RACE/ETHNICITY DETERMINES THE RELATIONSHIPS BETWEEN OXIDATIVE STRESS MARKERS AND BLOOD PRESSURE IN INDIVIDUALS WITH HIGH CARDIOVASCULAR DISEASE RISK

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Abstract

Oxidative stress (OS) and cardiovascular (CV) reactivity are related to CV morbidity and mortality. However, little is known about the relationships between these CV risk factors and their confounders. We hypothesize that higher OS is linked to higher blood pressure (BP) reactivity to acute laboratory stressors and in the natural setting. We studied 137 subjects with a family history of hypertension and early myocardial infarction. There were 63 European Americans (EA's) (38 males) and 74 African Americans (AA's) (35 males), aged 19 to 36(27.6+/−3.1). The protocol included a competitive video game, cold stressor, and ambulatory BP recording. Blood samples were drawn 6 times for OS markers (8-OHdG and 8-Isoprostane) assay. Repeated measures analyses of covariance were used to test for mean differences and Pearson correlations were used to test OS and BP associations. There were no significant race/ethnicity differences in BP reactivity to either stressor (both p's>0.48). 8-OHdG levels were significantly lower across all time points for AA's than for EA's ($p<0.05$) while levels of 8-isoprostane did not differ significantly ($p>.10$). Averaged 8-OHdG levels significantly correlated with SBP reactivity (r=0.45, <0.01) and 24-hour, daytime, and nighttime SBP (r range=0.37 to 0.42, all p's<0.02) for EA's but not for AA's, whereas 8-isoprostane levels were significantly correlated with reactive SBP and nighttime DBP (both r's=0.38, p<0.01) for AA's but not for EA's.

These findings suggest a link between OS and BP changes in subjects at high risk for CV disease. Further, race/ethnicity determines which OS marker will impact BP variation implying race/ethnicity differences in OS related mechanisms of CVD.

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No conflicts of interest to report.

Keywords

Blood Pressure; Oxidative Stress; Race/Ethnicity

INTRODUCTION

African Americans (AA's) have earlier onset and higher prevalence of essential hypertension (EH) and greater associated end-target organ damage than European Americans (EA's)[1–3]. This race/ethnicity disparity may be partially explained by varied mechanistic pathways including race/ethnicity differences in chronic stress exposure, stress induced BP reactivity, vasoactive substance release (e.g., epinephrine, endothelin-1, angiotensin II, brain natriuretic peptide, and nitric oxide) and sodium handling[4–11]. Unfortunately, biobehavioral and pharmacological interventions targeting the above mechanisms have failed to completely expunge race/ethnicity differences in BP prompting the search for other possible candidate risk factors[12–16].

Free radicals such as reactive oxygen (ROS) and reactive nitrogen species are continuously produced during cell metabolism[17]. A myriad of oxidative stress biomarkers have been developed that probe the effects of the short living free radical and 8-hydroxydeoxyguanosine (8-OHdG) reflects DNA damage[18, 19]. For instance, 8-isoprostane characterizes lipid peroxidation[20] and 8-hydroxydeoxyguanosine (8-OHdG) reflects DNA damage[18][19]. Compared to EA's, AA's are reported to have higher levels of oxidative stress markers and lower levels of antioxidant scavengers[21–23]. Yet, the significance of different oxidative stress biomarkers as a function of race/ethnicity has not been reported.

Data from a number of animal and human studies imply that increased oxidative stress contributes to BP elevation[24, 25]. Therefore, we hypothesize that higher oxidative stress is linked to higher blood pressure reactivity to laboratory and natural setting stressors. The present study examined such relationships among normotensive AA and EA adolescents and young adults at high risk of developing CV disease due to a family history of hypertension and/or MI.

METHOD

Subjects were 137 apparently healthy individuals, normotensive for age and sex, who are participating in a longitudinal study of development of cardiovascular disease risk factors. Family history of essential hypertension (EH) was defined as the occurrence of EH (i.e., SBP 140 mm Hg and/or DBP 90 mm Hg or antihypertensive medication) in 1 or both biological parents and a family history of premature myocardial infarction (MI) which was defined as the occurrence of MI in either biological parent or any biological grandparent before 55 years of age. Diagnosis of EH and of premature MI was verified by the subject's physician or medical records[26, 27]. Inclusion criteria were: 1) African American or European American; 2) Healthy with no history of congenital heart defect or any chronic illness or health problem requiring pharmacological treatment. Exclusion criteria include: 1) Pregnant; 2) History of psychiatric problems.

After obtaining written informed consent, each subject was escorted to a quiet, temperature-controlled room where anthropometric measurements (e.g., height, weight, waist and hip circumferences, suprailliac, subscapular, and triceps skinfold thicknesses) were recorded using established protocols[28]. The subject was then fitted with equipment for recording BP and HR (Dinamap Model 1846 SX, Critikon Inc, Tampa, FL).

After attachment of the BP cuff to the dominant arm, the subject assumed a supine position on a hospital bed. The elbow of the non-dominant arm was stabilized with an arm board; a 21-gauge butterfly needle was inserted into the antecubital vein, and a three-way plastic stopcock was attached. Immediately after needle placement, a 5-ml blood sample was drawn, transferred to a 10-ml prechilled EDTA tube vacutainer, and maintained on ice. All subsequent blood collection followed this procedure. One ml of 0.9% saline was infused at 2 to 3 minute intervals to try to help maintain patency. Blood was centrifuged at 4°C and plasma collected and stored at −80°C until analysis.

Hemodynamic Evaluations and Blood Collections

After the initial blood draw, the subject was given standardized instructions to relax as completely as possible for 20 minutes. Hemodynamic measurements (i.e., SBP, DBP) were obtained every 5 minute (readings at minutes 15 and 20 were averaged and subsequently used as baseline values). At minute 20, 5-ml blood samples were drawn. Following the baseline evaluation, the subject engaged in two laboratory stressors (viz., video game and forehead cold) using standardized protocols[26, 27, 29]. The 10-minute video game stressor "Break Out" (Atari Inc, USA) was presented under a monetary incentive challenge. The video game controller was secured at a position comfortable for use with the subject's dominant hand. The game was presented on a 635-mm diagonal color television located 2 m from the subject at a position comfortable for viewing. Hemodynamic readings were obtained during minutes 1, 3, 5, 7, and 9 of the video game task and a 5-ml blood sample was obtained immediately at its completion. The hemodynamic measurements were averaged and the averages were used in data analyses as values for the video game phase. A blood sample was also taken at 20 minutes following the game during the video game recovery phase. The forehead cold-stimulation task was based on a protocol developed in our laboratory[30]. A plastic bag containing 6 cups of crushed ice and 1.5 cups of water was placed on the subject's forehead for 1 minute. Hemodynamic measurements and blood samples were concomitantly obtained immediately on completion of the stressor. A blood sample was also obtained at minute 20 during recovery. Hemodynamic measurements were obtained every 3 minutes during the recovery periods and the averages of the last 2 readings were used as the values for the video game recovery phase and forehead cold recovery phase. Descriptive statistics for subjects are given in Table 1.

Ambulatory Blood Pressure (ABP)

After completion of the laboratory protocol an ABP monitor (Spacelabs Model 90207) was fitted to the non-dominant arm and calibrated (Spacelabs, Inc.; Redman, WA). The monitor was programmed to repeat a reading if values were outside acceptable ranges of 70 to 285 mm Hg for SBP, 40 to 150 mm Hg for DBP, or 40 to 180 bpm (beats per minute) for HR. Adequacy of readings was based on acceptable readings using previously established

criteria[31]. A subject had to have more than 75 % of expected BP readings for data to be used in subsequent analyses. Typically measurements were obtained every 20 min. during the daytime (8AM to 10PM) and every 30 min. during the nighttime (12 midnight to 6AM). The subject was given instructions for wearing the monitor (e.g., cessation of body movement at pre-inflation auditory cue while awake and the method for adjusting a slipped cuff). The data retrieved from the ambulatory blood pressures recorder were entered into an ABP analyzer for editing and analysis following these criteria: systolic blood pressure between 70 and 180 mm Hg, diastolic blood pressure between 45 and 100mm Hg, pulse pressure 20mm Hg or more, and HR 40 to 180 bpm. These criteria represent the 90th percentile of each parameter. For data analyses purposes, ambulatory hemodynamic values were the averages of the hourly values for the daytime hours, nighttime hours, and the 24 hours.

Oxidative Stress Assays

8-OHdG enzyme immunoassay (EIA) was quantified using competitive assay that utilizes anti-mouse IgG-coated plate and a tracer consisting of an 8-OHdG enzyme conjugate (Cayman Chemical Company, Ann Arbor, Michigan, USA). This EIA recognizes both free 8-OHdG and DNA incorporated 8-OHdG since plasma is comprised of a mixture of DNA fragments and free 8-OHdG.

Also, plasma 8-isoprostane EIA was assayed from EDTA samples. The assay is based on competition between 8-isoprostane and 8-isoprostane acetylcholinesterase conjugate 8-8-isoprostane (tracer) for limited number of 8-isoprostane specific rabbit antiserum binding sites (Cayman Chemical Company, Ann Arbor, Michigan, USA).

The intra-assay and inter-assay variabilities were 8% and 7% respectively for isoprostane, and for 8-OHdG intra- and inter- assay variabilities were less than 10%.

Statistical Analyses

Repeated Measures Analyses of Covariance (RmANCOVA's) were used to test statistical significance of the protocol phase, race/ethnicity, and sex, and their interactions for SBP, DBP, 8-OHdG, and 8-isoprostane. BMI was used as a covariate. For SBP and DBP there were 5 phases (viz., resting, videogame stressor, videogame recovery, ice stressor, ice recovery). For 8-OHdG and 8-isoprostane there was an initial baseline phase prior to the resting phase. Post-hoc analyses for protocol phase were done using paired t-tests. Pearson correlations were computed for 8-OHdG and 8-isoprostane with reactive SBP and with ambulatory SBP and DBP.

RESULTS

Systolic Blood Pressure

For SBP, there were significant phase, race/ethnicity and sex effects (all p's<0.001) but no significant interaction effects (all p's>0.35). During each phase males had higher SBP than females and AA's had higher SBP than EA's. Across the phases, SBP was highest for the ice stressor, followed by the videogame stressor. The lower values for the initial resting phase, the video game recovery phase, and the ice recovery phase were not significantly

different from one another. Results for DBP were similar to those for SBP except there was no significant sex effect.

Oxidative Stress

Results for 8-OHdG showed a significant sex effect (males>females, p<0.001), but no significant race/ethnicity, phase, or interaction effects (all p's>0.22). For 8-isoprostane, the phase effect was significant (p<0.001) as was the race/ethnicity by sex interaction (p<0.02). There were no significant interactions involving the phase effect (all p's>0.14). The phase effect was characterized by increasingly higher values across the phases with a slight drop during the ice recovery. The race/ethnicity by sex interaction was characterized by EA males having the lowest values followed by AA females, then AA males and finally EA females. These relative rankings applied to all phases. Figure 1 shows proportional changes relative to the baseline for 8-isoprostane and 8-OHdG at all phases.

Association between Systolic Blood Pressure and Oxidative Stress

Pearson correlations were computed between the 8-isoprostane levels and the BP reactivity values (videogame and ice stressor values – baseline values) separately by race/ethnicity. For AA's, SBP reactivity to the videogame stressor was significantly related to 8–isoprostane level (r=0.38, p<0.01), whereas, for EA's the correlation was not statistically significant (r= −0.18, p>0.17) (Figure 2).

Similar correlations for 8-OHdG were significant for EA's (r=0.45, <0.01) but not for AA's (r=0.15, p>0.29) (Figure 3).

8-OHdG levels were significantly correlated with 24-hour, daytime, and nighttime BP for EA's (r range=0.37 to 0.42, all p's<0.02) but not for AA's (r range=0.11 to 0.27, all p's>0.05) (Figure 4).

Correlations were also computed for daytime, nighttime, and 24-hour ambulatory BP with 8-isoprostane levels. The correlation of 8-isoprostane levels with nighttime DBP was significant for AA's (r=0.38, p<0.01), but not for EA's (r=0.16, p>0.18) (Figure 5).

DISCUSSION

The major findings of this study are twofold. First, oxidative stress markers are related not only to blood pressure reactivity, but also to blood pressure levels in the field. Secondly, there is a race/ethnicity dependent relationship between oxidative stress markers and BP changes. 8-OHdG levels were significantly correlated with systolic blood pressure reactivity for EA but not for AA, whereas 8-isoprostane levels were significantly correlated with reactive systolic blood pressure for AA but not for EA. These findings suggest that race/ethnicity and measure of oxidative stress should be taken into account when examining the relationship between oxidative stress and blood pressure.

Although oxidative stress has been recognized as a contributor to blood pressure elevation, the link between oxidative stress and BP reactivity to acute stressors and in the field remain unclear. As such, 8-isoprostane has been shown to be a potent pulmonary and renal

vasoconstrictor[32, 33]. It may increase BP via increased renal vascular resistance[34, 35] and enhanced vasoconstrictive response to stress[36]. Levels of 8-OHdG increase in the early stage of hypertension and decrease with blood pressure lowering therapy[37] suggesting that blood pressure elevation may be the precursor of oxidative stress.

Previous studies have linked acute and chronic stress to oxidative stress[38, 39]. However, in the present study, the changes in lipid peroxidation could not be definitively linked to a videogame challenge and cold stressor stimulation since 8-isoprostane levels increased even in resting condition and the videogame challenge elicited mild increase. Also, the cold challenge induced elevation of blood levels of 8-isoprostane but was not greater than that observed during the resting period. Finally, the recovery periods between tasks were not accompanied by a drop in blood levels of 8-isoprostane. Meanwhile, 8-OHdG levels remained constant during the experimental protocol. These findings are in contrast to those of Huang et al[40] who found that oxidative stress, as probed by 8-isoprostane, increased following a dual challenge of physical (i.e., cycling) and mental stress (arithmetic challenge and Stroop effect) in healthy participants. The differences between the two studies could be due to study protocol and design (cold stressor vs. exercise; video game vs. mental arithmetic and Stroop effect).

In the present study we found that higher blood levels of oxidative stress markers paralleled higher BP in males, but not in females. Relationships between higher oxidative stress and increased BP have been consistently shown in males[41]. However, in pre-menopausal females such an association has been hard to prove because of possible sex differences in anti-oxidant capacity and the possible buffering effect of estrogen[42, 43]. Most studies have linked fat and oxidative stress[44–46]. Animal and human fat have been shown to increase free radical production[47, 48]. This contributes to increased oxidative stress in the vascular wall, endothelial dysfunction and hypertension[49]. Adiposity is plausibly associated with lipid peroxidation. Olusi[44] showed that BMI is an independent predictor of lipid peroxidation and decreased cytoprotective enzymes in humans. Therefore, we believe that adiposity might confound the relationship between oxidative stress and BP rather than mediating it. Taking in account this phenomenon we covaried out BMI when probing the relationship between BP and oxidative stress.

The current study is the only study of which we are aware to show race/ethnicity dependent association between blood pressure and oxidative stress markers. Our findings are very provocative because they imply that free radical induced lipid peroxidation and DNA damage have different BP effects depending on race/ethnicity. Indeed, lipid peroxidation was related to BP variability in AA's while it had no effect in EA's. Alternatively, DNA damage contributed to BP reactivity in EA's not in AA's. The fact that the association of BP and measures of oxidative stress vary between ethnic groups indicates differences in BP control in these groups and could explain BP disparity and inspire race/ethnicity targeted treatment.

Study Limitations

Although provocative, our findings should be interpreted in the light of some unavoidable limitations such as: (1) we used an automatic device to measure blood pressure (i.e., Dinamap 1846 XT). The validity of blood pressure readings using this model of Dinamap

has been questioned[50]. However, the advantage of Dinamap, in general, is that it is easy to operate, it reduces the need for highly trained technicians, and it has an apparent objectivity of measurement, reducing digit preference and other possible technician biases. (2) We have found that the needle insertion almost invariably induces an increase in BP and HR, but that these values typically return to pre-insertion levels within 15 to 20 minutes of insertion. The effect of obtaining values that are higher than the actual baseline would be to underestimate reactivity values and the differences between the baseline phase and the stressor phases. Since the baseline phase values of the hemodynamic variables were not significantly different from their values during the stressor recovery phases, we feel somewhat confident that the 20 minute resting period after needle insertion was sufficient. (3) It would be interesting to evaluate other indices of redox status, such as antioxidant capacity, to further test the hypothesis. It would also be interesting to find out whether antioxidant capacity is inversely related to blood pressure and whether it differs between racial/ethnic groups. Overall, our findings suggest that BP change is linked with free radical induced DNA damage in EA's while it is related to free radical induced lipid peroxidation in AA's.

Perspectives

The results in the present study suggest a physiological link between oxidative stress and BP elevation. Our findings validate and extend the existing literature of the deleterious effect of free radicals on BP. Furthermore, we demonstrated that the relationship between oxidative stress and BP is race/ethnicity dependent. This represents a breakthrough in our understanding of the mechanisms of oxidative stress actions in different race/ethnicity groups. It is clear not only that oxidative stress could contribute to BP elevation, but it can be one of the mechanisms of race/ethnicity related differences in BP levels.

Acknowledgments

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What is known about this topic

- A positive family history of hypertension and/or myocardial infarction predisposes to cardiovascular disease.

- Cardiovascular reactivity is predictive of future manifestations of hypertension.

- Several previous animal and human studies have reported that oxidative stress is equally linked to the pathogenesis of hypertension.

What this study adds

- The results in the present study confirm a physiological link between oxidative stress and BP elevation. Furthermore, we demonstrate that the relationship of BP to oxidative stress is race/ethnicity dependent.

- Contrary to previous studies, we report that AA's have lower oxidative stress than their EA counterparts.

- Race/ethnicity determines which oxidative stress marker (e.g., lipid or DNA) will impact BP variation suggesting race/ethnicity differences in oxidative stress related mechanisms of CVD.
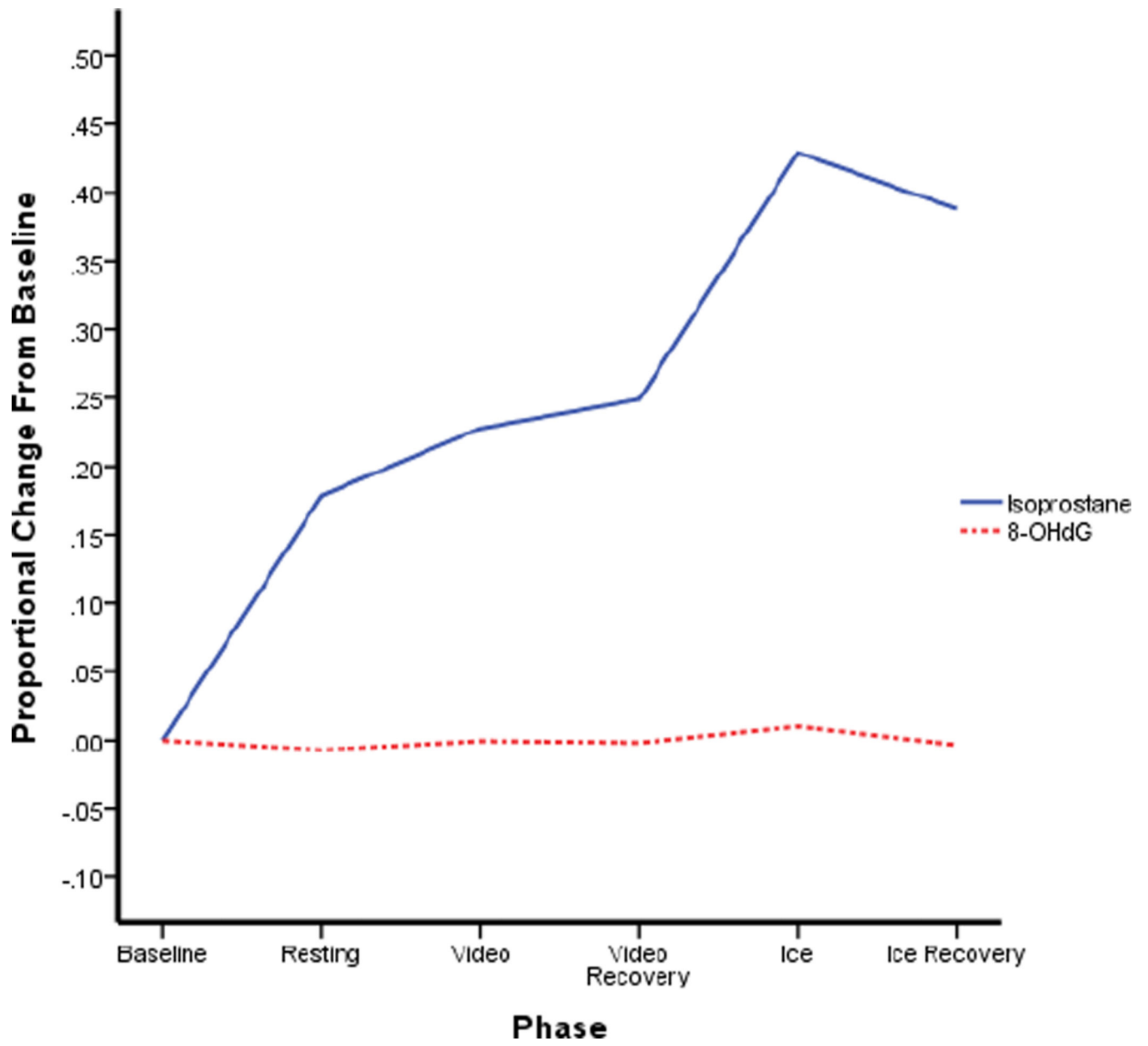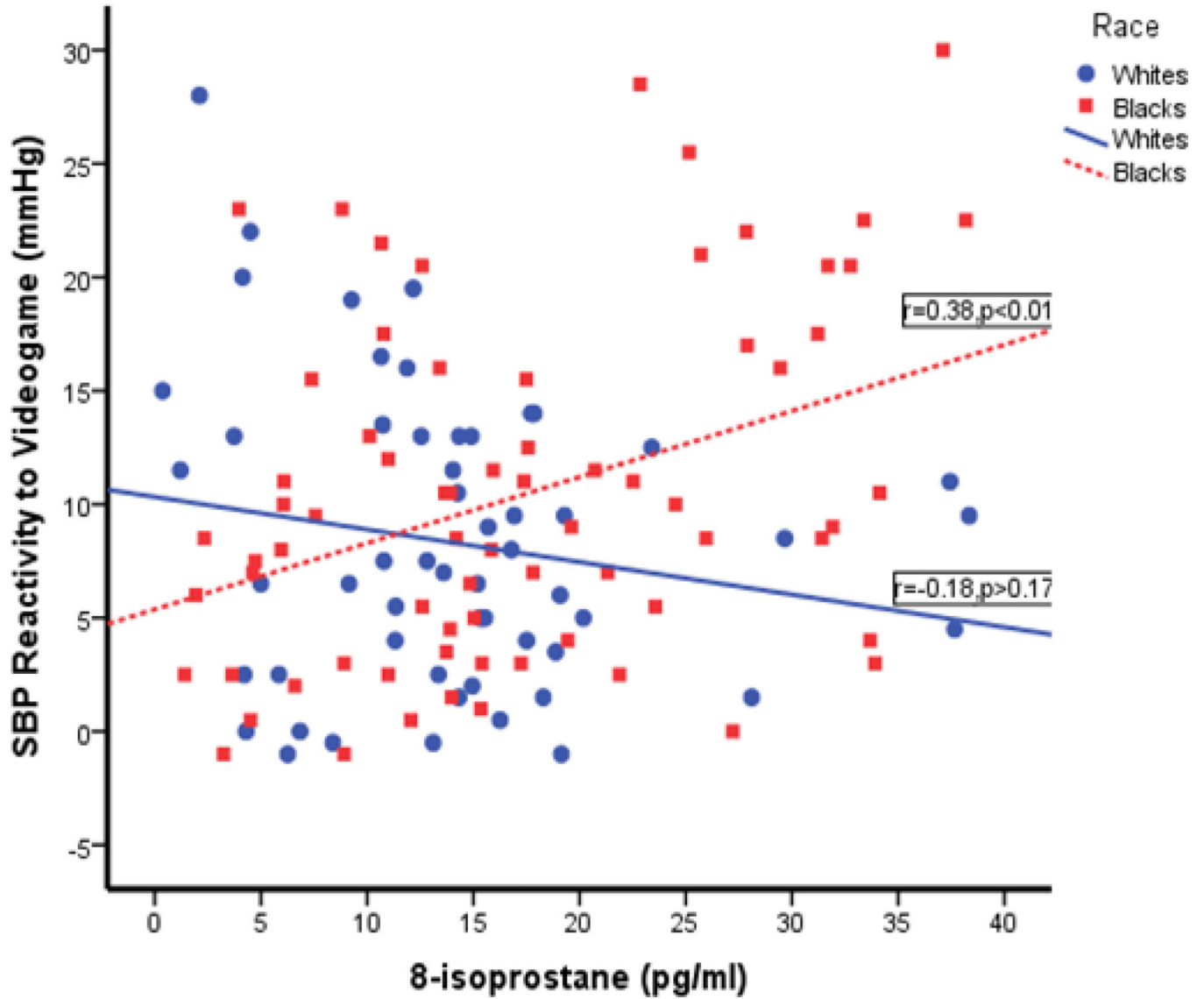
Figure 1.
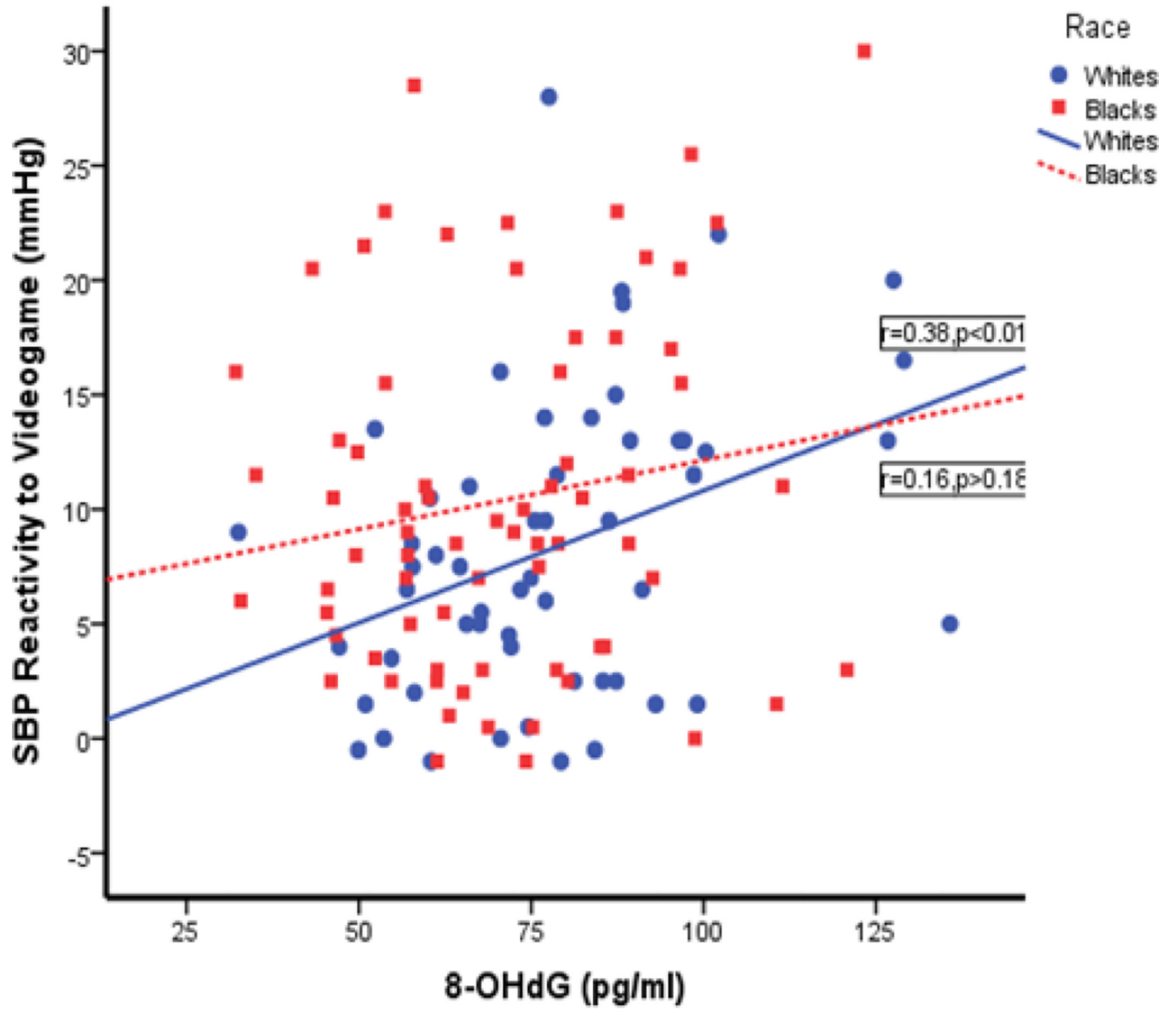Oxidative Stress Measures Across Protocol Phases

Figure 2.
Relationship between SBP Reactivity and 8-isoprostane Level by Race
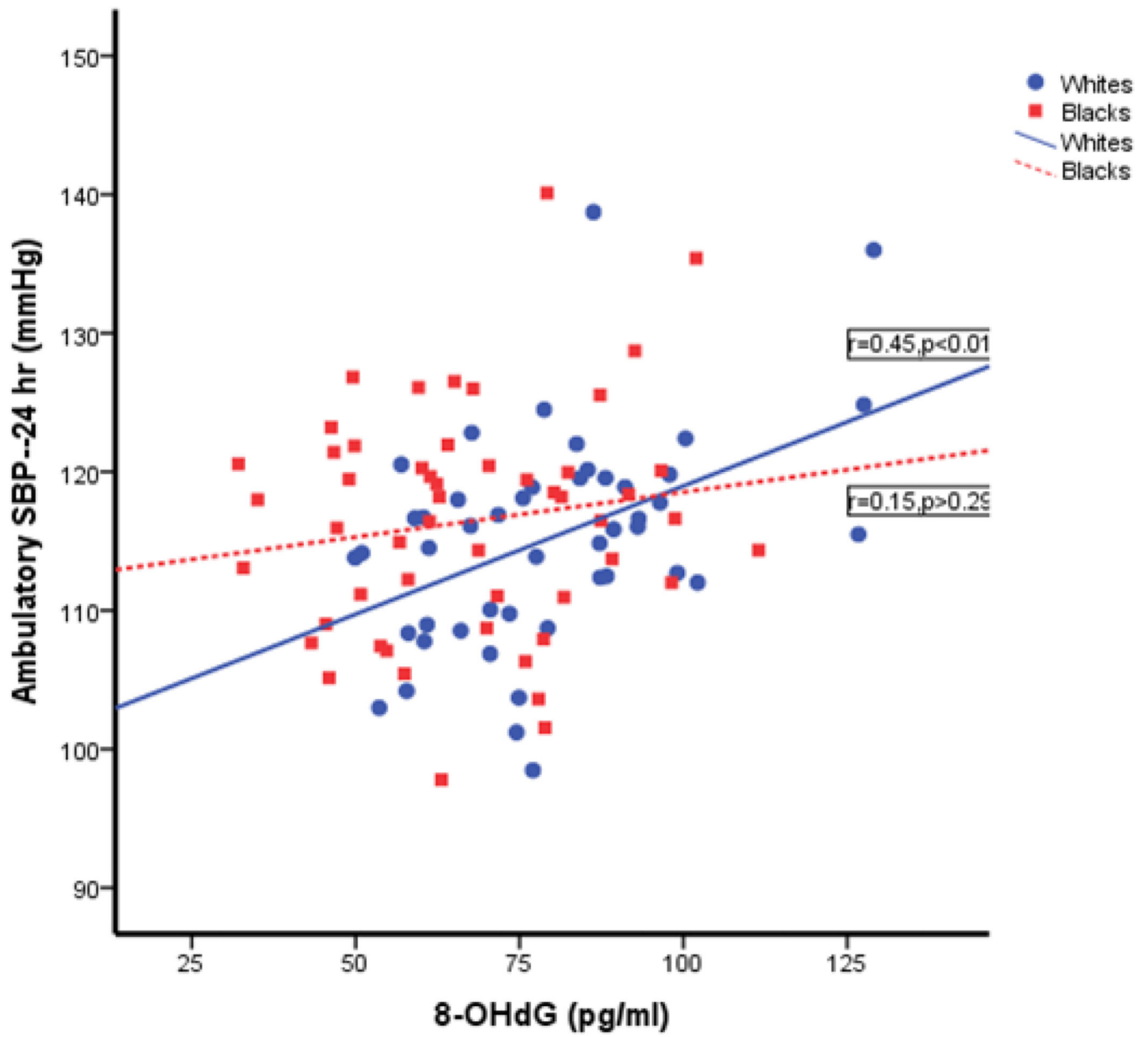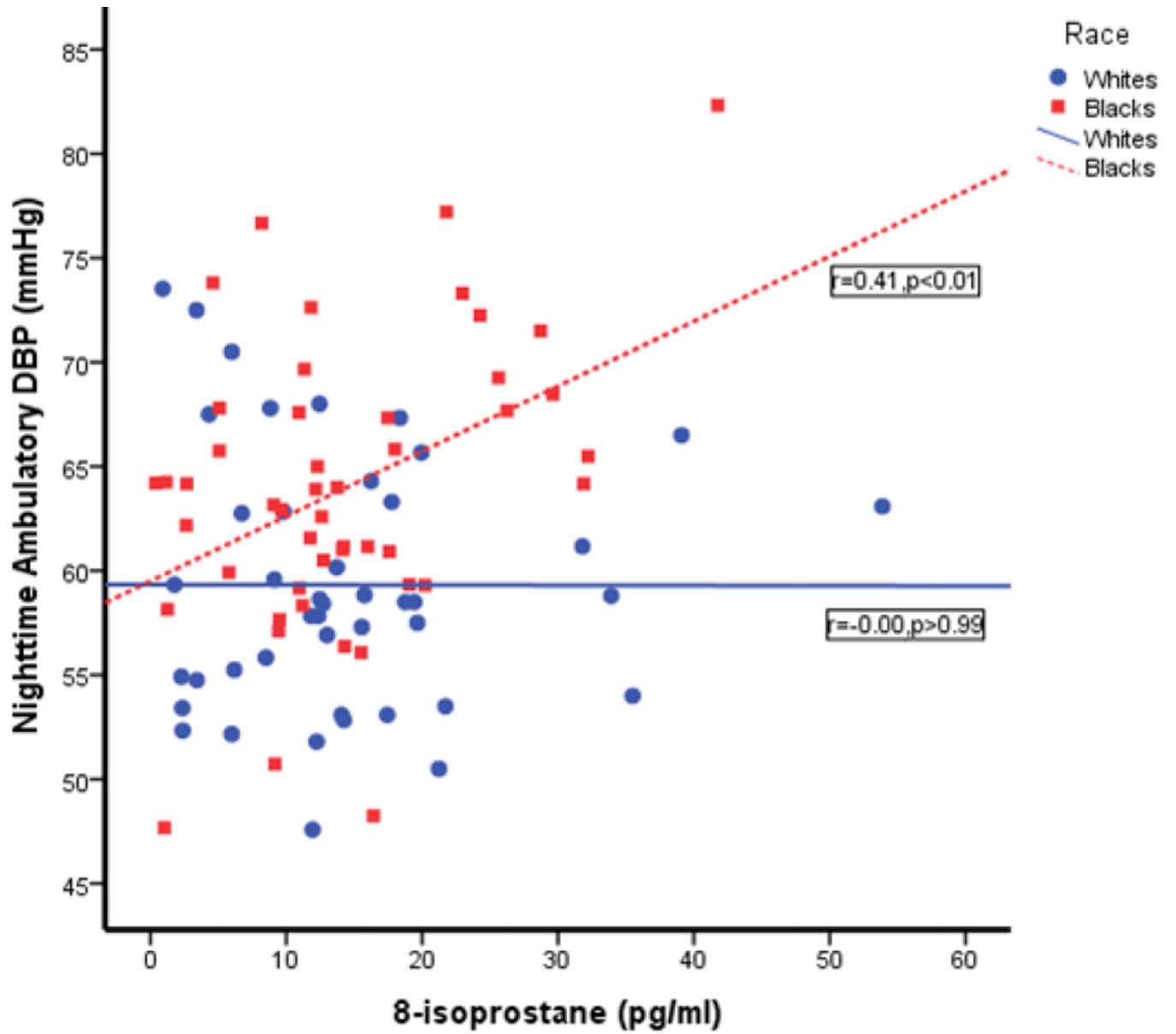
Figure 3.
Relationship between SBP Reactivity and 8-OHdG Level by Race

Figure 4.
Relationship between Ambulatory SBP and 8-OHdG Level by Race

Figure 5.
Relationship between Nighttime Ambulatory DBP and 8-isoprostane Level by Race

Table 1

Subject Characteristics (mean ± SD)

Variable	EA Males (n=38)	EA Females (n=25)	AA Males (n=35)	AA Females (n=39)	P values
Age	27.2±3.3	28.1±2.8	27.7±3.2	27.7±3.0	(R)ace=0.97, (S)ex=0.45, R × S =0.41
Height (cm)	178.3±7.0	163.9±7.0	177.0±7.0	165.3±6.7	R=0.93, S=0.001,R × S =0.27
Weight (kg)	85.6±16.7	79.9±26.2	93.3±26.9	85.0±22.5	R=0.10, S=0.08,R × S =0.74
BMI (kg/m^2)	26.9±4.9	29.9±9.1	29.6±7.7	31.0±7.8	R=0.15, S=0.08,R × S =0.54
SBP (mmHg)	113.5±9.4	103.8±10.9	121.1±11.5	114.8±11.8	R=0.001, S=0.001,R × S =0.38
DBP (mmHg)	64.3±8.4	63.9±8.2	69.8±7.4	69.5±7.8	R=0.001, S=0.81,R × S =0.95
HR (bpm)	59.8±8.3	67.7±10.1	60.5±10.7	66.1±8.1	R=0.79, S=0.001,R × S =0.48