Greater Orthostatic Tolerance in Young Black Compared With White Women

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Abstract—We hypothesized that orthostatic tolerance is higher in young, healthy black compared with white women. To determine orthostatic tolerance, 22 women (11 black and 11 white) underwent graded lower body negative pressure to presyncope. We measured blood pressure, heart rate, and R-R interval (ECG) continuously at baseline and through all of the levels of lower body negative pressure. Blood samples were taken at baseline along with presyncope for the measurement of plasma catecholamine concentrations, serum aldosterone concentration, and plasma renin activity. Cumulative stress index, the sum of the product of time and lower body negative pressure, was the indicator of orthostatic tolerance. Orthostatic tolerance in the black women was greater than in the white women [cumulative stress index: −1003 (375) versus −476 (197); P<0.05]. Although plasma concentrations of norepinephrine increased in both groups at presyncope, the increase was greater in black [Δplasma concentrations of norepinephrine: 167 (123)] versus white women [86 (64); P<0.05], as was the increase in PRA [ΔPRA 2.6 (1.0) versus 0.6 (0.9) ng of angiotensin II · mL⁻¹ · h⁻¹; P<0.05, for black and white women, respectively]. Although heart rate increased and R-R interval decreased to a greater extent during lower body negative pressure in black women compared with white women (ANOVA; P<0.05), baroreflex function (ie, slope R-R interval versus systolic blood pressure) was unaffected by race. These data indicate that orthostatic tolerance is greater in black compared with white women, which appears to be a function of greater sympathetic nervous system responses to orthostatic challenges. (Hypertension. 2010;56:00-00.)

Key Words: blood pressure ▪ racial differences ▪ arterial stiffness ▪ sympathetic nervous system

Orthostatic tolerance is a measure of the ability to maintain consciousness during changes in posture. Orthostatic stress induced by changes in posture, or by lower body negative pressure (LBNP), causes blood volume shifts to the lower extremities resulting in a fall in central blood volume. This fall in central blood volume stimulates both cardiopulmonary and arterial baroreceptors, leading to compensatory increases in heart rate (HR) and peripheral vasoconstriction. Despite the complex physiological systems evolved to maintain blood pressure during changes in posture, orthostatic intolerance is a relatively common blood pressure dysfunction in healthy young people and is more common in women than in men.1,2

Racial differences in blood pressure regulation have been well documented with regard to hypertension and on the whole have indicated that hypertension is more prevalent in the black versus white population.3 Moreover, hypertension manifests at a younger age in black compared with white people, and there are racial differences in the mechanisms that regulate blood pressure.4,5 With regard to orthostatic tolerance, in response to a 3.75-minute standing test, mean arterial pressure (MAP) increased in black subjects but fell in white and Asian subjects, indicating differences in response to postural challenges across the 3 races.6 Finally, although black subjects display smaller increases in muscle sympathetic nerve activity (MSNA) during baroreceptor unloading compared with white subjects,4 forearm vasoconstriction is greater in black subjects, which would suggest enhanced sympathetic vascular transduction.4,5

Although orthostatic intolerance disproportionally affects women, studies that have addressed racial differences in cardiovascular responses to maximal LBNP have focused on men4 or have not determined sex differences if women were included in the study.5 In light of the documented sex differences in orthostatic tolerance and racial differences in blood pressure regulation, we speculated that black and white women would respond differently to orthostatic stress induced by LBNP. We hypothesized that orthostatic tolerance would be greater in black compared with white women.

Methods

Subjects

Twelve black and 12 white women were recruited into the study. Subjects self-identified race, which in all cases was consistent with their visually observed phenotype. Given documented differences in blood pressure regulation and disparities in related clinical outcomes...
between black and white people, we chose to focus solely on these 2 populations excluding other races. Twenty-four women completed the experimental protocol. Two individuals, 1 black and 1 white, were excluded from data analysis because of a failure to experience presyncopal symptoms at LBNP test termination, so 11 subjects in each group were included in the analysis. One test was terminated because of technical difficulties, and the second was prematurely because the subject did not comply with the experimental protocol: she ended the test in the absence of any symptoms and told investigators that she had not felt any symptoms but ended the test prematurely because she felt nervous (white subject). Thus, 22 women were included in the analysis. All of the subjects were young, healthy, nonsmoking women with normal body mass index (BMI) who were not taking hormonal contraceptives or any other medication. All of the women provided written informed consent; this investigation was approved by the Yale University School of Medicine Human Investigation Committee.

Experimental Protocol
All of the testing was conducted in an environmental chamber (ambient temperature = 28°C). On arrival, hydration state was immediately assessed from urine-specific gravity. Specific gravity was 1.001 to 1.020 in all of the subjects. After the urine sample, the subject was weighed to the nearest 10 g on a balance beam, positioned in an LBNP chamber, and instrumented for the measurement of beat-to-beat arterial pressure and HR (Finometer, Finapres Medical Systems) on the middle finger of the right hand and R-R interval (ECG, PowerLab, AD Instruments). Blood pressure measurements for all of the results were derived from beat-to-beat blood pressure measurements from the Finometer. An automated blood pressure cuff (Colin Medical Instruments) was also placed on the left arm for standard brachial artery measurements. A 21-gauge Teflon catheter was placed in an antecubital or forearm vein of the left arm and maintained with a heparin block (20 U/mL).

Assessment of Orthostatic Tolerance
We used graded LBNP to presyncope to determine orthostatic tolerance.2–4 The subjects lay supine, sealed at the iliac crest enclosed in the LBNP box. All of the measurements were preceded by a 30-minute quiet rest period. At the end of this 30-minute rest period, a blood sample was taken for the measurement of catecholamines (epinephrine and norepinephrine [NE]), plasma renin activity (PRA), and serum aldosterone (S_ALD). After the blood sample, we recorded HR, R-R interval (ECG), and beat-to-beat blood pressure for 3 minutes while the subjects rested quietly. After this resting phase, maximal orthostatic tolerance was determined using similar methods to Fu et al.10,11 in which progressive LBNP is applied to presyncope. LBNP began at −15 mm Hg for 3 minutes and then increased to −20 mm Hg, followed by an increase of −10 mm Hg every 3 minutes until presyncope. Presyncope was defined as a decrease in systolic blood pressure (SBP; finger blood pressure, Finometer) to <80 mm Hg, a decrease in SBP to <90 associated with symptoms of lightheadedness, nausea, sweating or diaphoresis, or progressive symptoms of presyncope accompanied by a request from the subject to terminate the test.12 In this phase, all of the women experienced presyncope symptoms, and most achieved an SBP <90 mm Hg, with only 1 black and 1 white subject experiencing symptoms at SBP >90 mm Hg. A blood sample was drawn immediately after presyncope for the measurement of catecholamines, S_ALD, and PRA.

Determination of Orthostatic Tolerance
We used a cumulative stress index (CSI) to determine orthostatic tolerance. The CSI was calculated as the sum of the product of time and level of LBNP,10,11 and the LBNP tolerance index was calculated as the sum of the product of duration spent at each negative pressure and change in pressure from the previous stage.13 A more negative CSI, or greater LBNP tolerance index, indicated a higher negative pressure attained before presyncope symptoms and, thus, higher orthostatic tolerance. We assessed baroreflex responses by examining the slope of the average R-R interval (from ECG) as a function of SBP and of LBNP.14 The average R-R interval over the last 2 minutes of each stage and the corresponding stage of LBNP for each subject were used to determine the linear relationship between R-R and SBP/LBNP. We also determined R-R interval and LBNP over the last minute and the minute before the final minute to allow for comparisons among women who experienced syncope at different levels of LBNP. All of the data were recorded using a 16-channel PowerLab system with LabChart 6 software (AD Instruments).

Blood Analysis
Blood samples were separated immediately into aliquots. The first was added to a plain tube with no additive for analysis of S_ALD, a second aliquot was placed in a prechilled K+ EDTA tube containing EGTA and glutathione for analysis of plasma concentrations of epinephrine and plasma concentrations of norepinephrine (P[NE]+), and a final aliquot was also placed in a prechilled K+ EDTA tube for the analysis of PRA. All of the tubes were centrifuged and the plasma or serum pipetted off for analysis.

Catecholamines were analyzed using high-performance liquid chromatography with electrochemical detection (Colorchem Detector, ESA Corp). Serum concentrations of aldosterone and PRA were measured using competitive binding radioimmunoassay methods. Intra-assay and interassay coefficients of variation for the midrange standards were, respectively, as follows: S_ALD (175 pg/mL): 3.05% and 2.26% (Siemens Healthcare Diagnostics) and PRA (3.9 to 7.5 ng/mL per hour) 2.36% and 2.43% (DiaSorin).

Data Analysis
The statistical analysis was performed using SAS statistical software version 9.1 (SAS Institute Inc). Independent t tests were used to assess between group differences in CSI, LBNP tolerance index, age, BMI, baseline MAP, SBP, diastolic blood pressure, HR, R-R interval, and the slopes obtained from regression analysis for analysis of R-R interval and blood pressure relationships. Repeated-measures ANOVA determined trends in MAP, SBP, diastolic blood pressure, HR, and R-R interval response over time during LBNP. Not all of the subjects completed all of the LBNP levels, repeated-measures ANOVA was conducted only for stages completed by all of the subjects (0, −15, and −20). Separate ANOVAs were used to analyze variables at the final completed stage of LBNP for each subject and the final 2 minutes of LBNP preceding presyncope. Survival analysis was used to predict the probability of presyncope at each stage of LBNP. This probability was obtained from the hazard ratio according to the following calculation: hazard ratio (HR) = odds/[1 − odds], where p = HR/[1 + HR]. We also used survival analysis to predict the odds of presyncope for black compared with white women at each stage of LBNP. Data are expressed as mean (SD) in all of the tables; however, for clarity, SEs are shown in graphs. Differences were considered statistically significant when P < 0.05.

Sample size calculations were based on our primary outcome variable of interest, CSI (orthostatic tolerance). The desired statistical test was 2-sided, and we assumed an α level of P = 0.01 for our sample size calculations to account for multiple comparisons.15 We used a difference in CSI of 272 (102) to calculate statistical power.11 A sample size of 8 women per group allowed us >80% statistical power (1−β > 0.80) to detect a 35% difference in CSI between groups.

Results
Physical characteristics were similar between the racial groups (Table 1), as were resting cardiovascular variables (Table 2) and blood hormone concentrations (Table 3). The CSI was lower [−1003.5 (375.8) versus −476 (197.5); P < 0.05; Figure 1], and LBNP tolerance index was higher [218 (44.8) versus 150.8 (40.2); P < 0.05] in black versus white women. For all of the blood pressure and HR variables, presyncope decreases from baseline, recovery from presyncope, and recovery from baseline were similar for the racial groups.
The relationship among R-R interval, SBP, and LBNP was examined through baroreflex responses. We had to remove one (white) subject who was presyncopal before −40 mm Hg from the analysis to facilitate meaningful comparisons between the 2 groups. Race did not impact baroreflex response during increasing LBNP [slopes: −14.6 (6.4) and −16.8 (8.3) R-R interval in milliseconds per SBP in millimeters of mercury, for black and white subjects, respectively; Figure 3A and 3B]. We also examined the relationship between R-R interval and LBNP, including the stages 0, −15, −20, the final completed stage, and the final 2 minutes immediately preceding presyncope and test termination. Race did not impact baroreflex responses during increasing LBNP [slopes: −5.7 (2.0) and −3.5 (4.0), R-R interval in milliseconds per LBNP in millimeters of mercury, for black and white subjects, respectively].

**Hormonal Responses**
Plasma NE concentration increased from baseline in both racial groups, but $P_{[NE]}$ was greater in black versus white women at presyncope (Table 3; $P<0.05$), and there was a trend for a greater increase in $P_{[NE]}$ from baseline to presyncope in the black women ($P<0.05$). There were no racial effects on plasma concentrations of epinephrine, $S_{[ALD]}$, or PRA at presyncope, but the change in PRA from baseline to presyncope was greater in black versus white women, because PRA was slightly lower in the black women at baseline (Table 3; $P<0.05$).

**Discussion**
This is the first study to investigate racial differences in orthostatic tolerance in young healthy women. Our primary finding is that black women had greater orthostatic tolerance than white women of similar age, BMI, and health status.
Resting cardiovascular and hormonal variables were similar between the two groups, and key physical characteristics and cardiovascular variables known to impact blood pressure regulation were also similar between the two groups. LBNP induced greater increases in $P_{\text{NE}}$ from baseline to presyncope in black subjects compared with white subjects, and $P_{\text{NE}}$ was greater at presyncope in black compared with white subjects. Moreover, PRA increased in response to LBNP only in black subjects, suggesting some increase in renal sympathetic activity and that the renin-angiotensin system may play a role in the higher orthostatic tolerance in these young black women. Most importantly, these data suggest that mechanisms involved in hypertension in middle age and older black women.16–19 A recent study in black and white adolescent subjects demonstrated that race is a strong predictor of arterial stiffness,16 and there are a number of studies indicating lower compliance in the cardiovascular system of black versus white adult subjects.17–19 This is of particular interest because early changes in endothelial function, arterial stiffness, and intima wall thickness in young, normotensive individuals is associated with a greater risk of hypertension in later years.17–19 In the present investigation, we did not see racial differences in the baroreflex response, as measured by the relationship between R-R interval and SBP, supporting the contention that the mechanism for the racial differences in orthostatic tolerance might lie in the periphery. The extent to which LBNP translocates blood volume depends on the compliance of the vascular system. Thus, greater venous compliance could potentially increase the extent of blood pooling during LBNP leading to greater orthostatic stress.

**Table 3. Blood Hormone Responses to LBNP**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Black</th>
<th>White†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Presyncope</td>
</tr>
<tr>
<td>$P_{\text{NE}}$, pg/mL</td>
<td>197 (144)</td>
<td>365 (174)*</td>
</tr>
<tr>
<td>$P_{\text{EP}}$, pg/mL</td>
<td>20 (18)</td>
<td>64 (62)</td>
</tr>
<tr>
<td>$S_{\text{ALD}}$, pg/mL</td>
<td>98.9 (43.5)</td>
<td>107.7 (45.6)</td>
</tr>
<tr>
<td>PRA, ng Ang I mg/L h$^{-1}$</td>
<td>0.9 (0.5)</td>
<td>2.8 (1.5)</td>
</tr>
</tbody>
</table>

Blood hormone concentration at baseline, presyncope, and the change from baseline to presyncope. Values are mean (SD). Differences were considered statistically significant at $P<0.05$. Ang indicates angiotensin.

*Data were significantly different between black and white women.
†One subject was removed from the analysis because of an insufficient blood sample.
Race and sex differences in vascular reactivity to \( \beta_2 \)-adrenergic activation may also have influenced our findings. White women are more sensitive to \( \beta_2 \)-adrenergic receptor stimulation compared with white men, as demonstrated by greater forearm vasodilation in response to albuterol infusions. \(^23\) Within both sexes, black subjects have attenuated NO-dependent vasodilation relative to their white counterparts. \(^24,25\) likely the result of decreased NO production and endothelial dysfunction. \(^25,26\) Moreover, black subjects have reduced \( \beta_2 \)-adrenergic sensitivity as demonstrated by a blunted pulse wave velocity response to isoproterenol when compared with white subjects matched for age, sex, and BMI. \(^27\) Thus, differential interactions among sympathetic activity, endothelial function, and \( \beta_2 \)-receptors may contribute to the different responses between the black and white women to the orthostatic challenge in the present investigation.

PRA increased to a greater extent in black compared with white women during LBNP and may reflect increased sympathetic nervous system activity at the kidney. Our findings are consistent with earlier studies demonstrating that low PRA is associated with reduced orthostatic tolerance. \(^28\) Thus, the PRA response in the black women likely indicates renin-angiotensin-aldosterone system stimulation, resulting in greater peripheral vasoconstriction in response to the loss of central blood volume induced by the LBNP challenge. \(^28\) The renin-angiotensin-aldosterone system has been identified as an important mechanism for hypertension in both black men and women. \(^29\) The greater PRA responses in black women during LBNP appear to support an important role for this system in blood pressure regulation and perhaps are an early reflection of blood pressure dysregulation.

In summary, our data demonstrated significantly greater orthostatic tolerance in young, healthy black women compared with their white counterparts. This difference in orthostatic tolerance was not associated with any racial difference in baroreflex function but was associated with greater increases in \( P_{\text{NEj}} \), suggesting a greater sympathetic nervous system response to LBNP in the black subjects. The high orthostatic tolerance in the black women may also reflect vascular stiffening, or lower compliance, and perhaps contribute to hypertension later in life. \(^16\)–\(^18\)

**Limitations**

LBNP has been used in this study as a model orthostatic of stress, because many of the physiological changes are similar to standing and to head-up tilt. Most importantly, both head-up tilt and LBNP result in central hypovolemia and similar baroreceptor unloading. \(^30\) However, LBNP is not a perfect model for orthostatic stress, because some of the redistribution of blood volume during LBNP does not specifically mimic that of standing. For example, splanchnic...
volume decreases during application of LBNP but increases during head-up tilt, the latter being an action more similar to standing.31

Another limitation of this investigation is that we did not measure resting cardiovagal or sympathetic baroreceptor responses to acute changes in blood pressure. Future research into the mechanisms contributing to greater orthostatic tolerance in young black and white women should include measures of endothelial function and cardiovascular stiffness. Thus, further study of racial differences in orthostatic tolerance is necessary to elucidate the mechanisms behind, and the potential clinical consequences of, racial differences in orthostatic tolerance. Another limitation in our study is that we did not control for menstrual cycle phase. Although controlling for phase of the menstrual cycle is ideal, orthostatic tolerance does not change across the cycle.32,33 Moreover, the magnitude of the difference between the black and white subjects suggests that there would be minimal impact of reproductive hormones on these racial differences. However, although phase of the menstrual cycle can influence baroreceptor sensitivity and sympathetic outflow, these changes do not lead to alterations in vascular resistance.34 Finally, although the differences in orthostatic tolerance between the racial groups were striking, our sample size was low, so these data may be interpreted with caution.

Perspectives

The racial differences in orthostatic tolerance that we observed in this study were substantial and physiologically meaningful. We defined women as high (CSI: >755) or low (CSI: <425) tolerance, which is consistent with published literature10,11; there were 3 white women with high orthostatic tolerance, but there was only 1 black woman who would be defined as having low tolerance. Although enhanced orthostatic tolerance may be advantageous in these young women, this advantage may be a harbinger of the well-documented differences.

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Disclosures

None.

References

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