Orthostatic Tolerance

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 [plasma 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;56:75-81.)

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 presyncope 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 ended 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 beam balance, 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. The subjects lay supine, sealed at the iliac crest and maintained with a heparin block (20 U/mL). 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. The subjects lay supine, sealed at the iliac crest, and maintained with a heparin block (20 U/mL).

**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 duration and level of LBNP, and the LBNP tolerance index was calculated as the sum of the product of duration spent at each negative pressure and level of LBNP, and the LBNP tolerance index was calculated as the sum of the product of time spent at each negative pressure and level of LBNP. We used a cumulative stress index (CSI) to determine orthostatic tolerance.7–9 The subjects lay supine, sealed at the iliac crest and maintained with a heparin block (20 U/mL). 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 beam balance, 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).

**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. Because 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 − p), 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. We used a difference in CSI of 272 (102) to calculate statistical power. 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.

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**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.
Baroreflex Responses or R-R Interval-SBP Relationship

The relationship among R-R interval, SBP, and LBNP was examined through −40 mm Hg negative pressure to measure 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 men and women may already be present in young healthy women.

LBNP induces a downward shift of blood volume, with pooling of blood in the lower limbs, rendering this volume no longer available for central hemodynamics. Cardiopulmonary and arterial baroreceptors, located in the in pulmonary vessels, the carotid sinus, and aortic arch, sense changes in central pressure induced by the volume shift and send signals to the nucleus tractus solitarius of the brain to protect blood pressure and maintain consciousness. The sympathetic nervous system plays a crucial role in this baroreceptor-mediated blood pressure regulation by activating systems that increase vasoconstriction in the periphery to maintain blood pressure as long as possible. During a fall in central pressure, sympathetic nervous system activation also leads to renin and angiotensin II release, which would also contribute to increases in peripheral resistance. Thus, peripheral vascular resistance plays a critical role in maintaining blood pressure during orthostatic challenges, such as LBNP.

Our findings are consistent with earlier data indicating lower compliance, or greater stiffness (as measured by pulse wave velocity), in the peripheral vascular system in black subjects. A recent study in black and white adolescent subjects demonstrated that race is a strong predictor of arterial stiffness, and there are a number of studies indicating lower compliance in the cardiovascular system of black versus white adult subjects. 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. 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. A
system with greater compliance and lesser venous tone results in a slower response, because greater volume shifts are required to induce a change in central venous pressure. For example, orthostatic tolerance is reduced in well-trained athletes who have a more compliant vascular system.12

We recognize that P[NE] is not a direct measure of sympathetic nervous system activity; however, because NE is released from sympathetic nerve endings during sympathetic nervous system activation, changes in NE are an indirect indicator of the magnitude of a sympathetic response and are correlated with more direct measures, such as MSNA.20 Moreover, enhanced NE responses during LBNP are usually associated with greater orthostatic tolerance.21 The primary limitation in interpreting plasma catecholamine concentrations is that a single measurement does not distinguish between changes in NE release or uptake. Using microneurography, Ray and Monahan5 demonstrated that young black men and women exhibit lower MSNA in response to baroreceptor unloading but greater peripheral vasoconstriction for a given increase in MSNA relative to their white counterparts.5 These findings are consistent with an earlier study demonstrating white and black men to have similar orthostatic tolerance and similar increases in forearm vascular conductance despite relatively smaller changes in sympathetic activity in the black subjects.4 Taken together, these studies indicate greater vascular reactivity to sympathetic stimulation in black versus white men. The application of these MSNA studies in men to the women in our study may be limited, because, although MSNA is an excellent predictor of peripheral vascular resistance in men, this is not the case in women.22 This observation has been interpreted to indicate that sympathetic nerve activity plays a greater role in total peripheral resistance in young men than it does in young women.22

Race and sex differences in vascular reactivity to β2-adrenergic activation may also have influenced our findings. White women are more sensitive to β2-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 β2-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 β2-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 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[NE], 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 stiffness, 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. 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. 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. 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 literature; 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 higher cardiovascular disease more prevalent in black women later in life. Moreover, women are typically described as having lower orthostatic tolerance than men, but these observations have been made primarily in white women or in mixed groups. Our data suggest that this generally accepted sex difference might not be appropriate for black women. Our studies should be followed up with more direct measures of sympathetic nervous system activity (ie, MSNA), as well as measures of arterial stiffness, such as pulse wave velocity.

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Disclosures

None.

References
