

Effects of Black Race on Forearm Resistance Vessel Function

David F. Kahn, Stephen J. Duffy, Douglas Tomasian, Monika Holbrook, Lynn Rescorla, Judson Russell, Noyan Gokce, Joseph Loscalzo, Joseph A. Vita

Abstract—Presentation, response to therapy, and clinical outcome in hypertension differ according to race, and these observations could relate to differences in microvascular function. We examined forearm microvascular function in age-matched black (n=56) and white subjects (n=62) using intra-arterial agonist infusion and venous occlusion plethysmography. In normotensive subjects (n=70; 34 black and 36 white normotensives), methacholine-, sodium nitroprusside-, and verapamil-induced vasodilation was equivalent in black and white subjects. In hypertensive subjects (n=48; 22 black and 26 white hypertensives), the vasodilator response to methacholine was markedly lower in black subjects compared with white subjects ($P<0.001$). The vasodilator responses to sodium nitroprusside and verapamil, however, were equivalent in black and white hypertensive subjects. Acute ascorbic acid infusion improved the methacholine response equally in black and white hypertensive patients, suggesting that a difference in a rapidly reversible form of oxidative stress does not explain these findings. Thus, the present study demonstrates important racial differences in vascular function and a marked impairment in endothelial vasomotor function in black patients with hypertension. Further studies will be required to elucidate the mechanisms and determine whether these insights will lead to more appropriately tailored management of hypertension and its complications. (*Hypertension*. 2002;40:195-201.)

Key Words: endothelium ■ hypertension, essential ■ race ■ blacks ■ oxidative stress

There is increasing recognition that presentation, response to therapy, and clinical outcome differ according to race for patients with hypertension.¹ For example, black Americans have a higher prevalence of hypertension, are more likely to be salt-sensitive, and are more prone to left ventricular hypertrophy than white Americans. Despite the many advances in the understanding and treatment of cardiovascular disease, black patients continue to have increased morbidity and mortality from the end-organ complications of hypertension.¹ The explanations for these observations remain incompletely understood, but genetic differences, environmental factors, or maladaptive renal, endocrine, and autonomic responses have been proposed to account for the interracial differences in hypertension.²⁻⁴

Racial differences in vascular function, particularly in the bioavailability of endothelium-derived nitric oxide, have also been suggested to play an important role. Several previous studies have demonstrated impaired vascular function in forearm resistance vessels of healthy young black subjects compared with whites.⁵⁻⁸ These differences are likely to be clinically important because endothelium-derived nitric oxide plays a major role in vascular homeostasis via its effects as a vasodilator and as an inhibitor of platelet activity, monocyte adhesion, and smooth muscle proliferation.⁹ Furthermore,

recent studies have demonstrated that impaired endothelial function in the microvasculature is predictive of future cardiovascular disease events.¹⁰⁻¹²

We recently observed no racial differences in endothelial function in the conduit brachial artery of normotensive subjects and no racial difference in the degree of impairment associated with hypertension.¹³ Although the function of conduit vessels may be important in the complications of hypertension, the function of the microvasculature is likely to be more relevant to the pathogenesis of the disease, as well as to renal failure associated with hypertension. The effects of race on resistance vessel responses in hypertensive subjects are incompletely understood. The purpose of the present study was to explore racial differences in the function of resistance vessels of normotensive and hypertensive subjects.

Methods

Research Subjects

Patients with a clinical history of hypertension (on treatment for hypertension and/or systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg) and normotensive volunteers were recruited for the study. Subjects were predominantly from an urban population and black race was defined by self-report. Within the normotensive and hypertensive groups, black and white subjects were matched according to age. Patients were excluded if they had a

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From the Evans Department of Medicine and Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston, Mass.

Correspondence to Joseph A. Vita, MD, Section of Cardiology, Boston Medical Center, 88 East Newton Street, Boston, MA 02118. E-mail jvita@bu.edu

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history of coronary artery disease, congestive heart failure, peripheral vascular disease, diabetes mellitus (on hypoglycemic medications or with a fasting glucose >140 mg/dL), serum LDL >190 mg/dL,¹⁴ malignant hypertension, or end-stage renal disease. All subjects provided written informed consent as approved by the Institutional Review Board of Boston Medical Center.

Study Protocol

All subjects were fasting and had refrained from alcohol, caffeine, and cigarette smoking (if applicable) for at least 12 hours before study. The last dose of antihypertensive medication was at least 24 hours before study. The studies were performed in a quiet, dimmed, temperature-controlled vascular laboratory (24°C). Using sterile conditions and local anesthesia, a 20- or 22-gauge polyethylene catheter (Arrow International) was inserted in the nondominant brachial artery for measurement of blood pressure and infusion of drugs. After catheter insertion, 5% dextrose in water (Baxter Healthcare Co) was infused at 0.4 mL/min for at least 30 minutes while stable baseline flow and blood pressure conditions were established. Forearm blood flow was measured by venous occlusion plethysmography with calibrated mercury-in-silastic strain gauges and automatic venous-cuff occlusion at 40 mm Hg (Hokanson, Inc), as previously described.¹⁵

Serial 5-minute infusions of methacholine (0.3, 1.0, 3.0, and 10 μ g/min; Metapharm, Inc), sodium nitroprusside (0.3, 1.0, 3.0, and 10 μ g/min; Baxter Anesthesia and Critical Care), and/or verapamil (10, 30, 100, and 300 μ g/min; Abbott Hospital Products) were made into the brachial artery. Dextrose control was infused for 30 minutes between agonists to reestablish control conditions, and the order of agonists was randomized. In some patients, methacholine infusions (0.3, 1.0, 3.0, and 10 μ g/min) were completed before and during infusion of ascorbic acid (American Regent) at 2.4 mg/min and 24 mg/min (final estimated concentrations of 1 and 10 mmol/L), as previously described.¹⁵ Forearm vascular resistance was calculated as mean arterial blood pressure divided by flow and was expressed as the percentage change in resistance from baseline to adjust for baseline differences in resistance, as described previously.¹⁶

Biochemical Analysis

Total cholesterol, high-density lipoprotein (HDL), triglycerides, glucose, and creatinine were measured by an automated analyzer (Hitachi Model 717, Hitachi Instruments). Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula.¹⁷

Statistical Analysis

Patients were categorized as black or white and as normotensive or hypertensive. To explore group differences for continuous and categorical variables, we used 2-sample *t* tests, χ^2 tests of proportions, or Fisher exact tests, as appropriate. The forearm blood flow responses to agonist infusion were examined using the general linear models repeated-measures procedure. Models included terms for agonist dose, race, and/or ascorbic acid treatment. When examining the effect of race on vasodilator responses, some models included as covariates other factors that differed between races, including total cholesterol, serum triglycerides, body mass index, and diuretic treatment. Statistical analyses were performed using SPSS for Windows, version 10 (SPSS Inc). All data are presented as mean \pm SD unless otherwise indicated, and $P < 0.05$ was considered significant.

Results

Subjects

A total of 70 normotensive subjects (34 black and 36 white) and 48 hypertensive subjects (22 black and 26 white) were enrolled in the study and their clinical characteristics are displayed in Tables 1 and 2, respectively. As shown, blacks and whites were comparable in age, gender, and other clinical parameters among normotensive subjects, as well as hyper-

TABLE 1. Clinical Characteristics of Normotensive Subjects

Characteristic	Black (n=34)	White (n=36)	P
Mean age, y	39 \pm 7	39 \pm 8	0.91
Male, %	56	61	0.66
Prior history of smoking, %	12	19	0.41
Body mass index, kg/m ²	27 \pm 5	25 \pm 4	0.05
Systolic BP, mm Hg	123 \pm 13	121 \pm 10	0.51
Diastolic BP, mm Hg	72 \pm 11	76 \pm 11	0.16
Total cholesterol, mg/dL	170 \pm 34	167 \pm 29	0.71
HDL cholesterol, mg/dL	49 \pm 13	49 \pm 16	0.87
LDL cholesterol, mg/dL	105 \pm 31	96 \pm 29	0.21
Triglycerides, mg/dL	81 \pm 30	109 \pm 81	0.06
Fasting glucose, mg/dL	93 \pm 11	94 \pm 14	0.69
Serum creatinine, mg/dL	0.8 \pm 0.2	0.8 \pm 0.2	0.17

Data are mean \pm SD or percent. There were no significant differences between groups. BP indicates blood pressure; HDL, high-density lipoproteins; LDL, low-density lipoproteins.

tensive subjects. Sixty-seven percent of hypertensive subjects had a systolic blood pressure >140 mm and/or a diastolic blood pressure >90 mm. The proportion of patients receiving antihypertensive treatment and the duration of hypertension were equivalent among black and white hypertensive subjects. The types of antihypertensive medications used were also comparable, except for diuretics, which were more often used by black than by white hypertensive subjects.

Relation Between Race and Microvascular Function in Normotensive Subjects

As shown in Figure 1 (top), resting forearm blood flow was equivalent in black and white normotensive subjects

TABLE 2. Clinical Characteristics of Hypertensive Subjects

Characteristic	Black (n=22)	White (n=26)	P
Mean age, y	51 \pm 11	54 \pm 10	0.19
Male, %	50	69	0.18
Prior history of smoking, %	23	40	0.21
Body mass index, kg/m ²	30 \pm 5	30 \pm 6	0.75
Systolic BP, mm Hg	147 \pm 19	147 \pm 18	0.98
Diastolic BP, mm Hg	94 \pm 14	90 \pm 13	0.30
On antihypertensive medication, %	73	62	0.41
Diuretics, %	56	13	0.01
ACE inhibitors, %	25	44	0.26
Calcium channel blockers, %	44	38	0.72
Beta blockers, %	25	25	1.0
Number of medications	1.1 \pm 0.9	0.9 \pm 0.8	0.33
Years of hypertension	6 \pm 5	9 \pm 7	0.19
Total cholesterol, mg/dL	186 \pm 28	202 \pm 33	0.08
HDL cholesterol, mg/dL	52 \pm 15	47 \pm 14	0.29
LDL cholesterol, mg/dL	112 \pm 26	123 \pm 29	0.19
Triglycerides, mg/dL	110 \pm 71	159 \pm 99	0.06
Fasting glucose, mg/dL	98 \pm 18	104 \pm 12	0.17
Serum creatinine, mg/dL	0.8 \pm 0.2	0.8 \pm 0.2	0.86

Data are mean \pm SD or percent. There were no significant differences between groups unless otherwise indicated.

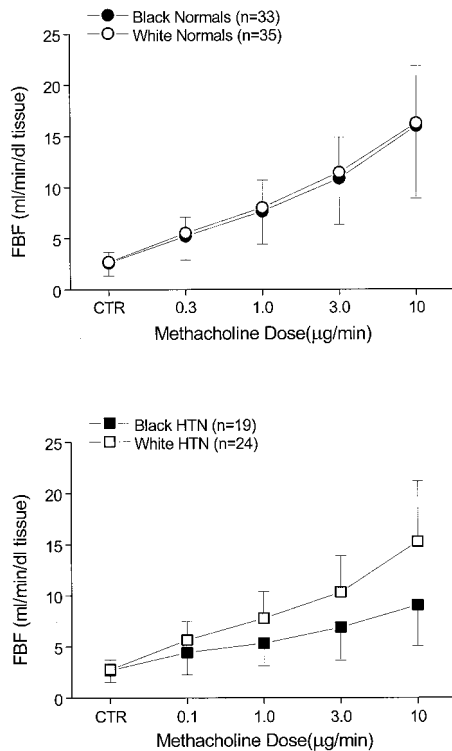


Figure 1. Racial differences in forearm blood flow (FBF) responses to methacholine. FBF responses to intra-arterial methacholine infusion were measured using venous occlusion plethysmography as described in Methods. Top, Vasodilator responses to methacholine were similar in age-matched black and white normotensive subjects ($P=0.86$ by repeated-measures ANOVA). Bottom, Methacholine responses were lower in black hypertensive subjects compared with age-matched white hypertensive subjects ($P<0.001$ by repeated-measures ANOVA).

(2.6 ± 1.3 and 2.7 ± 1.0 mL/min per deciliter of tissue, respectively, $P=0.75$). The endothelium-dependent vasodilator methacholine produced dose-dependent increases in forearm blood flow that were equivalent in black and white subjects ($P=0.86$ by repeated-measures ANOVA) with peak responses of 16.0 ± 7.1 and 16.2 ± 5.6 mL/min per deciliter of tissue, respectively. Mean blood pressure was unaffected by methacholine, and black and white normotensives had equivalent decreases in forearm vascular resistance in response to methacholine (data not shown).

As shown in Figure 2 (top), sodium nitroprusside, which induces vasodilation by non-endothelium-dependent release of nitric oxide, also produced dose-dependent increases in forearm blood flow in black and white normotensive subjects. The vasodilator responses were comparable in black and white subjects ($P=0.12$ by repeated-measures ANOVA) with peak responses of 11.9 ± 4.4 and 14.1 ± 4.7 mL/min per deciliter of tissue, respectively. Systemic blood pressure was unaffected by sodium nitroprusside, and black and white normotensives had equivalent decreases in forearm vascular resistance in response to nitroprusside (data not shown).

As shown in Figure 3 (top), the forearm blood flow responses to the non-nitric-oxide-dependent vasodilator verapamil were equivalent in black and white subjects ($P=0.71$

by repeated-measures ANOVA), with peak responses of 14.7 ± 4.8 and 14.5 ± 4.7 mL/min per deciliter of tissue, respectively. The decreases in vascular resistance were also equivalent (data not shown).

In light of the trends for normotensive black subjects to have higher body mass index (BMI) and serum triglycerides (Table 1), these analyses were repeated with inclusion of these variables as covariates in the model. After controlling for BMI and serum triglycerides, the vasodilator responses to methacholine ($P=0.83$), sodium nitroprusside ($P=0.46$), and verapamil ($P=0.74$) remained equivalent in black and white normotensive subjects (data not shown).

Relation Between Race and Microvessel Function in Hypertensive Subjects

As shown in Figure 1 (bottom), resting forearm blood flow was equivalent in black and white hypertensive patients (2.7 ± 1.2 and 2.8 ± 1.0 mL/min per deciliter of tissue, respectively, $P=0.87$) and methacholine produced dose-dependent increases in forearm blood flow in both groups of patients. However, in contrast to the normotensive subjects, the response to methacholine was markedly lower in the black patients compared with white patients ($P<0.001$ by repeated-measures ANOVA), with peak responses of 9.0 ± 4.0 and 15.3 ± 5.9 mL/min per deciliter of tissue, respectively. Similarly, the decrease in vascular resistance was also signifi-

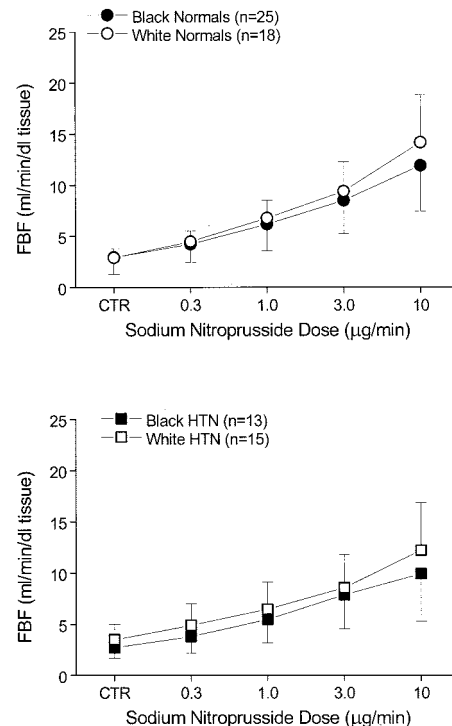


Figure 2. Racial differences in FBF responses to sodium nitroprusside. FBF responses to intra-arterial sodium nitroprusside infusion were measured in age-matched normotensive subjects (top) and age-matched hypertensive subjects (bottom) using venous occlusion plethysmography as described in Methods. There were no racial differences in the response to nitroprusside in normotensive ($P=0.12$) and hypertensive subjects ($P=0.41$ by repeated-measures ANOVA).

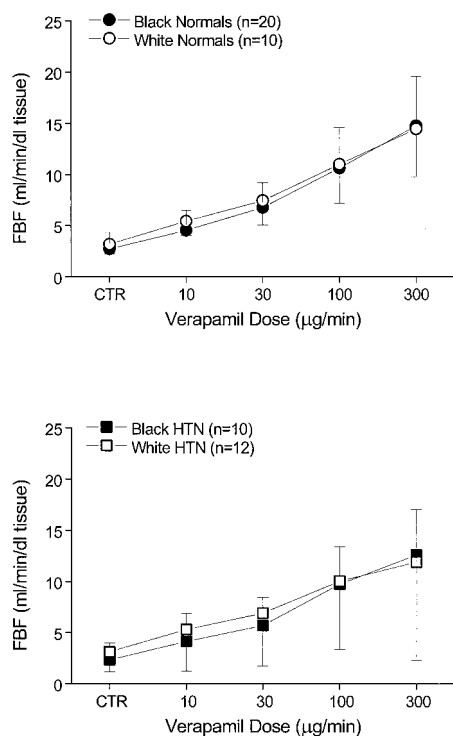


Figure 3. Racial differences in FBF responses to verapamil. FBF responses to intra-arterial verapamil infusion were measured in age-matched normotensive subjects (top) and age-matched hypertensive subjects (bottom) using venous occlusion plethysmography as described in Methods. Vasodilator responses to verapamil were similar in black and white normotensive subjects ($P=0.71$) and hypertensive subjects ($P=0.66$ by repeated-measures ANOVA).

cantly lower ($P=0.01$) in black hypertensive subjects compared with white hypertensives (data not shown).

We explored the possibility that antihypertensive treatment might be influencing the findings. Overall, the vasodilator responses to methacholine were equivalent in patients receiving antihypertensive medications compared with those who were not (data not shown). Furthermore, when considering only those patients who never received antihypertensive treatment, the vasodilator response to methacholine was significantly lower in the 6 black hypertensive subjects than in the 10 white hypertensive subjects ($P=0.009$ by repeated-measures ANOVA), with peak responses of 8.4 ± 2.1 and 16.3 ± 6.7 mL/min per deciliter of tissue, respectively. Finally, after controlling for diuretic use by including it as a covariate in the repeated measures model, the methacholine response remained lower in the black hypertensive subjects ($P=0.001$ by repeated-measures ANOVA).

As shown in Figure 2 (bottom), sodium nitroprusside produced dose-dependent vasodilation in hypertensive patients. The vasodilator responses were not significantly different in black and white patients ($P=0.41$ by repeated-measures ANOVA), with peak responses of 9.9 ± 4.6 and 12.2 ± 4.7 mL/min per deciliter of tissue, respectively. Similarly, as shown in Figure 3 (bottom), there was no racial difference in the vasodilator response to verapamil ($P=0.66$ by repeated-measures ANOVA), with peak responses of

12.6 ± 10.3 and 11.9 ± 5.1 mL/min per deciliter of tissue, respectively. These agonists had no effect on systemic blood pressure (data not shown). When expressed as vascular resistance, the vasodilator responses to sodium nitroprusside and verapamil were equivalent in black and white hypertensive subjects (data not shown).

In light of the trends for hypertensive black subjects to have lower total cholesterol and serum triglycerides than hypertensive white subjects (Table 2), the analyses were repeated with inclusion of these variables as covariates in the repeated-measures models. After controlling for total cholesterol and triglycerides, the vasodilator responses to methacholine remained significantly lower in black hypertensives compared with white hypertensives ($P<0.001$). As in the unadjusted models, the vasodilator responses to sodium nitroprusside and verapamil were equivalent in black and white hypertensive subjects (data not shown).

Racial Differences in the Response to Ascorbic Acid

Previous work has demonstrated that intra-arterial ascorbic acid reverses endothelial dysfunction in forearm microvessels of hypertensive patients, suggesting a role for increased oxidative stress as a pathophysiological mechanism.^{15,18} Furthermore, a recent preliminary study suggests that genetic differences in antioxidant defenses may lead to a state of increased oxidative stress in black Americans.¹⁹ To explore the potential importance of oxidative stress as a pathophysiological mechanism for the racial differences in microvascular endothelial function in hypertension, we examined the effects of ascorbic acid on the response to methacholine in 19 hypertensive patients (10 white and 9 black). As shown in Figure 4, ascorbic acid infusion improved forearm blood flow response to methacholine in black hypertensive subjects ($P=0.001$ by repeated-measures ANOVA), with the peak methacholine response increasing from 7.7 ± 2.3 to 11.9 ± 4.0 mL/min per deciliter of tissue. Similarly, ascorbic acid also improved the forearm blood flow response to methacholine in white hypertensive subjects ($P=0.02$ by repeated-measures ANOVA), with the peak methacholine response increasing from 14.1 ± 7.7 to 18.7 ± 6.8 mL/min per deciliter of tissue. The extent of improvement in methacholine response with ascorbic acid (10 mmol/L estimated final concentration) was similar in black and white patients ($P=0.29$ by repeated-measures ANOVA), with the peak response increasing by 4.6 ± 7.2 and 4.2 ± 3.6 mL/min per deciliter of tissue, respectively. A 10-fold lower concentration of ascorbic acid (1 mmol/L estimated final concentration) had no significant effect on the peak methacholine response in both black and white hypertensive subjects.

Discussion

This study demonstrated no significant racial differences in resistance vessel function in normotensive subjects. In the setting of hypertension, the vasodilator response to methacholine was more severely reduced in black subjects compared with age-matched white subjects, whereas the responses to sodium nitroprusside and verapamil were similar. These findings suggest that the resistance vessel endothelium

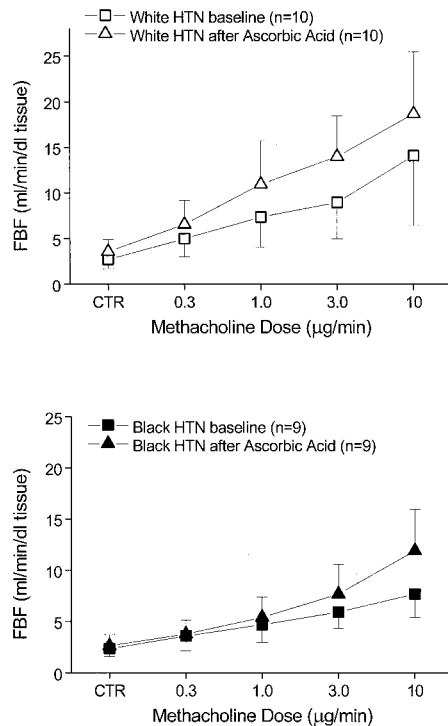


Figure 4. Effect of ascorbic acid on the vasodilator response to methacholine in black and white patients with hypertension. FBF responses to intra-arterial methacholine infusion were measured before and during ascorbic acid infusion (24 mg/min) using venous occlusion plethysmography as described in Methods. Top, Ascorbic acid infusion increased the vasodilator response to methacholine in black patients with hypertension ($P < 0.001$). Bottom, Ascorbic acid infusion increased the vasodilator response to methacholine in white patients with hypertension ($P = 0.02$).

is more susceptible to the adverse effects of hypertension in black patients than in white patients. The racial difference in endothelial function could not be attributed to the presence of antihypertensive therapy or the increased diuretic use in black hypertensive subjects, and there were no other discernible differences in the severity, duration, or presence of antihypertensive therapy. Ascorbic acid increased endothelium-dependent vasodilation to an equivalent extent in white and black hypertensive subjects. This finding argues against a role for racial differences in a rapidly reversible form of oxidative stress.

Several prior studies have examined racial differences in vascular function in normal subjects. For example, exercise-induced,⁵ ischemia-induced,²⁰ and mental stress-induced⁷ forearm vasodilation were reported to be lower in healthy black subjects compared with healthy white subjects. Lang and colleagues observed lower forearm blood flow responses to intra-arterial isoproterenol infusion in healthy black men compared with white men.²¹ The same group subsequently observed similar reductions in the vasodilator responses to methacholine and sodium nitroprusside, suggesting a generalized abnormality of vasodilator function in healthy black subjects.⁶ Cardillo and colleagues reported a similar generalized abnormality of vasodilator function with impaired responses to acetylcholine, sodium nitroprusside, and isoproterenol in healthy black subjects.⁸

In contrast to those prior studies, the present study demonstrated no racial differences in the resistance vessel responses to methacholine, sodium nitroprusside, or verapamil in normotensive subjects. The reasons for this discrepancy remain unclear but most likely are attributable to differences in the study populations. The findings of the current study may be more reliable because of our relatively large sample size and certainly suggest that not all black normotensive subjects have impaired vasodilator function. Notably, our findings are also consistent with work by Houghton and colleagues²² demonstrating no racial differences in acetylcholine-mediated and adenosine-mediated dilation of coronary resistance vessels.

Our finding that microvascular endothelial function is similar in black and white normotensive subjects is also consistent with a recent study from our laboratory that demonstrated similar findings in the conduit brachial artery.¹³ However, that study demonstrated an increased dilator response to nitroglycerin, whereas the present study demonstrated no significant racial difference in the vasodilator response to sodium nitroprusside. These findings emphasize that vascular function may differ importantly according to vascular bed (conduit versus resistance vessel) and that different nitrovasodilators may have different vascular effects.²³

The present study revealed a markedly worse vasodilator response to methacholine in black hypertensive subjects compared with white hypertensive subjects. No prior study examined racial differences in the forearm circulation of hypertensive subjects. Regarding potential mechanisms for these findings, several points are relevant. The racial difference in the response to methacholine, but not to sodium nitroprusside and verapamil, suggests a specific impairment of endothelial function in hypertensive blacks rather than a generalized impairment of vascular function or structure. We investigated the potential role of higher oxidative stress in the vasculature as a mechanism for this finding by examining the effects of a brief, high-dose ascorbic acid infusion on the response to methacholine. When administered in this fashion, ascorbic acid has been shown to improve endothelial function in a wide assortment of disease states²⁴ and may act by scavenging superoxide anion in the vasculature.^{15,25} The lack of a racial difference in the response to ascorbic acid argues against a racial difference in this form of increased oxidative stress, which could simply be a consequence of elevated blood pressure leading to stretch-induced superoxide production in the vasculature.²⁶

A preliminary study from our laboratory suggests that glucose-6-phosphate dehydrogenase (G6PD) deficiency is associated with increased plasma and urinary levels of 8-epi PGF_{2α}, a marker of *in vivo* lipid peroxidation.¹⁹ This condition is associated with decreased availability of nicotinamide adenine dinucleotide phosphate (NADPH), which is required for the normal function of a number of key antioxidant enzymes and the normal activity of endothelial nitric oxide synthase (eNOS). G6PD deficiency is much more frequent in black Americans (11% to 15%) than in white Americans (<1%). Because products of lipid peroxidation are known to interfere with endothelial function,²⁷ it is conceivable that this

or other genetic differences contribute to racial variation in vascular function in hypertension. Another possibility to consider is the known increased incidence of salt-sensitive hypertension in black Americans,²⁸ because this condition is also associated with impaired vascular function in human subjects,²⁹ evidence of decreased nitric oxide production,³⁰ and increased oxidative stress in experimental models.³¹ It is also possible that the results are attributable to different distributions of genetic variants of adrenergic receptors⁴ or eNOS.³² Further investigation of these and other potential mechanisms was beyond the scope of the present study.

Our study has several limitations. The degree of blood pressure elevation was relatively modest in our patient population, and it remains possible that the results might have been different in patients with more severe hypertension. Another concern is the potentially confounding effects of antihypertensive therapy or an effect of these medications to obscure a racial difference in the severity of hypertension. However, it seems unlikely that a medication effect explains our findings because the results were similar after adjusting for diuretic use and because the groups were balanced in terms of the use of other antihypertensive medications, total number of medications, and duration of hypertension. Furthermore, the results were similar in the subgroup of patients who never received antihypertensive therapy, and a prior study indicated that withholding antihypertensive medications for as long as 2 weeks does not alter responses to methacholine and nitroprusside.³³ The ascorbic acid portion of the study provides only limited mechanistic information because ascorbic acid may improve endothelial function by several mechanisms and because other forms of oxidative stress could account for a racial difference in vascular function.²⁴ Finally, the present study was considerably larger than prior studies of the relations between race and resistance vessel function, and thus we had greater statistical power to adjust for other factors known to influence endothelial function. However, it remains possible that some of the differences between the present and prior studies reflect the confounding effects of measured and unmeasured clinical factors.

In conclusion, in contrast to prior studies, we observed no racial differences in endothelium-dependent and endothelium-independent vasodilator function in normotensive subjects. In hypertensive subjects, we demonstrated that black patients have a markedly greater impairment of endothelium-dependent vasodilation in forearm resistance vessels compared with hypertensive white patients. These findings suggest that the endothelium may be more susceptible to the adverse effects of hypertension in blacks. Another possibility to consider is that endothelial dysfunction plays a more prominent role in the pathogenesis of hypertension in blacks. The results are likely to be clinically relevant, given the link between impaired endothelial function in the forearm circulation and increased cardiovascular disease risk.^{11,12} Further studies will be required to elucidate the mechanisms for this racial difference in vascular function and to determine whether these insights will lead to more appropriately tailored management of hypertension and its complications.

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