ORIGINAL RESEARCH

Hypertension in Obese Black Women is Not Caused by Increased Sympathetic Vascular Tone

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***Background*—**Black women have one of the highest prevalence rates of hypertension and obesity in the United States. We previously reported that sympathetic activation induced by obesity is a significant contributor to hypertension in white patients. It is unknown whether sympathetic activity similarly contributes to hypertension in obese black women.

***Methods and Results*—**We studied 42 obese women (16 white, body mass index 36±4 kg/m^2, 44% with hypertension; 26 black, body mass index 35±4 kg/m^2, 46% with hypertension). Antihypertensive medications were discontinued for 2 weeks before the day of the study. All patients underwent complete autonomic blockade with trimethaphan at a dosage of 4 mg/min. Resting sympathetic activity determined from muscle sympathetic nerve recordings was similar between obese black women with hypertension and those with normotension. In whites, sympathetic activity was elevated in obese patients with hypertension compared with normotension; the decrease in mean arterial blood pressure produced by trimethaphan was greater in obese white patients with hypertension compared with those with normotension (−26.8±9.7 mm Hg versus −14.8±7.9 mm Hg, *P*=0.02). In contrast, there was no difference in the depressor responses induced by trimethaphan between obese black women with hypertension and those with normotension (−15.5±10.5 mm Hg versus −12.3±10.2 mm Hg, *P*=0.45). Mean arterial blood pressure remained elevated in obese blacks with hypertension compared with those with normotension during trimethaphan infusion (83.7±15.0 mm Hg versus 71.7±9.8 mm Hg, *P*=0.02). Heart rate increased similarly with trimethaphan between white (*P*=0.11) and black (*P*=0.76) women with hypertension and normotension.

***Conclusions*—**These findings suggest that sympathetic activity does not contribute to hypertension in obese black women and provide further evidence for racial differences in hypertension mechanisms. **(*J Am Heart Assoc*. 2017;6:e006971. DOI: 10.1161/JAHA.117.006971.)**

Key Words: black • hypertension • obesity • sympathetic nervous system • women

Obesity has a greater detrimental impact on the health of black women than on any other racial or sex group. For example, hypertension develops at a younger age in black women and is associated with a 5-fold increase in coronary heart disease (versus 2-fold in men).[1] Blacks have higher cardiovascular and renal damage at any level of blood pressure (BP) compared with whites,[2] contributing to high cardiovascular morbidity and mortality in this group. Each year, cardiovascular disease causes the death of ≈54 000 black women in the United States.[1]

The high prevalence rate of hypertension in black women could be in part attributed to the finding that ≈80% of this population is overweight or obese. Obesity is associated with increased sympathetic activity. Microneurography, which directly measures baroreflex-modulated sympathetic traffic to skeletal muscle, is directly associated with with body mass index (BMI), fat mass, and most notably visceral fat mass.[3–5] This sympathetic overactivity contributes to obese-associated hypertension. We previously reported that complete sympathetic withdrawal with the ganglionic blocker trimethaphan induced a greater reduction in BP and total peripheral resistance in obese patients with hypertension compared with obese and lean patients with normotension.[6] However, the majority of studies examining sympathetic contributions to obesity-associated hypertension have been performed in whites.

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/6/11/e006971/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Black women have one of the highest prevalence rates of hypertension and obesity in the United States.
- Obesity is associated with increased sympathetic activity, which contributes to hypertension in whites.
- In the present study, we demonstrated that acute withdrawal of sympathetic tone has a limited effect on blood pressure in obese black women.

What Are the Clinical Implications?

- These findings suggest that nonsympathetic mechanisms have a more significant role in blood pressure maintenance and regulation, which has major implications for treatment options in this population.

To the best of our knowledge, only 1 other study has examined this issue and reported that the association between sympathetic activity and obesity is less strong in black women.[7] Therefore, in the present study, we tested the hypothesis that increased sympathetic vascular tone is elevated in obese black women with hypertension versus those with normotension and this contributes to the pathogenesis of obesity-induced hypertension in black women. For this purpose, we determined sympathetic vascular tone modulation as measured by the change in mean arterial BP during acute infusion of trimethaphan in black obese women with hypertension and normotension and in matched obese white women as positive controls.

Methods

Study Patients

Recruitment was conducted at the Vanderbilt University Medical Center. Eligibility included obesity, defined as BMI between 30 and 45 kg/m^2, African or European ancestry based on 4 grandparents of the same heritage, and hypertension defined as seated BP (≥140/90 mm Hg) on 2 occasions or use of antihypertensive agents. Patients were excluded if they were pregnant or breastfeeding, were postmenopausal, had type 1 or 2 diabetes mellitus, had a history of smoking, or had a change in weight ≥5% in the previous 3 months. All studies adhered to the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects. Vanderbilt's institutional review board approved these studies, and they were conducted in accordance with institutional guidelines. All participants provided informed consent, and the studies were registered at ClinicalTrials.gov, identifiers NCT01122407 and substudy NCT00179023.

Experimental Design

The study was a cross-sectional design with 4 groups: black women with normotension, black women with hypertension, white women with normotension, and white women with hypertension. Patients were matched for age and BMI and BP across race and within hypertension status. In order to ensure adequate matching within the hypertension group, we only enrolled patients between the ages of 30 and 50 years with BMI values between 30 and 45 kg/m.[2]

Participants reported to the Vanderbilt Clinical Research Center for screening that included a medical history, physical examination, vital signs, laboratory analyses (complete blood cell count, lipid profile, metabolic panel, and fasting insulin) and body composition evaluation (dual-energy x-ray absorptiometry; Luna iDXA, GE Healthcare).

All measurements were conducted in the morning after a minimum 8-hour fast. Patients discontinued antihypertensive medications for at least 2 weeks before the study and were excluded if their BP was ≥180/110 mm Hg off medication. Participants were kept on a weight maintenance plan with a sodium-balanced diet (50% carbohydrates, 30% fat, 20% protein, and 150 mEq sodium) that was free of methylxanthine-containing food and beverages consumed for 3 days before the day of the study. All efforts were made to perform assessments during the follicular phase of the menstrual cycle (days 1–12).

An antecubital intravenous line was placed in each arm, one for drug administration and the other for blood sampling. BP and heart rate (HR) were monitored throughout the study using the VITAL-GUARD 450c monitor (Ivy Biomedical Systems). BP was continuously monitored with finger arterial pressure contour analysis (Nexfin, BMEYE). Muscle sympathetic nerve activity (MSNA) was obtained with microneurography, as previously described.[8]

After instrumentation, all participants were allowed to rest in a quiet, thermoneutral environment (≈23°C) for 30 minutes. We obtained baseline hemodynamics (BP, HR, CO) and recorded continuous BP and HR for spectral analyses.

During baseline, incremental boluses of phenylephrine (α_1-adrenergic agonist, West-Ward) sufficient to increase systolic BP (SBP) by 25 mm Hg were given starting at a dose of 25 μg IV. This allowed us to assess for baroreflex-mediated reciprocal changes in HR. We then induced autonomic blockade with continuous infusion of trimethaphan (Cambridge Pharmaceuticals), starting at dosages of 1 mg/min up to 4 mg/min; this dose induced complete autonomic blockade in obese patients.[6] The efficacy of autonomic blockade was determined by the lack of HR changes in response to a 25-mm Hg

increase in BP produced by phenylephrine bolus and by the abolition of spontaneous baroreflex function. All patients reached the trimethaphan maximum dosage of 4 mg/min. We repeated all hemodynamic measurements after the medication was infused for 15 minutes.[6]

The primary end point of this study was the decrease in mean arterial BP (ΔMAP) induced by ganglionic blockade with trimethaphan (tonic sympathetic contribution to BP). Ganglionic blockade with trimethaphan has been previously validated for studying the contribution of sympathetic activity to BP.[9] Secondary end points included the increase in HR induced by ganglionic blockade (ΔHR, parasympathetic modulation of HR), other measurements of sympathetic activity (MSNA, low-frequency variability of SBP [LF_{SBP}], plasma norepinephrine), parasympathetic activity high-frequency variability of HR (HF_{RRI}), and spontaneous baroreflex sensitivity. LF_{SBP}, HF_{RRI}, and baroreflex sensitivity were measured by spectral analysis of HR and BP variability as described below.

Spectral Analysis of HR and BP Variability

Hemodynamic data were recorded using the WINDAQ data acquisition system (DI-220, DATAQ, 14-bit, 1000 Hz), and were processed offline using a custom-written software in PV-WAVE language (Visual Numerics Inc.), developed by one of the authors (AD). Detected beat-to-beat values of R-R intervals (RRIs) and BP were interpolated and low-pass filtered (cutoff 2 Hz). Data segments of at least 180 seconds were used for spectral analysis. Linear trends were removed, and power spectral density was estimated with the fast Fourier transform–based Welch algorithm. The total power and the power in the low- (0.04 to <0.15 Hz) and high- (0.15 to <0.40 Hz) frequency ranges were calculated according to previously described methods.[9]

Measurements of Baroreflex Sensitivity

Cross spectra, coherence, and transfer function analysis were used to capture inter-relationships between RRI and SBP. The baroreflex gain was determined as the mean magnitude value of the transfer function in the low-frequency band, with negative phase and a squared coherence value >0.5.[9]

Microneurography

This technique allows recording efferent muscle sympathetic activity. Briefly, the peroneal nerve was identified via transdermal electrical stimulation, followed by transdermal insertion of a recording electrode and a reference electrode 1 cm apart. Once an adequate recording site was identified, the signal was filtered (bandwidth=700–2000 Hz), rectified, and integrated with a time constant of 0.1 seconds. The mean voltage of the filtered raw nerve signal and the integrated nerve activity was recorded with a total system gain of 99 900. This last signal appears as upright bursts, which can be quantified as bursts per minute.[8]

Statistical Analysis

Differences in baseline demographic and clinical variables among groups were assessed based on descriptive statistics such as means and SDs for continuous variables. Logarithmic transformations of sympathetic activity (LF_{SBP}) and parasympathetic activity (HF_{RRI}) were used to normalize the data.

The sample size was calculated based on the ability to detect a ΔMAP with trimethaphan between black patients with normotension and hypertension (primary end point). A sample size of 12 patients per group had >90% power to detect a difference in means of 12 mm Hg (≈13% reduction in MAP) with an SD of 8 mm Hg using a 2-group *t* test with a 0.05 2-sided significance level. A similar sample size was used in our previous study to detect differences in BP between obese white patients with normotension and those with hypertension during trimethaphan infusion.[6]

For the primary analyses, data for the 2 groups (black women with hypertension and those with normotension) were compared by 2-tailed *t* test. All tests were 2-tailed, and a *P* value <0.05 was considered significant. For the secondary analyses, data for the 4 groups (black women with hypertension and those with normotension and white women with hypertension and those with normotension) were compared by 1-way ANOVA adjusted for multiple comparisons.

Analyses were performed using SPSS for Windows (version 23.0; SPSS Inc).

Results

Patient Characteristics

We enrolled a total of 42 obese women: 26 black (12 with hypertension and 14 with normotension) and 16 white (7 with hypertension and 9 with normotension). Table 1 shows the patients' demographic characteristics. There were no differences in age, BMI, fat mass, and fat-free mass between black women with hypertension and those with normotension (Table 1). Black women with hypertension were treated with diuretics (n=5), angiotensin receptor blockers (n=3), β-blockers (n=1), and calcium channel blockers (n=1), or diet and exercise (n=2). As expected, seated SBP was higher in black women with hypertension versus black women with normotension (131.7±13.6 mm Hg versus 114.9±10.3 mm Hg, *P*<0.01). The BP values in Table 1 were obtained at the screening visit while the patient was taking an antihypertensive regimen and had normal BP (<140 mm Hg), indicating

Table 1. Demographic Characteristics of Study Patients

Parameters	Black Women		*P* Value	White Women		*P* Value
	Hypertension	Normotension		Hypertension	Normotension	
No.	12	14		7	9	
Age, y	40.3±5.9	36.6±5.7	0.11	44.7±7.0	36.1±9.2	0.06
BMI, kg/m^2	34.0±3.7	36.2±4.4	0.18	36.3±3.6	35.7±4.0	0.79
Seated SBP, mm Hg	131.7±13.6	114.9±10.3	<0.01*	126.5±7.6	121.3±10.9	0.33
Seated DBP, mm Hg	82.1±9.2	74.9±9.3	0.06	73.7±9.1	78.9±7.6	0.26
Seated HR, bpm	72.5±9.0	79.7±12.3	1.11	67.8±11.2	79.3±16.3	0.17
Waist size, cm	101.0±7.0	100.9±10.0	0.99	102.9±12.9	102.4±11.1	0.94
Hip, cm	115.1±7.5	115.5±9.3	0.90	117.4±5.4	121.4±7.4	0.32
Waist to hip ratio	0.9±0.1	0.9±0.1	0.95	0.9±0.1	0.9±0.2	0.75
BUN, mg/dL	12.1±3.6	10.0±2.4	0.10	12.7±1.3	11.8±4.1	0.57
Creatinine, mg/dL	0.9±0.1	0.7±0.1	<0.01*	0.7±0.2	0.7±0.1	0.91
Cholesterol, mg/dL	160.5±60.3	165.6±25.9	0.80	183.2±20.3	176.1±21.8	0.57
HDL, mg/dL	48.9±8.3	51.4±6.3	0.44	51.8±10.3	52.9±9.1	0.84
LDL, mg/dL	107.9±30.3	100.2±21.6	0.50	100.4±20.1	103.4±16.1	0.76
Triglycerides, mg/dL	79.5±40.7	69.6±31.1	0.53	155.0±75.2	99.0±31.4	0.07
Glucose, mg/dL	88.8±9.3	88.2±9.2	0.87	87.7±6.4	88.9±16.6	0.86
Insulin, mU/mL	8.6±4.7	9.8±4.8	0.54	8.5±4.3	7.7±2.4	0.69
Body fat%	44.4±2.6	43.9±5.0	0.79	47.5±4.7	50.2±4.0	0.26
Fat mass, kg	38.3±5.5	41.0±9.6	0.40	43.9±10.3	54.6±22.9	0.31
Lean mass, kg	50.6±4.6	54.0±6.1	0.13	50.1±6.1	49.3±7.0	0.83

Value expressed as the mean±SD. BMI indicates body mass index; BUN, serum urea nitrogen; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; SBP, systolic blood pressure.
*$P \leq 0.05$ by unpaired, 2-tailed Student *t* test.

that their hypertension was well controlled on their current regimen. We also performed a racial comparison (Table S1) that showed significant racial differences in triglyceride levels and body fat percentage, which have been previously reported.[10,11]

White women with hypertension received treatment with diuretics (n=3), angiotensin receptor blockers and a diuretic (n=1), β-blockers (n=1), and diet and exercise (n=2). None of the participants were diagnosed with resistant hypertension; antihypertensive medication discontinuation was tolerated well with no serious adverse events.

Basal autonomic parameters

There were no significant differences in spectral indices of sympathetic activity (LF_{SBP}, LF/HF ratio), parasympathetic activity (SD of the RRI, $Mean_{RRI}$, Ln HF_{RRI}), or spontaneous baroreflex sensitivity between obese black women with hypertension or normotension. On the contrary, obese white women with hypertension compared with those with normotension had increased sympathetic activity (LF_{SBP}, 12.4±6.9 mm Hg^2 versus 4.0±2.1 mm Hg^2, P=0.03), reduced baroreflex sensitivity (4.5±1.5 ms/mm Hg versus 18.4±11.0 ms/mm Hg, P=0.02), and decreased parasympathetic activity (Ln HF_{RRI}, 4.8±1 ms^2 versus 6.5±1.7 ms^2, P=0.04). The neurohormonal assessment showed no differences in supine plasma norepinephrine or epinephrine levels between women with normotension and those with hypertension in either racial group (Table 2).

Racial Differences in Sympathetic Vascular Tone

A representative tracing of the continuous BP, HR, and sympathetic nerve activity at baseline and during trimethaphan infusion is presented in Figure 1. Absolute BP values and BP variability decreased as a result of sympathetic withdrawal, and absolute HR values and HR variability increased as a result of parasympathetic withdrawal. MSNA was almost undetectable during complete autonomic blockade (trimethaphan dosage of 4 mg/min).

At baseline, obese black women with hypertension had higher values of supine SBP (132.2±10.9 mm Hg versus 112.0±9.9 mm Hg in black women with normotension,

Table 2. Autonomic and Neuroendocrine Characteristics of Black and White Women With Normotension and With Hypertension

	Black Women			White Women		
	Hypertension	Normotension	*P* Value	Hypertension	Normotension	*P* Value
SDNN, ms	49.1±14.1	63.3±34.5	0.22	34.1±15.1	72.6±46.4	0.08
$Mean_{RRI}$, ms	977.5±66.1	875.6±158.1	0.06	885.2±96.1	974.5±129.2	0.19
LF_{SBP}, mm Hg^2	7.1±6.1	7.3±6.6	0.95	12.4±6.9	4.0±2.1	0.03*
Ln HF_{RRI}	5.8±0.8	5.6±2.2	0.88	4.8±1	6.5±1.7	0.04*
LF/HF	0.02±0.02	0.06±0.09	0.21	0.16±0.21	0.02±0.03	0.15
BRS, ms/mm Hg	8.3±2.8	11.6±6.4	0.13	4.5±1.5	18.4±11.0	0.02*
Norepinephrine, pg/mL	267.6±112.7	231.6±69.5	0.37	270.6±151.7	256.3±133.8	0.86
Epinephrine, pg/mL	11.0±7.8	10.0±8.1	0.77	7.6±4.9	7.7±6.7	0.97

Value expressed as the mean±SD. BRS indicates baroreflex sensitivity; LF_{SBP}, low-frequency systolic blood pressure variability; LF/HF ratio, low-frequency and high-frequency ratio; LN HF_{RRI}, natural logarithm of the high-frequency heart rate variability; $Mean_{RRI}$, mean RR interval; SDNN, SD of the RR interval.
*$P \leq 0.05$ by unpaired, 2-tailed Student *t* test.

P<0.01) and diastolic BP (82.6±6.6 mm Hg versus 69.9±6.5 mm Hg in black women with normotension, *P*<0.01). Black women with hypertension had lower HR (62.5±3.4 versus 70.8±12.0 in black women with normotension, *P*=0.026). MAP was significantly elevated in black women with hypertension (99.2±7.3 mm Hg versus 84.0±7.3 mm Hg in black women with normotension, *P*<0.01). Similarly, at baseline, obese white women with hypertension had higher supine values of SBP (133.7±9.9 versus 116.2±9.7 in white women with normotension, *P*<0.01) and diastolic BP (80.3±6.8 versus 69.1±5.5 in white women with normotension, *P*<0.01). HR was similar in white women with hypertension and those with normotension (66.5±6.9 versus 63.3±8.8, *P*=0.439). MAP was significantly elevated in white women with hypertension (98.1±7.8 mm Hg versus 84.8±6.5 mm Hg in white women with normotension, *P*<0.01).

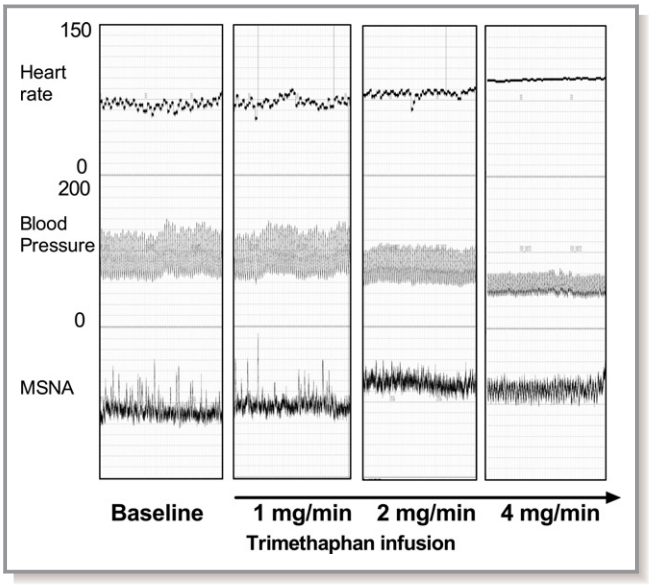

Figure 1. Acute ganglionic blockade removed sympathetic vascular modulation of blood pressure. The 4 panels left to right show heart rate (upper row), continuous blood pressure (middle row), and muscle sympathetic nerve activity (MSNA; lower row) at baseline and during trimethaphan infusion at doses of 1, 2, and 4 mg/min, respectively. The decrease in blood pressure from baseline to 4 mg/min is an index of sympathetic vasomotor activity. Heart rate during trimethaphan infusion significantly increases from baseline, which indicates parasympathetic withdrawal. Both heart rate and blood pressure variability decreased during ganglionic blockade and MSNA completely disappeared at 4 mg/min. Δ indicates change.

Autonomic blockade with trimethaphan induced a similar decrease in MAP in black women with hypertension and those with normotension (−15.5±10.5 mm Hg versus −12.3±10.2 mm Hg, *P*=0.45). In contrast, MAP significantly decreased in white women with hypertension versus white women with normotension (−26.8±9.7 mm Hg versus −14.8±7.9 mm Hg, *P*=0.02) (Figure 2). MAP remained elevated in obese blacks with hypertension during trimethaphan infusion (83.7±15.0 mm Hg versus 71.7±9.8 mm Hg, *P*=0.02), whereas MAP was similar between whites with hypertension and those with normotension (71.3±7.4 mm Hg versus 70.0±7.5 mm Hg, *P*=0.74). The increase in HR with trimethaphan was similar between blacks with hypertension and normotension (22.3±7.3 versus 21.1±12.4, *P*=0.76) and between whites with hypertension and normotension (9.1±6.1 versus 15.9±9.0, *P*=0.11).

There was a significant difference in the decrease in MAP among the 4 groups (*P*=0.02). Whites with hypertension had a greater decrease in MAP compared with blacks with hypertension (mean difference −11±5 mm Hg, *P*=0.032).

We obtained MSNA at baseline and during trimethaphan infusion in 14 black women (9 with hypertension and 5 with normotension). There were no differences in baseline MSNA between blacks with hypertension and those with

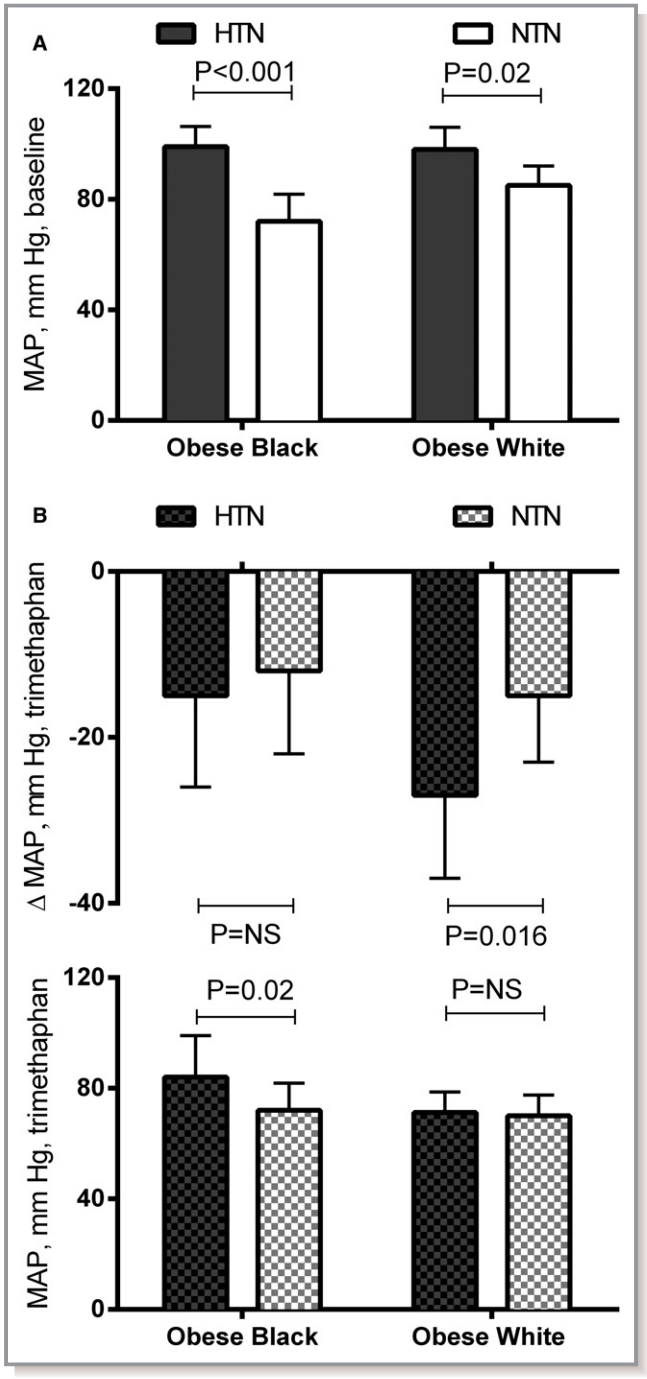

Figure 2. Ganglionic blockade does not normalize blood pressure in obese black (AA) women with hypertension (HTN). A, Mean arterial pressure (MAP) in obese black and white women with HTN and normotension (NTN) at baseline. B, The change in MAP during trimethaphan infusion (A) and the MAP deprived of acute autonomic modulation (B) in those with HTN, blacks with NTN, and white obese women. Δ indicates change; NS, not significant.

normotension (21.1±9.7 bursts/min versus 21.2±3.3 bursts/min, *P*=0.99). There was a similar dose-dependent decrease in MSNA between black women with hypertension and those with normotension during escalating trimethaphan infusion. MSNA was almost undetectable during complete ganglionic blockade (Figure 3).

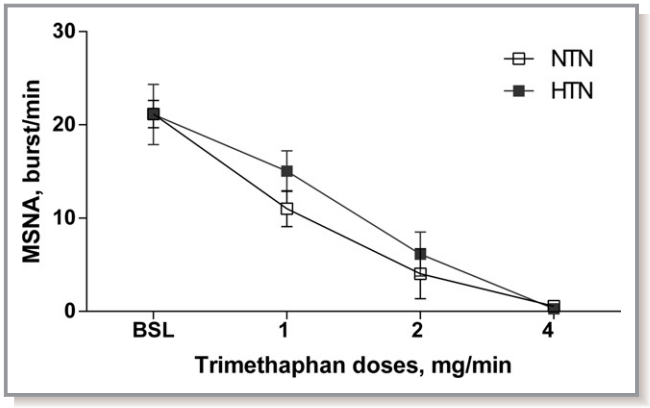

Figure 3. Muscle sympathetic nerve recording in black women with hypertension (HTN) and those with normotension (NTN). A similar dose-dependent decrease in muscle sympathetic nerve activity (MSNA) was observed during trimethaphan infusion between black women with HTN (baseline, n=9; trimethaphan 1, 2, and 4 mg/min, n=6) and those with NTN (baseline, n=5; trimethaphan 1 and 2 mg/min, n=3; 4 mg/min, n=2).

Discussion

The main finding of this study is that racial differences exist in the mechanism underlying obesity-associated hypertension in women. Similar to our previous findings,[6] obese white women with hypertension have an excess sympathetic activity that contributes to hypertension as measured by BP variability (LF_{SBP}). In contrast, obese black women with hypertension do not have elevated measures of sympathetic activity, and BP without sympathetic vascular tone remained elevated in these women. These findings suggest that hypertension in obese black women is independent of increased sympathetic vascular tone.

Previous studies have evaluated the contribution of the sympathetic nervous system to BP regulation in black patients. Calhoun et al[12] showed that blacks have similar resting MSNA compared with whites. MSNA was increased after painful stimuli such as cold pressor test, but only in black patients with a family history of hypertension.[13] Subsequently, in a large cohort of black men and women, Abate et al[7] reported that MSNA was positively associated with BMI in black women with normotension but not in men; however, this association was less strong compared with in white women. These previous studies did not enroll patients with hypertension, and therefore it remains unknown whether obese black patients with hypertension have greater sympathetic activity than whites, and whether it contributes to hypertension.

In our study, we did not find evidence of increased sympathetic activity in obese women with hypertension

compared with black women with normotension. MSNA was similar between the groups and equally decreased in a dose-dependent manner during ganglionic blockade (Figure 1). This is in stark contrast to obese white patients with hypertension who have increased sympathetic activity, decreased parasympathetic activity, and decreased baroreflex function compared with their normotensive counterpart (Table 2). Removal of sympathetic activity via ganglionic blockade did not affect BP in obese blacks with hypertension, whereas it normalized BP in obese whites with hypertension.

There is evidence that sympathetic activity may not be uniformly distributed throughout the body. Rumantir et al[14] reported that renal norepinephrine spillover was elevated (twice the normal) in obese patients with normotension, whereas cardiac norepinephrine spillover was increased only in obese patients. As such, our findings may only reflect sympathetic modulation of vascular tone. It is feasible that increased renal sympathetic nerve activity, renal norepinephrine spillover, or both contribute to hypertension in obese black women by acting chronically to influence the renal handling of sodium and water excretion, a hypothesis that we have not addressed in this study. Nevertheless, studies using chronic sympatholytic showed greater BP effect in whites compared with blacks.[15]

The mechanism linking obesity to increased sympathetic activity is likely multifactorial. Several hormonal signals have been postulated. Among them, insulin has been shown to increase MSNA during euglycemic clamps[16]; leptin, the ob gene product, particularly the protein-bound form, is positively associated with MSNA[17] and with norepinephrine spillover activity in humans[18]; free fatty acids increase MSNA and BP[19]; and angiotensin II level, known to increase with adiposity,[20] has been shown to contribute to increased sympathetic activity.[21] These observations are all based on acute exogenous infusion or correlation studies in whites. Considering that these hormonal signals are induced by positive energy balance that promotes weight gain, a negative energy balance and weight reduction would decrease these signals and normalize sympathetic activity and BP. This theory, however, does not appear to apply to obese black women, in whom, after caloric restriction and weight reduction (≈8 kg), there are significantly decreased fasting plasma insulin and leptin levels. These changes were followed by an ≈40% decrease in MSNA, yet 24-hour BP remained the same.[22] Similarly, Lang et al[23] observed a similar reduction in sympathetic activity as measured by norepinephrine spillover in black and white patients following intravenous treatment with the α_2-adrenergic agonist clonidine. Nevertheless, BP decreased by only 10% in blacks as compared with 21% in whites.

It could be possible that a greater reduction in norepinephrine is needed to achieve similar BP responses in blacks and whites. This is based on previous evidence that blacks have decreased β-adrenergic vasodilation.[24] In our study, however, trimethaphan decreased norepinephrine concentrations to levels similar to those observed in pure autonomic failure, a disease characterized by severe autonomic failure.[25] MSNA disappeared during the higher trimethaphan dosage of 4 mg/min, yet BP remained elevated in obese black women with hypertension.

While changes in HR could account in theory for variation of the BP from ganglionic blockade, we did not observe differences in the change of HR within comparison groups.

Collectively, this evidence supports our findings that sympathetic activity does not play a significant role in BP regulation in obese black women with hypertension and that nonautonomic mechanisms play a greater role in the maintenance of hypertension in this group. Indeed, controlled clinical trials show that blacks respond less well to monotherapy with β-blockers[26] and to the combination of β- and α-blockers,[15] whereas black and white patients respond equally to calcium channel blockers and diuretics.[15,27,28]

Several other mechanisms have been implicated in the pathophysiology of hypertension in obese blacks. For instance, obesity in humans results in increased secretion of cortisol and aldosterone. Recent experiments with human subcutaneous adipocytes suggest that adipokines sensitize human adrenocortical cells to angiotensin II–mediated aldosterone release.[29] These observations could be of particular relevance to the excess of hypertension and obesity-linked salt sensitivity, as well as to high circulating aldosterone levels that directly correlate with BP level and renal vascular resistance in blacks with hypertension.[30] In addition, numerous studies showed macrovascular and microvascular structural and functional abnormalities in blacks that could contribute to hypertension. Blacks have a blunted response to endothelium-dependent vasodilation induced by acetylcholine,[31,32] methacholine,[33] isoproterenol,[33] exercise,[34] and mental stress.[35] Furthermore, the protective role of estrogen on endothelial function is lost in black women as compared with whites.[36]

Study Limitations

Our study has several limitations. We did not enroll black men in our study. Victor et al[7] reported that black men have excess sympathetic activity independent of levels of adiposity. Therefore, our findings may not apply to obese black men because of these sex differences.[37]

Furthermore, it is possible that the lack of difference in sympathetic contribution to BP in obese blacks with hypertension and those with normotension is related to a type II error. However, using the observed mean difference in the decrease in MAP between black women with hypertension and those with normotension (≈4 mm Hg) in the present study, we estimated the sample size to reject the null

hypothesis that differences in MAP with trimethaphan infusion are equal between obese black women with hypertension and those with normotension. We would need to study 147 per group (obese black women with hypertension and those with normotension) with 90% power and a type I error probability of 0.05, which is not feasible.

Even though our black and white patients with hypertension had higher BP than those with normotension, these values were still normal based on current guidelines. These measurements were obtained while patients were supine with minimal sympathetic stimulation. It could be possible that stress-induced sympathetic activation could contribute to hypertension in blacks.

Moreover, vasopressin levels increase during trimethaphan infusion and could contribute to the observed changes in BP.[25] However, we have validated ganglionic blockade to assess sympathetic tone by combining the infusion with multiple measurements of sympathetic activity such as direct sympathetic nerve recording and BP variability. Isolating the contribution of vasopressin on BP during ganglionic blockade in humans is not feasible because the use of a vasopressin antagonist could induce severe hypotension.

In this study, we did not measure MSNA in whites. We[6] and others[38] previously reported differences in sympathetic activity between lean, obese, and obese patients with hypertension in this population. Finally, the present study did not identify the specific cause of hypertension in obese black women with hypertension.

Conclusions

Our study showed that BP deprived of autonomic modulation in obese black women remained elevated. This suggests that nonsympathetic mechanisms have a greater role in the maintenance and regulation of BP in this population.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Demographics of ~~AA vs. Caucasians~~

Parameters	~~AA~~	~~Caucasian~~	*P value*
N	26	16	
Age	38.3 ± 6.0	39.9 ± 9.2	0.55
BMI, kg/m^2	35.2 ± 4.1	36.0 ± 3.7	0.53
Seated SBP, mm Hg	122.9 ± 14.5	123.5 ± 9.7	0.90
Seated DBP, mm Hg	78.3 ± 9.8	76.6 ± 8.3	0.59
Seated HR, bpm	76.2 ± 11.2	74.4 ± 15.0	0.66
Waist size, cm	100.9 ± 8.4	102.6 ± 11.3	0.62
Hip, cm	115.3 ± 8.3	119.84 ± 6.7	0.10
Waist hip ratio	0.9 ± 0.1	0.9 ± 0.1	0.61
BUN, m/dl	11.0 ± 3.2	12.2 ± 3.1	0.25
Creatinine, mg/dl	0.8 ± 0.1	0.7 ± 0.1	0.07
Cholesterol, mg/dl	163.0 ± 45.3	178.6 ± 20.8	0.24
HDL, mg/dl	50.1 ± 7.3	52.5 ± 9.1	0.40
LDL, mg/dl	104.0 ± 26.0	102.4 ± 16.9	0.83
Triglycerides, mg/dl	74.5 ± 35.7	119.0 ± 55.9	0.006*
Glucose, mg/dl	88.4 ± 9.1	88.4 ± 12.8	0.99
Insulin mU/ml	9.2 ± 4.7	8.0 ± 3.2	0.42

Body fat%	44.1 ± 4.0	49.0 ± 4.4	0.001*
Fat mass, kg	39.7 ± 7.9	50.0 ± 18.8	0.02*
Lean mass, kg	52.4 ± 5.6	49.6 ± 6.4	0.16

Value expressed as the mean ± standard deviation (SD). *$p \leq 0.05$ by unpaired, two-tailed Students *t*-test. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein.