Effects of Race and Hypertension on Flow-Mediated and Nitroglycerin-Mediated Dilation of the Brachial Artery

Noyan Gokce, Monica Holbrook, Stephen J. Duffy, Serkalem Demissie, L. Adrienne Cupples, Elizabeth Biegen, John F. Keaney, Jr, Joseph Loscalzo, Joseph A. Vita

Abstract—Black Americans have increased morbidity and mortality rates from cardiovascular disease, greater prevalence of hypertension, and altered responses to vasodilator medications compared with those of white Americans. Hypertension and black race have been linked to impaired vascular function in the microcirculation. To examine these effects and their interaction in the conduit vasculature, we examined vasomotor responses of the brachial artery by using high-resolution vascular ultrasound in 228 subjects (48% hypertensive, 54% black). Subjects had no history of diabetes mellitus and were matched for age and gender. Flow-mediated dilation (8.5±5.3% versus 11.7±6.3%, P<0.001) and nitroglycerin-mediated vasodilation (14.9±6.0 vs 18.5±7.8, P=0.003) were both impaired in hypertensive compared with normotensive individuals. Multivariate analysis identified higher systolic blood pressure (P=0.003) and larger baseline vessel (P<0.001) size as independent predictors of lower flow-mediated dilation. Race did not significantly influence flow-mediated dilation. In contrast, blacks had a greater vasodilator response to nitroglycerin compared with whites (17.7±7.5% versus 15.0±6.2%, respectively; P=0.02). By multivariate analysis, black race (P=0.004), smaller vessel size (P=0.001), lower serum glucose (P=0.02), lower systolic blood pressure (P=0.02), and lower serum total cholesterol (P=0.04) were independent predictors of higher nitroglycerin-mediated dilation. Thus, hypertension is associated with impaired NO–mediated vasodilation in the conduit brachial artery. Overall, race did not influence flow-mediated dilation, but black race was associated with an enhanced response to sublingual nitroglycerin. This later observation provides further evidence of racial differences in the responses to medical therapy that may be relevant to the treatment of patients with cardiovascular disease. (Hypertension. 2001;38:1349-1354.)

Key Words: blacks • endothelium • hypertension, essential • race • nitroglycerin

Black Americans have a higher prevalence of hypertension and increased cardiovascular complications compared with that of white Americans.1 Recent studies have emphasized that race also influences the therapeutic effectiveness of cardiovascular medications.2 The reasons for these racial differences are incompletely understood. Genetic factors, environmental influences, and maladaptive endocrine and autonomic responses have all been proposed as potential mechanisms.

Recent studies suggest that racial differences in vascular function may be important. Loss of the biological activity of endothelium-derived NO may contribute to the pathogenesis of hypertension3 and to cardiovascular disease events.4 NO–dependent vasodilation has been reported to be impaired in arm conduit5 and resistance vessels of normotensive young black subjects compared with matched white subjects.6–8

Hypertension itself is associated with endothelial dysfunction, although it remains controversial whether this impairment is a primary or secondary phenomenon. Impaired vasodilator responses of resistance vessels have been demonstrated in most,9 but not all,10 studies involving hypertensive subjects. There also is evidence that hypertension impairs endothelial function in conduit coronary and peripheral arteries,11,12 although few, if any, of the subjects were black in those studies.

The cardiovascular complications of hypertension largely involve conduit vessels (eg, coronary and carotid arteries). This study was designed to test the hypothesis that black race would be associated with an impairment of conduit vessel function and that hypertension would have a more marked effect on vascular function in black individuals, possibly explaining their increased cardiovascular disease risk.

Methods

Study Subjects

We recruited black and white hypertensive patients and age- and gender-matched normotensive subjects by advertisement. Race was defined by self-reporting. Hypertension was defined as a clinical
Study Protocol

Subjects fasted overnight and took their last dose of antihypertensive therapy at least 24 hours before the study. Supine blood pressure was measured after a 10-minute rest period with an automated monitor (Dinamap, Johnson and Johnson Medical), and the average of 3 measurements was recorded. Flow-mediated and nitroglycerin-mediated vasodilation of the brachial artery were determined in a blinded manner as previously described, with the occlusion cuff on the upper arm.13

Statistical Analysis

Patients were categorized as black or white and as normotensive or hypertensive. The effects of these two factors on categoric clinical variables were explored by means of $\chi^2$ tests of proportions or Fisher’s exact tests, as appropriate. The effects of these factors on continuous clinical variables were explored by 2-way ANOVA with Tukey all-pairwise post hoc comparison. The study was powered to detect a difference between groups in flow-mediated dilation of 2.2 percentage points and nitroglycerin-mediated dilation of 2.5 percentage points with 80% power ($\alpha=0.05$) with the sample size of 228 subjects.

Multiple linear regression analysis was used to identify independent predictors of the outcome variables of interest (flow- or nitroglycerin-mediated dilation). Variables considered for inclusion in the multivariate model included baseline vessel size, systolic blood pressure, gender, age, family history of coronary disease, pack-years of cigarette smoking, heart rate, total cholesterol, HDL cholesterol, triglycerides, glucose, extent of reactive hyperemia, and body mass index. In the regression models, first we assessed the significance of the selection criteria of $P<0.10$. All data are presented as mean±SD, except as indicated, and a value of $P<0.05$ was considered significant.

Results

Clinical Characteristics

The clinical characteristics of the 228 studied subjects are displayed in Table 1. Notably, the patients were well matched for age and gender, as prespecified. Although higher than the normotensive subjects, the degree of blood pressure elevation was modest in the hypertensive group. A total of 47% of the hypertensive patients were receiving at least one antihypertensive medication. Other interracial differences and differences between normotensive and hypertensive individuals are detailed in Table 1.

Brachial Artery Responses

For the entire group of 228 subjects, mean brachial artery flow-mediated dilation was 10.1±6.0%. In the 159 subjects who received sublingual nitroglycerin, the mean brachial dilation was 2.5±1.3%.
dilation response was 16.6±7.1%. As detailed in Figures 1 and 2, flow-mediated dilation was lower in patients with hypertension (8.5±5.3%) compared with normotensive subjects (11.7±6.3%, \( P<0.001 \)) and was not different between blacks and whites (10.2±6.3 versus 10.1±5.7%, respectively, \( P=0.83 \)). Nitroglycerin-mediated dilation was lower in hypertensive compared with normotensive individuals (14.9±6.0 versus 18.5±7.8, respectively, \( P=0.003 \)) and higher in blacks compared with whites (17.7±7.5 versus 15.0±6.2%, respectively, \( P=0.02 \)). There were no significant differences among groups for baseline vessel size, extent of reactive hyperemia, or resting pulse (Table 2).

The analysis was repeated after excluding patients receiving antihypertensive medications, and the findings were comparable. In this subgroup (n=175), flow-mediated dilation was lower in hypertensive patients (\( P<0.001 \)) and was not affected by race (\( P=0.86 \)). Among the patients not taking antihypertensive medications who received nitroglycerin (n=118), the brachial dilator response was also lower in hypertensive patients (\( P=0.02 \)). There was a tendency for greater vasodilator responses to nitroglycerin in blacks (18.1±8.0) compared with whites (15.6±6.1, \( P=0.17 \)).

**Figure 1.** Brachial artery flow-mediated dilation (FMD, lower panel) and nitroglycerin-mediated dilation (NTG, upper panel) are plotted according to race among all subjects (hypertensive and normotensive). There are no racial differences in flow-mediated dilation \( (P=0.89) \). However, the vasodilator response to nitroglycerin is higher in black subjects compared with white subjects \( (P=0.02) \). Data are mean±SEM.

**Figure 2.** Brachial artery flow-mediated dilation (FMD, lower panel) and nitroglycerin-mediated dilation (NTG, upper panel) are plotted according to presence or absence of hypertension among all subjects (black and white). Both flow-mediated dilation \( (P<0.001) \) and nitroglycerin-mediated dilation \( (P<0.001) \) are impaired in hypertensive subjects. Data are mean±SEM.

**Independent Predictors of Vasodilator Responses**

We sought to determine whether race and hypertension were independent predictors of vasodilator function when included with other clinical variables in a multivariate model. The univariate and multivariate predictors of higher flow-mediated dilation are shown in Table 3. The multivariate predictors of higher flow-mediated dilation were smaller baseline diameter and lower systolic blood pressure. When clinical history of hypertension, diastolic blood pressure, or pulse pressure was substituted for systolic blood pressure, the blood pressure variable and baseline diameter remained independent predictors of flow-mediated dilation in each model.

The univariate and multivariate predictors of higher nitroglycerin-mediated dilation are shown in Table 3. The multivariate predictors of higher nitroglycerin-mediated dilation were smaller baseline diameter, black race, lower serum glucose, lower systolic blood pressure, and lower total cholesterol. When history of hypertension or pulse pressure was substituted for systolic blood pressure, the blood pressure variable and baseline diameter remained independent predictors of flow-mediated dilation in each model.

**Table 2. Brachial Artery Parameters**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>Flow-mediated dilation, %</td>
<td>11.1±6.0</td>
<td>12.2±6.6</td>
</tr>
<tr>
<td>Nitroglycerin-mediated dilation, %</td>
<td>16.3±5.9</td>
<td>19.9±8.5</td>
</tr>
<tr>
<td>Baseline vessel diameter, mm</td>
<td>4.0±0.8</td>
<td>4.0±0.8</td>
</tr>
<tr>
<td>Hyperemic flow, % increase</td>
<td>811±493</td>
<td>786±399</td>
</tr>
</tbody>
</table>

Data are mean±SD.

*Hypertension, \( P<0.001 \); race, \( P=0.83 \); hypertension-race interaction, \( P=0.23 \).
†Hypertension, \( P=0.003 \); race, \( P=0.02 \); hypertension-race interaction, \( P=0.30 \).
Another study involving 500 subjects demonstrated that higher systolic blood pressure is a univariate predictor of lower flow-mediated dilation,14 but that relation was lost after controlling for vessel size and other coronary risk factors. The reason for those apparently discrepant findings in that latter study are unclear but could be related to differences in technique (that study used a lower arm cuff position, whereas the present study used an upper arm location of the inflation cuff) or differences in study population.

Regarding impaired nitroglycerin-mediated vasodilation in hypertension, Preik and colleagues15 observed a similar impairment of both endothelium-dependent and endothelium-independent vasodilator function in forearm resistance vessels of hypertensive patients, but no prior study has demonstrated such an effect in conduit vessels of hypertensive patients. Interestingly, Adams and colleagues16 reported that diabetes mellitus was independently correlated with impaired nitroglycerin-mediated dilation in a study that excluded patients with hypertension. Our findings suggest that hypertension may be associated with an alteration in the ability of vascular smooth muscle to respond to NO derived either from the endothelium or from an exogenous source. Alternatively, NO from any source might be “inactivated” before exerting its vasodilator effect. This latter mechanism would be consistent with the growing experimental and human evidence that resistance vessel endothelial dysfunction in hypertension is attributable to increased oxidative stress.17,18 Although unrelated to the primary hypothesis of the study, elevated serum cholesterol and glucose also were independent predictors of more impaired nitroglycerin-mediated dilation. These findings are consistent with previous work19 and a body of evidence linking these risk factors to increased vascular oxidative stress.

A seminal feature of this study was the lack of racial differences in flow-mediated dilation. This finding comes in the background of several prior studies that demonstrated impaired vasodilator responses to endothelium-dependent and endothelium-independent vasodilator stimuli in the microcirculation of blacks. For example, in a study involving 18 black subjects, Cardillo and colleagues20 showed that normotensive blacks have blunted forearm responses to mental stress. Similarly, in a study of 12 black subjects, the same group of investigators reported that forearm blood flow responses to acetylcholine, nitroprusside, and isoproterenol were uniformly reduced in black as compared with white individuals.8 It is possible that differential responses in conduit vessels and microvessels might account for the opposing findings in the prior studies cited above and the present study. However, a study by Perregaux and colleagues7 contrasts more directly with our findings. They reported that brachial artery flow-mediated dilation induced by lower arm cuff occlusion was nearly absent in 24 healthy normotensive young black subjects but was normal in 28 matched white subjects, with no racial difference in nitroglycerin-mediated responses. There is no obvious explanation for these apparently discrepant results, but our findings may be more definitive, owing to the larger sample size. By contrast, our findings are in close agreement with data reported by Houghton and colleagues,5 who also failed to observe racial differences in endothelium-dependent and endothelium-independent responses of the conduit coronary arteries of 80 patients with and without hypertension.21 Although prior studies have suggested increased cardiovascular risk in blacks,1 our findings and those of Houghton and colleagues suggest that conduit vessel

### Table 3. Predictors of Brachial Artery Dilation

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>R</td>
</tr>
<tr>
<td>Baseline diameter</td>
<td>-0.53</td>
<td>-0.46</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>-0.31</td>
<td>-0.20</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>-0.16</td>
<td>-0.04</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.31</td>
<td>0.04</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.13</td>
<td>-0.02</td>
</tr>
<tr>
<td>Nitroglycerin-mediated dilation</td>
<td>Baseline diameter</td>
<td>-0.44</td>
</tr>
<tr>
<td></td>
<td>Black race</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Serum glucose</td>
<td>-0.25</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure</td>
<td>-0.31</td>
</tr>
<tr>
<td></td>
<td>Total cholesterol</td>
<td>-0.23</td>
</tr>
<tr>
<td></td>
<td>HDL cholesterol</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Discussion

This study demonstrates that flow-mediated brachial artery dilation is significantly impaired in black and white hypertensive individuals. Nitroglycerin-mediated vasodilation was also impaired in hypertensive subjects, suggesting an impairment of overall vascular function, but not necessarily an impairment of endothelial function in hypertensive individuals. In contrast to our initial hypothesis and prior studies that examined the microvasculature, we observed no racial differences in conduit vessel flow-mediated dilation and no interaction between hypertension and race on this response. Interestingly, black race was associated with a greater vasodilator response to nitroglycerin in both normotensive and hypertensive individuals. This effect of race on the nitroglycerin response was highly significant after controlling for other clinical variables. In particular, these findings were not attributable to variation in baseline vessel size or extent of reactive hyperemia, suggesting that alterations in resting vessel tone or the stimulus for vasodilation do not explain our findings.

The present investigation represents one of the larger studies to date examining the relations among conduit artery vasomotor function and essential hypertension, and the sample size permitted an examination of whether the effect of hypertension is independent of other factors known to influence vascular function. Our finding that hypertension is independent of other factors known to influence vascular function. Our finding that hypertension is associated with impaired conduit vessel flow-mediated dilation is in agreement with previous smaller studies that examined brachial artery flow-mediated dilation and endothelium-dependent responses in the coronary circulation. Another study involving 500 subjects demonstrated that higher systolic blood pressure is a univariate predictor of lower flow-mediated dilation, but that relation was lost after controlling for vessel size and other coronary risk factors. The reason for those apparently discrepant findings in that latter study are unclear but could be related to differences in technique (that study used a lower arm cuff position, whereas
dysfunction per se may not explain the increased cardiovascular risk in blacks.

A novel finding of the present study is the increased vasodilator response to sublingual nitroglycerin in blacks that remained independent after controlling for other potentially confounding clinical variables. This finding seems to fit well with other recent studies indicating racial differences in the response to vasodilator therapy. In particular, a retrospective analysis of the Vasodilator-Heart Failure Trial (V-HeFT-1) study suggested a benefit of nitrate therapy for cardiovascular disease events in black subjects with heart failure but not in white subjects. Several studies suggest a greater benefit of ACE inhibitor therapy in whites compared with blacks. A unifying explanation for this pattern of responses might relate to the tendency for blacks to have a higher incidence of salt-sensitive/low-renin hypertension. Greater activity of the renin-angiotensin system leading to increased production of reactive oxygen species and “inactivation” of NO might account for reduced response to nitrates and greater response to ACE inhibitors in white compared with black subjects. However, such a mechanism would not account for the lack of a racial difference in flow-mediated dilation, a response that is also known to be NO dependent. However, these conflicting results emphasize that there may be important differences in the bioactivity, metabolism, and sites of action of endothelium-derived and nitroglycerin-derived NO.

Our study has several limitations. Although we observed no racial differences in conduit artery vasomotor function associated with hypertension, we wish to emphasize that such differences may exist in the microvasculature, as has been previously reported, and that such differences may contribute to abnormal vascular function and adverse outcomes in blacks. The majority of our subjects were only mildly hypertensive, and we therefore cannot exclude the possibility that racial differences in conduit vascular function occur in association with higher blood pressure. Finally, our study examined the brachial artery, and extrapolation of these results to the more relevant coronary and cerebral circulations and to cardiovascular disease must be made with caution, although flow-mediated dilation in the brachial artery has been shown to correlate with coronary endothelial function.

In conclusion, this relatively large study demonstrates that NO–dependent vasodilation of conduit vessels is impaired in hypertension and that this impairment is present to a similar degree in black and white individuals. Because hypertension is more prevalent in blacks, hypertension-mediated vascular dysfunction may contribute to their increased risk for cardiovascular disease. However, in contrast to prior studies of resistance vessel function, the present study does not support the hypothesis that there is an intrinsic biological difference in conduit vessel endothelial function in blacks. Because there is growing interest in the use of brachial artery flow-mediated dilation as a noninvasive method for assessment of cardiovascular disease risk and the response to interventions, another implication of the study is that this methodology may be equally useful in black and white populations. Finally, the study also indicates a racial difference in the vasodilator response to nitroglycerin that merits further investigation.

Acknowledgments

This work was supported by a Specialized Center of Research in Ischemic Heart Disease grant from the National Institutes of Health (HL-55993). Dr Gokce is supported by a Mentored Patient-Oriented Research Career Transition Award from the National Institutes of Health (K23-HL-04425). Dr Duffy is supported by the National Health and Medical Research Council of Australia Neil Hamilton Fairley Fellowship (No. 007139). Drs Keaney and Vita are the recipients of Established Investigator Awards from the American Heart Association. We are grateful to Liza Hunter and Peter Swerdloff for technical assistance.

References

18. Sherman DL, Keaney JF Jr, Biegeles ES, Duffy SJ, Coffman JD, Vita JA. Pharmacological concentrations of ascorbic acid are required for the


Effects of Race and Hypertension on Flow-Mediated and Nitroglycerin-Mediated Dilation of the Brachial Artery

Noyan Gokce, Monica Holbrook, Stephen J. Duffy, Serkalem Demissie, L. Adrienne Cupples, Elizabeth Biegelsen, John F. Keaney, Jr, Joseph Loscalzo and Joseph A. Vita

Hypertension. 2001;38:1349-1354
doi: 10.1161/hy1201.096575

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/38/6/1349

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/