Increased Vascular Adrenergic Vasoconstriction and Decreased Vasodilation in Blacks

Additive Mechanisms Leading to Enhanced Vascular Reactivity

C. Michael Stein, Chim C. Lang, Iqbal Singh, Huai B. He, Alastair J.J. Wood

Abstract—Blood pressure reactivity is enhanced in young black subjects through mechanisms that are poorly understood. We compared α-adrenergic–mediated vasoconstrictor and β-adrenergic vasodilator sensitivity and their relation to sympathetic activity in blacks and whites. Ten healthy black (age, 29.9±2.4 years) and 10 white (age, 28.3±1.9 years) men were studied. Forearm blood flow was measured with strain-gauge plethysmography after the intrabrachial artery administration of phenylephrine (1.25 to 20 μg/min) and isoproterenol (60 and 400 ng/min) after application of lower-body negative pressure and after a cold pressor test. Forearm and systemic norepinephrine spillover were measured with a radioisotope dilution technique. α-Adrenergic vasoconstriction was markedly increased (ANOVA P=0.008) and β-adrenergic vasodilation decreased (ANOVA P=0.02) in blacks. Phenylephrine (10 μg/min) decreased forearm blood flow by 58.0±2.5% in blacks but only by 26.6±6.0% in whites (P<0.001). Vasoconstrictor response to endogenous norepinephrine, stimulated by a cold pressor test, resulted in a higher forearm vascular resistance in blacks than in whites (107.3±13 versus 64.8±13 mm Hg · mL⁻¹ · 100 mL⁻¹, P=0.03). There were no significant ethnic differences in basal or stimulated forearm or systemic norepinephrine spillover. Increased vasoconstrictor and decreased vasodilator responses in blacks were not correlated. Increased sympathetically mediated vascular tone caused by enhanced vasoconstriction and attenuated vasodilation, effects that would be additive, and not increased sympathetic activity could enhance vascular reactivity and may play a role in the pathogenesis of hypertension in blacks. (Hypertension. 2000;36:945-951.)

Key Words: blacks ■ adrenergic agonists ■ vasoconstriction ■ vasodilation

Hypertension is more prevalent and more severe in black than in white Americans and is associated with greater morbidity and mortality. Several genetic and environmental factors have been proposed as potential explanations for these ethnic differences in the prevalence and severity of hypertension. Higher levels of psychosocial stress, enhanced sympathetic responses to such stress, and increased vascular reactivity to sympathetic stimulation have been suggested to contribute to interethnic differences in the regulation of vascular response and to the pathogenesis of hypertension in blacks. Enhanced hemodynamic responses to physiological or psychological stressors, mediated largely through an increase in peripheral vascular resistance, have been reported in normotensive blacks in many studies. Thus, it has been suggested that a greater increase in vascular tone in response to stress in blacks, occurring either because of increased sympathetic activity or because of altered vascular sensitivity to sympathetic stimulation, may result in increased peripheral vascular resistance and, coupled with higher levels of environmental stress, result in sustained hypertension. However, definitive studies demonstrating enhanced sympathetic activation or increased vascular adrenergic sensitivity in blacks have not been performed.

The purpose of this study was first to compare direct vascular vasoconstrictor responses to pharmacological α-adrenergic stimulation in blacks and whites through measurement of forearm blood flow responses to the intra-arterial infusion of phenylephrine, an α-1-adrenergic agonist. Second, we compared both vascular and sympathetic responses to physiological adrenergic stimulation through the application of lower-body negative pressure (LBNP) and a cold pressor test, exogenous stimuli that result in adrenergic activation. Third, because the overall result of altered vasoconstriction and vasodilation will be additive, we examined vasodilator responsiveness to the β-adrenergic agonist isoproterenol and vasoconstrictor sensitivity to the α-adrenergic agonist phenylephrine in the same individuals.

Methods

Subjects

Twenty healthy, nonsmoking, normotensive male volunteers were studied. All subjects provided written informed consent, and the
study protocol was approved by the Vanderbilt Committee for the Protection of Human Subjects. Subjects were compensated for participation. Ten subjects were black (age, 29.9 ± 2.4 years) and 10 subjects were white (age, 28.3 ± 1.9 years). No subject had clinically significant abnormalities on history, physical examination, or routine laboratory tests including complete blood count, prothrombin and partial thromboplastin times, renal and liver function tests, and ECG.

Six black subjects and 5 white subjects reported a family history of hypertension in a first-degree relative. Subjects were maintained on a diet that was free of alcohol and caffeine and contained 150 mmol of sodium and 70 mmol of potassium per day for 5 days before the study day. The diet was prepared under supervision of a dietitian by the metabolic kitchen of the Vanderbilt University Clinical Research Center. Subjects did not take any medications for at least 2 weeks before each study day.

**Experimental Protocol**

All experiments were performed in the morning, in the same temperature-controlled room, with the subjects resting supine in bed. An intravenous cannula was placed in an antecubital vein of both arms. After subdermal administration of 1% lidocaine, a 20-gauge polyurethane catheter (Cook Inc) was inserted into the brachial artery of the nondominant arm, allowing direct intra-arterial administration of drugs. Arterial catheter patency was maintained with an infusion of 5% dextrose in water infused at a rate of 40 mL/h. By altering the concentration of the drug infusion, the total flow rate through the cannula was maintained constant at 40 mL/h during the intra-arterial administration of drugs. Arterial blood pressure was measured by means of a pressure transducer (HP 1295C, Hewlett Packard) and heart rate was recorded from a continuous ECG monitor.

After the arterial line and intravenous catheters had been placed, subjects rested quietly for a 30-minute equilibration period. [H]Norepinephrine (norepinephrine levo-[ring-2,5,6]-H) 56.9 Ci/mmol, New England Nuclear) was then infused intravenously into the arm opposite to the arterial line for measurement of systemic and forearm norepinephrine spillover, as we have previously described.

Resting forearm blood flow, hemodynamic, and catecholamine measurements were obtained after 30 and 40 minutes of the tritiated norepinephrine infusion. These values were similar and were averaged. Forearm blood flow was measured by venous occlusion plethysmography with a mercury-in-silastic strain-gauge plethysmograph, as we have previously described. Immediately after the measurement of forearm blood flow, arterial and venous blood samples were drawn simultaneously for the determination of norepinephrine kinetics.

After resting measurements had been obtained, subjects were positioned in a chamber that enclosed the lower body below the waist. The LBNP chamber was sealed at the level of the iliac crests and connected to a vacuum source controlled by a roteast. LBNP at −15 mm Hg was applied for 10 minutes and then increased to −30 mm Hg for a further 10 minutes. Heart rate, blood pressure, and forearm blood flow were measured and arterial and venous blood was drawn during the last 2 minutes of each 10-minute LBNP period. Then, after a 15-minute recovery period during which measurements returned to their resting values, a cold pressor test was performed by immersing each subject’s left foot to the level of the malleoli in a slurry composed of equal parts water and crushed ice for 2 minutes. Subjects were instructed to breathe normally and to avoid straining or performing a Valsalva maneuver. Forearm blood flow, heart rate, and blood pressure measurement and drawing of blood for catecholamines were performed during the second minute of the cold pressor test.

After a 30-minute recovery period during which responses returned to baseline, phenylephrine was infused into the brachial artery in increasing doses (1.25 to 20 μg/min). Each dose was infused for 7 minutes by a Harvard infusion pump, with forearm blood flow recorded during the last 2 minutes of each dose. To minimize the risk of arterial thrombosis, if, during 2 consecutive doses of phenylephrine forearm blood flow decreased to <1 mL·min⁻¹·dL⁻¹, then higher doses of phenylephrine were not administered. After completion of the phenylephrine dose response, a 45-minute washout period was allowed to elapse. Then, to determine the relation between the attenuation of vasodilation in response to intra-arterial isoproterenol that we had previously observed in blacks and α-adrenergic vasoconstriction, we administered 2 doses (60 and 400 ng/min) of isoproterenol (Isuprel, Winthrop Pharmaceuticals). Each dose was administered for 7 minutes, and forearm blood flow was recorded during the last 2 minutes of the infusion. The dose ranges of isoproterenol and phenylephrine were selected to have a substantial effect on local forearm blood flow but to have no systemic hemodynamic effects.

**Blood Collection and Analysis**

Blood was drawn into cooled tubes with EGTA and reduced glutathione (Amersham), placed on ice, and centrifuged at 4°C. Samples of the [H]norepinephrine infusion solution were collected, stored, and later assayed, as described below for the blood samples, to allow determination of the actual rate of [H]norepinephrine infusion. Norepinephrine and epinephrine concentrations were measured by high-performance liquid chromatography with electrochemical detection, as we have described previously.

**Measurement of Forearm and Systemic Norepinephrine Spillover**

Measurement of sympathetic activity in vivo is complex because norepinephrine does not function as a circulating hormone but acts locally at the nerve terminal with a small amount “spilling over” into the circulation. Circulating plasma norepinephrine concentrations reflect not only the spillover from the nerve terminal but also the clearance of norepinephrine from plasma. Radioisotope dilution techniques, which determine the clearance of norepinephrine, allow more accurate determination of norepinephrine release (spillover)1,10 Systemic norepinephrine spillover provides a measure of global sympathetic activity, whereas forearm norepinephrine spillover measures norepinephrine release across the forearm. Norepinephrine and epinephrine samples were analyzed in duplicate, and the average value was used for the calculations. Calculations for the determination of norepinephrine kinetics by the isotope dilution method were performed as we and others have previously described.7,10

**Statistical Analysis**

For technical reasons, 1 black subject performed only the LBNP part of the protocol, another performed only the intra-arterial drug administration part of the protocol, and 1 white subject, the radiolabeled norepinephrine infusion was not completed. Two white subjects, one of whom became syncopal and another who became dizzy during the −15 mm Hg LBNP, did not go on to the higher −30 mm Hg LBNP part of the protocol, and their data have not been included in the analysis of those data.

Forearm blood flow tracings were analyzed by a single investigator who was not aware of the race of the subjects. The average of 8 to 10 flow curves was obtained for the measurement of forearm blood flow at any time point. For safety reasons, only 2 blacks as compared with 9 whites received doses of phenylephrine >10 μg/min. The repeated-measures ANOVA was performed on the phenylephrine dose response up to 10 μg/min. As a measure of sensitivity to phenylephrine, linear regression analysis was used to analyze individual phenylephrine dose-response curves with the line of best fit plotted through the linear portion of the log-linear dose-response curve. The dose required to decrease forearm blood flow 25% (P25) was calculated for each subject and then expressed as geometric means with 95% CIs for the 2 groups. The P25 was not calculated in 1 white subject because he was so insensitive to phenylephrine that his forearm blood flow decreased by only 12% after the highest dose of phenylephrine administered, without a clear linear dose-response relation. Statistical analyses were performed with the repeated-measures ANOVA, examining the effects of each intervention, and each intervention was analyzed by race (intervention×race), the unpaired t test, and Fisher’s exact test, as appropriate, with SPSS for Windows Release 6. All results are
expressed as mean±SEM. A 2-tailed P value of <0.05 was the criterion for statistical significance.

Results

Resting Hemodynamic and Catecholamine Measurements

The 2 study groups were well matched in terms of demographic characteristics (Table 1) and resting hemodynamic and catecholamine measurements (Table 2). The 2 groups did not differ significantly with regard to age, weight, height, body mass index, 24-hour urinary sodium excretion or resting heart rate, mean arterial pressure, forearm blood flow, norepinephrine spillover, and epinephrine concentrations.

Forearm Blood Flow Responses to Phenylephrine

Forearm blood flow decreased in response to increasing doses of phenylephrine, an α1-adrenergic agonist, in both blacks and whites. Responses to phenylephrine were significantly enhanced in black subjects (Figure 1). After phenylephrine (1.25 to 10 μg/min), forearm blood flow decreased from 1.9±0.2 to 0.83±0.01 mL · dl−1 · min−1 in blacks and from 2.1±0.4 to 1.5±0.3 mL · dl−1 · min−1 in whites (ANOVA, P=0.008). Phenylephrine (10 μg/min) decreased forearm blood flow by 58.0±2.5% in blacks and 26.6±6.0% in whites (P<0.001). Response to phenylephrine was not affected by the presence or absence of a family history of hypertension and was not correlated with resting blood pressure in blacks, whites, or all subjects (data not shown). Because of the increased vascular sensitivity to phenylephrine in blacks, only 2 black subjects as opposed to 9 white subjects received doses of phenylephrine >10 μg/min. The dose of phenylephrine required to decrease forearm blood flow by 25% (P50) was significantly lower in blacks than in whites (2.7 μg/min, 95% CI 2.1 to 3.4 μg/min compared with 6.0 μg/min, 95% CI 3.8 to 9.4 μg/min, P=0.003), indicating increased sensitivity to phenylephrine in blacks.

Forearm Blood Flow Responses to Isoproterenol

Isoproterenol (60 and 400 ng/min) resulted in a forearm blood flow of 3.4±0.7 and 9.1±1.8 mL · 100 mL−1 · min−1, respectively, in blacks and 6.4±1.7 and 19.6±1.4 mL · 100 mL−1 · min−1 in whites (P=0.02). There was no correlation between vasodilator response, measured as the forearm blood flow response to 400 ng/min isoproterenol, and vasoconstrictor response, measured as the response to 10 μg/min phenylephrine in whites (r²=0.09, P=0.8), blacks (r²=0.06, P=0.5), or all subjects (r²=0.07, P=0.28).

Hemodynamic and Catecholamine Responses to Physiological Adrenergic Stimulation

The physiological relevance of increased α-adrenergic and decreased β-adrenergic vascular sensitivity was examined by

### Table 1. Characteristics of Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Blacks (n=10)</th>
<th>Whites (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>29.9±2.4</td>
<td>28.3±1.9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>93.8±5.6</td>
<td>83.4±4.1</td>
</tr>
<tr>
<td>Height, cm</td>
<td>184.3±2.6</td>
<td>178.6±1.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.5±1.2</td>
<td>26.2±1.3</td>
</tr>
<tr>
<td>Forearm circumference</td>
<td>27.3±0.6</td>
<td>25.8±0.5</td>
</tr>
<tr>
<td>24-h Na⁺ excretion</td>
<td>154±15</td>
<td>131±18</td>
</tr>
</tbody>
</table>

### Table 2. Forearm Blood Flow and Hemodynamic and Sympathetic Values at Rest and After Application of Lower Body Negative Pressure in Normotensive Black (n=10) and White (n=8) Men

<table>
<thead>
<tr>
<th>Variable</th>
<th>Resting</th>
<th>LBPN, 15 mm Hg</th>
<th>LBPN, 30 mm Hg</th>
<th>ANOVA P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>Blacks</td>
<td>Whites</td>
<td>Blacks</td>
<td>Whites</td>
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<tr>
<td></td>
<td>56±3</td>
<td>56±4</td>
<td>56±3</td>
<td>60±4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60±4</td>
<td>68±4</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>96.8±3</td>
<td>92.6±3</td>
<td>98.9±2</td>
<td>92.0±3</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>92.2±3</td>
<td>90.6±3</td>
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<tr>
<td>Forearm blood flow, mL · 100 mL−1 · min−1</td>
<td>2.4±0.4</td>
<td>2.4±0.5</td>
<td>1.5±0.3</td>
<td>2.0±0.5</td>
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<td></td>
<td></td>
<td></td>
<td>1.2±0.2</td>
<td>1.6±0.3</td>
</tr>
<tr>
<td>Forearm vascular resistance, mm Hg · mL−1 · min−1 · dl−1</td>
<td>48±6</td>
<td>46±6</td>
<td>79±12</td>
<td>60±9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>94±15</td>
<td>68±10</td>
</tr>
<tr>
<td>Arterial norepinephrine, pg/mL</td>
<td>104±11</td>
<td>149±14</td>
<td>152±16</td>
<td>196±17</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>198±21</td>
<td>278±25</td>
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<tr>
<td>Arterial epinephrine, pg/mL</td>
<td>35±4</td>
<td>49±11</td>
<td>47±5</td>
<td>58±16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>73±11</td>
<td>111±23</td>
</tr>
<tr>
<td>Forearm norepinephrine spillover, ng/min</td>
<td>1.2±0.4</td>
<td>1.3±0.2</td>
<td>1.2±0.3</td>
<td>1.4±0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.3±0.3</td>
<td>1.2±0.2</td>
</tr>
<tr>
<td>Systemic norepinephrine spillover, ng/min</td>
<td>307±47</td>
<td>357±38</td>
<td>457±85</td>
<td>441±32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>419±72</td>
<td>536±38</td>
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</table>
measuring the hemodynamic and catecholamine responses to LBNP and cold pressor testing. There was no evidence that sympathetic responses were greater in blacks than in whites. The application of LBNP increased epinephrine, norepinephrine, and norepinephrine spillover, measures of sympathetic activity, modestly and to a similar degree in both blacks and whites (Table 3). The application of a cold pressor test resulted in a higher forearm vascular resistance in blacks (107±13 mm Hg·mL⁻¹·min⁻¹·dL⁻¹) than in whites (65±13 mm Hg·mL⁻¹·min⁻¹·dL⁻¹) (P=0.03) (Figure 2). Norepinephrine concentrations and norepinephrine spillover after cold pressor testing increased significantly from resting values in both ethnic groups (P=0.03); however, they did so to a similar extent in blacks (637±300 ng/min) and whites (643±115 ng/min) (P=0.86) (Table 3), indicating that the higher vascular resistance in blacks in response to the cold pressor test was not due to increased sympathetic activity. Heart rate, mean arterial pressure, forearm blood flow, and epinephrine responses to cold pressor testing were similar in blacks and whites (Table 3).

The major findings of this study are first, that vascular α-adrenergic vasoconstrictor sensitivity is increased in normotensive black men; second, that an exogenous sympathetic stimulus, the cold pressor test, despite a similar increase in norepinephrine spillover in blacks and whites, resulted in a greater increase in peripheral vascular resistance in blacks; and third, that attenuated β-adrenoceptor–mediated vasodilation and enhanced α-adrenergic vasoconstrictor sensitivity in blacks were independent of each other and hence will produce additive effects.

Vascular responses to stress include vasodilation mediated by epinephrine, the endogenous β-adrenergic agonist, vasodilation mediated through nitric oxide, and vasoconstriction mediated through norepinephrine, which is predominantly an α-adrenergic agonist. This study suggests that increased sensitivity to α-adrenergic vasoconstriction would act to amplify the increase in vascular tone that would result from attenuated β-adrenergic and nitric oxide–mediated vasodilation in blacks under conditions of stress. Thus, our findings of increased α-adrenergic sensitivity coupled with an attenuated response to vasodilators explains the increased hemodynamic responses and peripheral vascular resistance in response to stress noted in blacks in many previous studies.

Adrenergic vasoconstrictor sensitivity in blacks, previously studied through measurement of blood pressure responses to systemic infusion of an α-adrenergic drug, has been poorly characterized. Dimsdale et al reported no ethnic difference in the pressor sensitivity to intravenous infusion of norepinephrine in normotensive subjects, whereas Sherwood et al reported that α-adrenergic sensitivity was increased, independent of blood pressure, in borderline hypertensive and normotensive blacks. However, extrapolation of the effects of systemic infusion of vasoactive drug on blood pressure to a measure of vascular sensitivity is complicated by the confounding effects of systemic reflex responses, including reflex sympathetic responses, that occur after the systemic infusion of vasoactive drugs.

A more rigorous technique for examining vascular sensitivity is to measure the vascular response to low doses of drug...
that do not have systemic effects infused directly into the blood vessel or vascular bed of interest. One such study has examined the dorsal hand vein responses to the local infusion of the α-adrenergic agonist phenylephrine and found decreased rather than increased sensitivity in blacks. However, that study also found that responses to isoproterenol in the hand vein were similar in blacks and whites, in contrast to the findings in the forearm vasculature. The hand vein model, although attractively simple, may not reflect arterial or resistance vessel responses. In the present study, we infused phenylephrine, an α-adrenergic agonist, directly into the brachial artery in healthy normotensive white and black subjects and showed that vasoconstriction in the forearm was markedly increased in blacks. Thus, these findings show that vascular sensitivity to an infused α-adrenergic vasoconstrictor is increased in normotensive blacks.

Forearm vasodilation in response to isoproterenol, whose actions are mediated both through β-adrenergic receptors and the release of nitric oxide, and in response to sodium nitroprusside, methacholine, and acetylcholine, whose actions are mediated through nitric oxide, is attenuated in blacks. These findings suggest that the local infusion of a concomitant enhanced α-adrenergic–mediated vasoconstriction. Vascular tone is the result of vasoconstricting and vasodilating forces. Thus, under conditions of stress and adrenergic activation, increased adrenergic vasoconstrictor sensitivity would serve to independently augment the vascular and hemodynamic effects of attenuated vasodilator responses.

In addition to altered vascular adrenergic sensitivity, it is important to consider increased endogenous adrenergic activation in blacks as a potential mechanism for enhanced cardiovascular response in blacks. Resting and stimulated plasma norepinephrine concentrations have generally been found to be similar in normotensive and hypertensive blacks and whites. However, measurement of plasma norepinephrine concentrations is not an ideal index of sympathetic activity because norepinephrine does not primarily function as a circulating hormone but acts locally at the postsynaptic receptor. Using a radioisotope dilution technique that measures norepinephrine clearance and thus provides a more accurate measurement of norepinephrine release, we have previously reported that resting systemic norepinephrine spillover was similar in blacks and whites. However, stress-stimulated sympathetic responses, the critical measure in defining the relation between stress-induced sympathetic activation and hemodynamic effects, have not previously been defined in blacks and whites through the use of this technique.

Two physiological stimuli, cold pressor testing and LBNP, were used to stimulate endogenous adrenergic activity in this study. By simultaneously measuring norepinephrine spillover and hemodynamic responses, we were able to determine the relation between sympathetic activation and hemodynamic responsiveness.

The effector limb of the sympathetic response can be tested by measuring neurohormonal and vascular responses to a cold stimulus. The cold pressor test resulted in a similar degree of sympathetic activation in blacks and whites; however, vascular responsiveness was increased in blacks. Thus, consistent with our findings of increased vascular α-adrenergic sensitivity as determined by increased sensitivity to phenylephrine, a significantly greater forearm vascular resistance in response to the cold pressor test in blacks occurred. There was no significant ethnic difference in the blood response to the cold pressor test. The probable reason is that the cold pressor response, in addition to the changes resulting from sympathetic activation, is also affected by the baroreflex response and the degree of discomfort perceived by the subjects.

We found that the increases in sympathetic activity in response to LBNP, as measured by increases in systemic norepinephrine spillover and in plasma epinephrine concentrations, were similar in blacks and whites. Similarly, hemodynamic responses were not significantly different in the two groups. One would expect from our findings of increased vascular sensitivity to phenylephrine and increased forearm vascular responses to cold pressor testing in blacks that LBNP, which resulted in a similar degree of sympathetic stimulation in blacks and whites, would result in enhanced vascular responses in blacks. Forearm vascular resistance in response to LBNP in blacks (94 ± 15 U) and whites (68 ± 10 U) was not significantly different (P = 0.23). Cold pressor testing is a powerful sympathetic stimulus inducing vasoconstriction in peripheral muscle beds that is thought to be largely mediated through peripheral α-adrenergic receptors, whereas subhypotensive LBNP, a relatively weak sympathetic stimulus, decreases the firing rate of low-pressure baroreceptors, thus increasing peripheral vascular resistance.

LBNP increased systemic spillover by ≈40% and, as found by others, did not increase forearm norepinephrine spillover. In contrast, cold pressor testing increased systemic norepinephrine spillover by >100%. It is possible that another stimulus that resulted in greater sympathetic activation than did subhypotensive LBNP may also have detected ethnic differences in vascular reactivity.

Several possible mechanisms for the attenuated response to multiple vasodilators and enhanced α-adrenergic–mediated vasoconstriction in blacks can be considered. The possibility that increased vasoconstrictor sensitivity to phenylephrine may have occurred because of an increased baseline vascular tone caused by attenuated vasodilation in response to the basal nitric oxide released by the endothelium was considered. This appears to be unlikely for several reasons. First, resting forearm blood flow was similar in blacks and whites; second, there was no correlation between the vasoconstrictor response to phenylephrine and the vasodilator response to isoproterenol in either ethnic group; and third, vascular responsiveness to phenylephrine in the human forearm is not altered by the basal production of nitric oxide.

The forearm blood flow technique has been used extensively to study local regulation of vascular response, primarily because it allows the measurement of vascular sensitivity free of the confounding effects of systemic reflex responses. This technique allows the delivery of an exact dose of drug directly into the forearm vascular bed, whose response is being measured and therefore also has the advan-
tage that the responses are unlikely to be confounded by interindividual or interethnic differences in drug disposition.

Recently, polymorphisms of the β2-adrenergic receptor have been described and found to be associated with race, salt sensitivity, hypertension, and forearm blood flow response to isoproterenol.25–27 Polymorphisms of the α1-adrenergic receptor subtypes also exist,28 and there are ethnic differences in their distribution.28 The relation between polymorphisms of α-adrenergic and β2-adrenergic receptors and of nitric oxide synthase genes and the interethnic differences in vascular responsiveness in blacks and whites has not been determined but might contribute to our findings.

The effector system of the G-protein–coupled α1-adrenergic receptor includes phospholipase C and phosphatidylinositol29 and differs from the adenylate cyclase–coupled β-adrenergic receptor and the guanylate cyclase–coupled effector system mediating vasodilation to nitric oxide agonists. This argues for ethnic differences either at several different sites or at a single site further downstream in the vascular smooth muscle.

Ethnicity can be considered to represent a clustering of genetic and environmental factors.30 In this study, we controlled for factors such as gender, diet, and sodium, caffeine, and alcohol intake, which might affect vascular responses. In addition, subjects were of similar educational backgrounds, and the two ethnic groups had a similar frequency of a family history of hypertension. Nevertheless, it is possible that other environmental factors, perhaps interacting with genetic factors, could account for our observation of increased adrenergic-mediated vasoconstriction. However, the confirmation of attenuated β-adrenergic–mediated and nitric oxide–mediated vasodilation in blacks by other investigators31 elsewhere in the United States, in a study population that included both men and women, supports the general significance of our findings.

Several limitations must be noted. First, although there is considerable information linking blood pressure reactivity to the future risk of hypertension,4 there are no data regarding the importance of α-adrenergic vascular sensitivity because it is not feasible to measure this in a large number of individuals. However, it is of interest that several studies that failed to find a difference between blacks and whites in blood pressure reactivity to stressors did find increased peripheral vascular resistance to these stressors in blacks.6 Second, for safety reasons, we could not determine the maximum responses to phenylephrine and thus could not obtain exact measures of maximum response or the dose required to produce 50% of the maximum response (ED50). However, in many biological experiments it is not feasible to produce maximum responses, and analysis of the linear portion of the dose-response curve allows comparisons of sensitivity between groups or individuals to be made. Third, we studied healthy normotensive men, and the more general significance of our findings will need to be tested in a wider range of subjects, including those with hypertension.

In summary, the decrease in forearm blood flow in response to phenylephrine is markedly increased in normotensive black men. Enhanced adrenergic-mediated vasoconstriction in blacks will further accentuate the increase in vascular tone that results from attenuated vasodilation to nitric oxide and to epinephrine, the endogenous β2-adrenergic receptor agonist. Our findings indicate that increased vasoconstriction, in addition to attenuated vasodilation, contributes to enhanced vascular reactivity to stress and may play a role in the pathogenesis of hypertension in blacks.

Acknowledgments

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References


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