Autonomic Function in Hypertension
Are There Racial Differences?

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Previous biochemical assessment of sympathetic nervous system activity including plasma catecholamines, plasma renin activity, and plasma dopamine-β-hydroxylase levels has suggested racial differences in the contribution of the sympathetic nervous system to the pathogenesis or maintenance of hypertension. We, therefore, performed physiological and pharmacological studies in white and black subjects with essential hypertension and their age-matched normotensive counterparts to assess autonomic and sympathetic nervous system function. One hundred one male subjects (47 white hypertensive, 17 black hypertensive, 22 white normotensive, and 15 black normotensive subjects) were evaluated for baroreceptor reflex sensitivity to low-pressure (amyl nitrite inhalation) and high-pressure (phenylephrine infusion) stimuli; cold pressor test heart rate and blood pressure responses; and blood pressure response to phentolamine α-adrenergic blockade. Hypertensive subjects exhibited an increase in resting heart rate, a decrease in baroreceptor reflex sensitivity, and an exaggerated decline in mean arterial pressure in response to phentolamine. These abnormalities were present to a comparable degree in black and white hypertensive subjects. Cold pressor testing revealed greater increases in heart rate in blacks as compared with whites; however, this racial difference was present regardless of blood pressure status, occurring in black normotensive and black hypertensive subjects to a comparable degree. Cold pressor test blood pressure increments were similar in the four groups. We conclude that both white hypertensive and black hypertensive subjects demonstrate similar abnormalities in autonomic and sympathetic nervous system function including blunting of baroreceptor reflex sensitivity and an increased α-adrenergic receptor participation in blood pressure maintenance. The results do not suggest major racial differences in autonomic pathogenetic mechanisms in hypertension. (Circulation 1990;81:1305–1311)

Previous studies have demonstrated racial differences in hypertension including a greater prevalence,1 greater severity,2 and a higher incidence of associated complications in blacks as compared with whites.3–9 These observations have suggested possible racial differences in the pathogenesis of hypertension.

Several lines of evidence suggest possible racial differences in sympathetic nervous system activity in hypertension. These include decreased plasma renin activity10–13 and decreased plasma dopamine-β-hydroxylase levels13–16 in blacks as compared with whites. Additionally, although plasma norepinephrine concentrations are similar, overall, between groups of white and black hypertensive subjects, subtle racial differences in plasma norepinephrine concentrations can occur, such as an inappropriate increase in basal values in young white hypertensive subjects as compared with black hypertensive subjects, and a smaller increase with upright posture in black hypertensive subjects as compared with white hypertensive subjects.17

Because these biochemical parameters suggest possible racial differences in sympathetic nervous system activity in hypertension, we performed physiological and pharmacological studies in white and black hypertensive subjects and their age-matched normotensive counterparts to assess several indices of autonomic and sympathetic nervous system function.
Methods

Subjects
We studied 101 adult men (47 essential hypertensive white men, 17 essential hypertensive black men, 22 normotensive white men, and 15 normotensive black men).

Subjects with essential hypertension were consistently hypertensive (diastolic blood pressure greater than 90 mm Hg on at least three outpatient visits) and had no evidence of secondary hypertension or of hypertensive end-organ damage as assessed by history, physical examination, and laboratory tests (i.e., chest x-ray; electrocardiogram; hemogram; blood urea nitrogen; serum creatinine and electrolytes; urinalysis; and urinary catecholamine, metanephrine, and vanillylmandelic acid excretion). These subjects either had never been treated or had withdrawn from all antihypertensive medication for at least 2 weeks before study. The age range of these subjects was 25–60 years.

The normotensive controls were healthy subjects who took no medications and had consistently normal blood pressure (diastolic blood pressure less than 90 mm Hg on at least three outpatient visits). The age range was 26–58 years.

All subjects gave informed written consent, and the study was approved by the Human Subjects Committee of the University of California, San Diego, California.

Procedures
Subjects were admitted to the Special Diagnostic and Treatment Unit of the San Diego Veterans Administration Medical Center for a 36–48-hour period for autonomic and baroreceptor reflex studies.

Arterial pressure was measured directly from the left brachial artery by an 18-gauge intra-arterial cannula connected to a Hewlett-Packard Model 1280-C pressure transducer (Hewlett-Packard Co., Palo Alto, California), with continuous arterial pressure and electrocardiographic monitoring. Arterial pressure and electrocardiographic lead V2 were recorded simultaneously on a two-channel Hewlett-Packard Model 7702-B recorder (Hewlett-Packard Co.) for analysis of beat-to-beat variations in blood pressure and heart rate.

The following studies to assess autonomic and baroreceptor reflex function were performed, as previously described by our laboratory:18–21:

Baroreceptor reflex sensitivity to high-pressure stimulus. High-pressure (carotid sinus and aortic arch baroreceptor) baroreceptor reflex sensitivity was evaluated by recording cardiac slowing in response to acute phenylephrine-induced hypertension.22 Changes in arterial pressure (mm Hg) and pulse interval (RR interval) (msec) were recorded continuously after 200–400 µg phenylephrine by intravenous bolus, which was sufficient to raise systolic arterial pressure by 25–30 mm Hg. Results are expressed in milliseconds per millimeter of mercury (msec/mm Hg).

Baroreceptor reflex sensitivity to low-pressure stimulus. This was evaluated by recording cardiac acceleration in response to an amyl nitrite–induced decline in blood pressure.23 The subject inhaled three times from a gas-filled ampoule of amyl nitrite broken under the nose. Results are expressed in milliseconds per millimeter of mercury (msec/mm Hg).

Cold pressor test. The cold pressor test assesses the early hemodynamic response to a cold stimulus and may be an index of the integrity of efferent sympathetic vasomotor function.24–26 It does not require performance of baroreceptor afferents. The subject places his right hand into ice water (noncirculating, 0°C) for 1 minute. Results are reported as change in mean arterial pressure in the contralateral arm (in mm Hg) and change in pulse interval (in msec).

Phentolamine α-adrenergic blockade. Change in blood pressure after phentolamine α-adrenergic blockade reflects participation of α-adrenergic mechanisms in sustaining blood pressure27–30 and, hence, of sympathetic stimulation of resistance vessels.29 Phentolamine mesylate (20 mg) was given by intravenous infusion for 1 minute, and the maximum blood pressure decrement was recorded (mm Hg). The dose of phentolamine was chosen to provide substantial α-adrenergic blockade28,29 without direct vasodilation.28,31 Results are expressed as a change in mean arterial pressure in millimeters of mercury (mm Hg).

The sequence of experimental events was as follows for each subject: initial (pretest) baseline measurements of mean arterial pressure and pulse interval, cold pressor test, equilibration period, amyl nitrite inhalation, equilibration period, phenylephrine bolus, equilibration period, and phentolamine infusion. Each equilibration period was for a minimum of 10 minutes, allowing blood pressure and heart rate to return to stable values as judged by continuous monitoring. Repeated-measures analysis of variance (ANOVA) revealed no significant differences between initial and subsequent mean arterial pressure baselines before each test for each of the four subject groups. A minimum of four consecutive RR intervals and simultaneous pressure waves were measured to provide an average RR interval and average mean arterial pressure during the control (baseline) portion of each maneuver and at the time of maximal response for the cold pressor and phentolamine tests.

Height and weight were recorded on admission. Body mass index was computed as weight (kg) divided by height squared (m²).32 A family history was considered positive for hypertension if the subject indicated that a parent or sibling had high blood pressure (diastolic blood pressure >90 mm Hg or requiring antihypertensive treatment) before the age of 60 years.

Statistics
All results are expressed as the mean value±SEM. The results were analyzed by two-way ANOVA,
TABLE 1. Baseline Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>White normotensives</th>
<th>Black normotensives</th>
<th>White hypertensives</th>
<th>Black hypertensives</th>
<th>BP status</th>
<th>Race</th>
<th>BP status–race interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>22</td>
<td>15</td>
<td>47</td>
<td>17</td>
<td>3.20</td>
<td>0.07</td>
<td>0.12</td>
</tr>
<tr>
<td>Age (yr) (±SEM)</td>
<td>39±2</td>
<td>39±2</td>
<td>43±2</td>
<td>44±3</td>
<td>107</td>
<td>&lt;0.0005</td>
<td>1.79</td>
</tr>
<tr>
<td>Systolic BP (mm Hg) (±SEM)</td>
<td>114±2</td>
<td>117±4</td>
<td>148±3</td>
<td>153±5</td>
<td>136</td>
<td>&lt;0.0005</td>
<td>4.80</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg) (±SEM)</td>
<td>72±2</td>
<td>74±3</td>
<td>97±2</td>
<td>104±2</td>
<td>16.2</td>
<td>&lt;0.0005</td>
<td>0.72</td>
</tr>
<tr>
<td>Heart rate (beats/min) (±SEM)</td>
<td>70±3</td>
<td>66±3</td>
<td>80±2</td>
<td>79±4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²) (±SEM)</td>
<td>26.1±1.0</td>
<td>28.0±1.3</td>
<td>28.0±0.6</td>
<td>30.0±1.4</td>
<td>3.80</td>
<td>NS</td>
<td>3.39</td>
</tr>
</tbody>
</table>

ANOVA, analysis of variance; BP, blood pressure.

factoring for the effects of both race (white versus black) and blood pressure status (normotensive versus hypertensive). Correlations were assessed by linear least-squares regression analysis. Statistical analyses were performed using MINITAB statistical computing programs on the University of California, San Diego, VAX mainframe computer.

Results

Subject Characteristics

Table 1 shows baseline subject characteristics for the four groups studied. Two-factor ANOVA demonstrated no significant differences in mean age among the four groups [F(1,97) not significant for both blood pressure status and race effects]. Mean baseline systolic and diastolic blood pressures were significantly greater in hypertensive subjects as compared with normotensive subjects. Additionally, diastolic blood pressures were greater in black subjects as compared with white subjects, as reflected in the ANOVA by a significant effect for race [F(1,97)=4.80, p<0.05]. Mean baseline heart rates were greater in both white hypertensive subjects and black hypertensive subjects as compared with their normotensive counterparts, as demonstrated in the ANOVA by a significant effect for blood pressure status, no effect for race, and no blood pressure status–race interaction. Body mass index did not differ among the four groups. Among hypertensive subjects, family history was positive for hypertension in 40% of white and 47% of black subjects (χ²=0.087, p=NS).

Baroreceptor Reflex Sensitivity

Results of autonomic and baroreceptor reflex function testing are shown in Figures 1–3, and the ANOVA results for these parameters are summarized in Table 2.

Baroreceptor reflex sensitivity to a low-pressure stimulus as assessed by amyl nitrite inhalation (Figure 1 and Table 2) was blunted in hypertensive subjects as compared with normotensive subjects [F(1,97)=17.4, p<0.0005, for blood pressure status effect]. There was no difference between white normotensive and black normotensive subjects, nor between white hypertensive and black hypertensive subjects [F(1,97)=0.76, p=NS, for race effect].

Similarly, high-pressure baroreceptor reflex sensitivity, tested by phenylephrine bolus (Figure 1 and Table 2), was decreased in hypertensive subjects as compared with normotensive subjects [F(1,83)=9.00, p<0.005]. Again, there was no effect by race [F(1,97)=0.23, p=NS], indicating that the degree of baroreceptor reflex sensitivity reduction was comparable in white and black hypertensive subjects.

Phentolamine α-Adrenergic Blockade

Results of phentolamine α-adrenergic blockade are shown in Figure 2 and Table 2. Mean arterial
pressure decreased in all four groups, and there was an exaggerated response in hypertensive subjects as compared with their normotensive counterparts [F(1,56)=10.1, p<0.005, for blood pressure status effect]. There were no racial differences in this response [F(1,56)=0.03, p=NS, for race].

**Cold Pressor Test**

Cold pressor test results are shown in Figure 3 and Table 2. The cold stimulus elicited substantial increases in heart rate (decreases in pulse interval) versus baseline in all four groups. The change in pulse interval was significantly greater in black subjects, occurring in both normotensive and hypertensive blacks to a comparable degree [F(1,94)=9.00, p<0.005 for race; no effect for either blood pressure status or blood pressure status–race interaction].

Mean arterial pressure during cold pressor testing increased in all four groups, and there were no differences in this response with respect to blood pressure status or race.

**Autonomic Function Correlations**

Linear regression revealed several weak but significant autonomic function correlations in white and black subjects (Table 3). Baroreceptor reflex sensitivity, as assessed by amyl nitrite inhalation, correlated inversely with initial baseline diastolic blood pressure for black subjects, for white subjects, and for all subjects taken as a whole, with similar regression coefficients for each group. High-pressure baroreceptor reflex sensitivity, tested by phenylephrine bolus, also correlated inversely with initial baseline diastolic blood pressure for black subjects, for white subjects, and for all subjects, again with similar r values. Similar correlations were found between baroreceptor reflex sensitivity and initial baseline systolic blood pressure (data not shown).

Phentolamine-induced decreases in mean arterial pressure correlated with initial baseline diastolic blood pressure for black subjects, for white subjects, and for all subjects. Once again, regression coefficients were similar for each group.

Cold pressor test responses (both change in mean arterial pressure and pulse interval change) did not correlate with initial baseline diastolic blood pressure.

Regression line slope values (m) for all of the above parameters were not different in black versus white subjects.

**Discussion**

Our results do not suggest major racial differences in autonomic function in hypertensive subjects as assessed by physiological and pharmacological means. Baroreceptor reflex sensitivity to both high-pressure and low-pressure stimuli, in agreement with previous studies, was blunted in hypertensive subjects as compared with their normotensive counterparts. These baroreceptor reflex sensitivity abnormalities were equally present in black and white hypertensive subjects. Additionally, phentolamine α-adrenergic blockade revealed an exaggerated blood pressure–lowering effect in hypertensive subjects as compared with normotensive subjects. The dose of phentolamine used (20 mg) was chosen to selectively block peripheral α-adrenergic receptors without producing nonspecific vasodilation. These results are in agreement with previous studies, suggesting enhanced α-adrenergic receptor participation in blood pressure maintenance in hypertensive subjects. The degree of this enhanced α-effect was not different between black and white hypertensive subjects.

Cold pressor testing suggested a heightened efferent sympathetic cardiac response to a cold stimulus in blacks as compared with whites. This racial difference, however, was present regardless of blood pressure status, occurring in black hypertensive subjects and black normotensive subjects to a comparable degree. Additionally, in black subjects, there was no correlation between the cold pressor test heart rate response and baseline blood pressure (r=0.065, p=NS) (Table 3). Thus, this racial difference is of
TABLE 2. Autonomic and Baroreceptor Reflex Function Results

<table>
<thead>
<tr>
<th>Baroreceptor reflex sensitivity (msec/mm Hg) (+SEM)</th>
<th>White normotensives</th>
<th>Black normotensives</th>
<th>White hypertensives</th>
<th>Black hypertensives</th>
<th>BP status-race interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyl nitrite</td>
<td>17.7±2.3</td>
<td>15.4±2.5</td>
<td>9.7±1.2</td>
<td>8.6±1.6</td>
<td>F 17.4 &lt;0.0005  p 0.76 NS  Race 0.10 NS</td>
</tr>
<tr>
<td>n</td>
<td>22</td>
<td>15</td>
<td>47</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>21.1±2.9</td>
<td>23.4±3.2</td>
<td>15.0±1.3</td>
<td>15.2±2.2</td>
<td>F 9.00 &lt;0.005  p 0.23 NS  Race 0.19 NS</td>
</tr>
<tr>
<td>n</td>
<td>20</td>
<td>15</td>
<td>39</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Phentolamine α-adrenergic blockade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ MAP (mm Hg) (+SEM)</td>
<td>15±3</td>
<td>15±3</td>
<td>27±3</td>
<td>26±4</td>
<td>F 10.1 &lt;0.005  p 0.03 NS  Race 0.02 NS</td>
</tr>
<tr>
<td>n</td>
<td>10</td>
<td>12</td>
<td>27</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Cold pressor test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔRR (msec) (+SEM)</td>
<td>85±17</td>
<td>146±30</td>
<td>72±15</td>
<td>142±28</td>
<td>F 0.20 NS  p 9.00 &lt;0.005  Race 0.04 NS</td>
</tr>
<tr>
<td>n</td>
<td>19</td>
<td>15</td>
<td>47</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>ΔMAP (mm Hg) (+SEM)</td>
<td>20±2</td>
<td>21±2</td>
<td>22±2</td>
<td>16±3</td>
<td>F 0.03 NS  p 1.51 NS  Race 1.90 NS</td>
</tr>
<tr>
<td>n</td>
<td>21</td>
<td>15</td>
<td>47</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

ANOVA, analysis of variance; BP, blood pressure; MAP, mean arterial pressure.

questionable importance to the pathogenesis or maintenance of hypertension. Recent studies by Victor et al. showed that changes in heart rate in response to a cold stimulus did not correlate with sympathetic nervous system activity measured directly by microneurographic methods in human muscle sympathetic fibers. On the other hand, the mean arterial pressure response to a cold stimulus was positively correlated with changes in muscle sympathetic nervous activity and might, thus, be a more appropriate index of sympathetic nervous system activity than the heart rate response during the cold pressor test. We found no differences in cold pressor test mean arterial pressure responses between white and black subjects.

In the present study, black subjects had higher baseline blood pressures than white subjects, a finding consistent with previous observations. Linear regression analysis (Table 3) to evaluate the influence of baseline blood pressure on autonomic function parameters, however, demonstrated similar regression coefficients and similar regression line slopes for black as compared with white subjects.

TABLE 3. Autonomic Function: Correlation With Diastolic Blood Pressure

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Group</th>
<th>n</th>
<th>r</th>
<th>p</th>
<th>m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baroreceptor reflex sensitivity, Amyl nitrite</td>
<td>All</td>
<td>101</td>
<td>-0.433</td>
<td>&lt;0.0005</td>
<td>0.249</td>
</tr>
<tr>
<td></td>
<td>Blacks</td>
<td>32</td>
<td>-0.425</td>
<td>&lt;0.02</td>
<td>-0.210</td>
</tr>
<tr>
<td></td>
<td>Whites</td>
<td>69</td>
<td>-0.440</td>
<td>&lt;0.0005</td>
<td>-0.272 NS</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>87</td>
<td>-0.342</td>
<td>&lt;0.002</td>
<td>-0.233</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Blacks</td>
<td>28</td>
<td>-0.325</td>
<td>&lt;0.10</td>
<td>-0.209</td>
</tr>
<tr>
<td></td>
<td>Whites</td>
<td>59</td>
<td>-0.347</td>
<td>&lt;0.01</td>
<td>-0.226 NS</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>60</td>
<td>0.353</td>
<td>&lt;0.01</td>
<td>0.281</td>
</tr>
<tr>
<td>Phentolamine ΔMAP</td>
<td>Blacks</td>
<td>23</td>
<td>0.416</td>
<td>&lt;0.05</td>
<td>0.292 NS</td>
</tr>
<tr>
<td></td>
<td>Whites</td>
<td>37</td>
<td>0.322</td>
<td>&lt;0.10</td>
<td>0.273</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>98</td>
<td>0.004</td>
<td>NS</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>Blacks</td>
<td>32</td>
<td>0.065</td>
<td>NS</td>
<td>0.420</td>
</tr>
<tr>
<td></td>
<td>Whites</td>
<td>66</td>
<td>-0.043</td>
<td>&lt;0.05</td>
<td>-0.256</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>100</td>
<td>0.023</td>
<td>NS</td>
<td>0.016</td>
</tr>
<tr>
<td>Cold pressor test</td>
<td>Blacks</td>
<td>32</td>
<td>-0.121</td>
<td>NS</td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td>Whites</td>
<td>68</td>
<td>0.101</td>
<td>NS</td>
<td>0.071</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure; NS, no significant difference in slope (m) between blacks and whites.
Thus, it is unlikely that further racial differences in autonomic function were obscured by the modest disparity in diastolic blood pressure elevation in black versus white hypertensive subjects (Table 1).

Several investigators\textsuperscript{37-43} have found enhanced cardiovascular reactivity to both physical and mental stressors in blacks as compared with whites, and have suggested that racial differences in sympathetic nervous system activity might contribute to racial differences in hypertension. These types of studies primarily have involved either children,\textsuperscript{37,40} or late adolescents or young adults\textsuperscript{41-43} with normal or marginally elevated blood pressures. The relation between sympathetic nervous system reactivity and subsequent development of hypertension, however, has not been established. Indeed, reactivity to cold, a physical stressor in several previous studies,\textsuperscript{37,41-43} has not predicted development of hypertension in either white or black subjects.\textsuperscript{44-46} A recent study in adults by Fredrickson\textsuperscript{47} found racial differences in vascular resistance responses to mental stress. These differences, however, were present regardless of blood pressure status, occurring in normotensive subjects, borderline hypertensive subjects, and established hypertensive subjects to a comparable degree. Dimsdale et al\textsuperscript{48} found increased pressor sensitivity to infused norepinephrine in black as compared with white hypertensive subjects but only after salt loading. Additional studies in hypertensive adults have yielded inconsistent results with some showing larger and some showing smaller cardiovascular reactivity responses in blacks as compared with white subjects.\textsuperscript{49,50} Our data are consistent with the report of Rowlands et al\textsuperscript{51} who documented similar baroreceptor reflex sensitivity and cardiovascular responses to pressor stimuli in white and black hypertensive subjects in the United Kingdom. Regional differences in socioeconomic status\textsuperscript{52} or, possibly, Caucasian genetic admixture\textsuperscript{53,54} among black subjects studied and the effects of these variables on autonomic function might also be responsible for differences between our results (gathered on the West Coast) and those of others (particularly in the South and southeastern United States).\textsuperscript{37-43} Indeed, Reed\textsuperscript{55} has reported that American blacks in the Northeast and West have a greater proportion of genes of Caucasian origin than do American blacks in the Southeast. Thus, although racial differences in the autonomic contribution to hypertension cannot be entirely excluded by the data we have presented, other factors such as disparity in renal sodium handling\textsuperscript{56-59} might be more central to pathogenetic differences in hypertension between whites and blacks.

Summarily, white and black hypertensive subjects demonstrate similar abnormalities in autonomic and sympathetic nervous system function, including blunting of baroreceptor reflex sensitivity and increased $\alpha$-adrenergic receptor participation in blood pressure maintenance, when assessed by physiological and pharmacological means. The results do not suggest major differences in autonomic pathogenetic mechanisms between black and white hypertensive subjects.

Acknowledgments

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