to forehead, an echocardiogram). The subjects included 69 African American and 52 Caucasian adolescents with a family history of HTN. The African Americans had a greater increase in BP averaged across

the tasks coupled with a smaller increase in $U_{Na}V$, indicating impaired SIPN.

The mechanisms underlying an impaired natriuretic response to stress are not fully understood. Three studies^{21–23} normalized the response pattern using angiotensin converting enzyme inhibitors that implicate the renin-angiotensin-aldosterone system. However, which component of this system is the key component is unclear. Both angiotensin II^{23–25} and aldosterone²⁶ have been implicated.

Overall, boys compared to girls, had a greater stress-induced increase in $U_{Na}V$. This was associated with a greater stress-induced increase in BP, which is consistent from the literature.^{27,28} Although there was a modest overall correlation between change in $U_{Na}V$ and change in TPR, we were unable to establish an overall correlation between change in $U_{Na}V$ and change in BP after adjusting for race and sex. This suggests that the concomitant mean changes seen in $U_{Na}V$ and BP for boys and girls may involve separate and distinct compensatory mechanisms that may be sex and/or race specific. We are aware of only one previous study²⁴ that examined sex differences in SIPN. In this study, we reported that boys did not show a greater increase in $U_{Na}V$ to compensate for their greater increase in BP to the stressor. The factors related to sex differences in the pressure natriuresis responses remain uncertain. In our previous study²⁴ cited above, we observed that angiotensin II contributed to sodium retention in boys but not girls. Differences in BP responses are often attributed to either the vasodilatory effects of estrogens, the vasoconstrictive effects of androgens, or impaired regulation of the renin-angiotensin-aldosterone system.^{29–32} However, we did not measure these in this study. Alternatively, the greater increase in BP in boys could be due to greater arousal. This explanation is not supported by the results for the change in heart rate, which was greater in girls for both races.

These findings are consistent with previous literature,^{27,33–35} which reported that greater changes in heart rate in females are coupled with smaller changes in BP.

In conclusion, the reduced natriuretic response to stress may be a marker or mechanism for the development of salt-sensitive HTN in African Americans. The race difference in the pressure natriuresis response within girls is of interest and worthy of further investigation. It is unclear if this difference represents a “protective” response pattern in the Caucasian girls or an “abnormal” response pattern in African American girls. The former is supported by the results that show Caucasian girls had the smallest increase in BP coupled with a good natriuretic response, as noted previously. The latter is supported by the finding that African American girls show a similar change in BP as the males, coupled with the smallest natriuretic response.

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AUTHOR CONTRIBUTIONS

Design concept of study: Harshfield, Hanevold, Dong
Acquisition of data: Kapuku, Castles
Data analysis and interpretation: Harshfield, Hanevold, Kapuku, Dong, Ludwig
Manuscript draft: Harshfield, Hanevold, Dong, Castles, Ludwig
Statistical expertise: Ludwig
Acquisition of funding: Harshfield, Hanevold
Administrative, technical, or material assistance: Kapuku, Dong
Supervision: Harshfield, Hanevold, Kapuku, Castles