African Americans With LVH Demonstrate Depressed Sensitivity of the Coronary Microcirculation to Stimulated Relaxation


Abstract—Excess coronary heart disease morbidity and mortality among African Americans remains an important yet unexplained public health problem. We hypothesized that adverse outcome is in part due to intrinsic or acquired abnormalities in coronary endothelial function and vasoreactivity. We compared dose-response curves relating changes in coronary blood flow and epicardial diameter to graded infusions of acetylcholine in 50 African American and 65 white subjects with hypertensive left ventricular hypertrophy (LVH) and normal coronary arteries. These groups were similar for age, body mass index, mean arterial pressure, and indexed left ventricular mass. The same protocol was conducted in 24 normotensive African American and 56 similar white subjects. We found significant depression in the coronary blood flow dose-response curve relation among African Americans when compared with white subjects with similar LVH ($P<0.03$). Racial differences were observed at all doses of acetylcholine but were less precisely estimated at the highest dose. The same testing among normotensive subjects revealed similar dose-response curves with no significant effect of race. Qualitatively similar results were found with respect to coronary diameter. Adenosine responses, a measure of endothelium-independent function, were similar after partitioning by LVH. Our study demonstrates that there are racial differences in sensitivity of coronary arteries to acetylcholine-stimulated relaxation among those with LVH. These results provide a mechanism whereby racial differences in coronary vasoreactivity might contribute to adverse coronary heart disease outcome among African Americans, a group in whom LVH is prevalent. (*Hypertension. 2003;42:269-276.*)

Key Words: endothelium ■ ethnicity ■ hypertension, chronic ■ vasodilation ■ hypertrophy, left ventricular ■ microcirculation

Excess coronary heart disease morbidity and mortality among African Americans, first described 20 years ago, remains an important yet unexplained public health problem. Furthermore, mechanisms supporting increased prevalences of severe hypertension, dilated cardiomyopathy, and left ventricular hypertrophy (LVH) among African Americans are poorly understood yet are probable contributory factors to the observed adverse prognosis. Contemporaneous studies in the thrombolytic era have shown a worse long-term prognosis after myocardial infarction among African Americans despite similar 30-day survival, similar LV function, and younger age. Prospective registry data comparing treatment practices in nearly 3000 subjects hospitalized for unstable angina in 1996 found that fewer nonwhite patients underwent indicated cardiac catheterization. Although nonwhites were twice as likely to have no significant coronary artery disease (CAD), in-hospital outcomes were similar. A number of issues have bearing on these observations, including racial differences in risk factor prevalences, presentation and treatment of ischemic heart disease, and socioeconomic status. It is unknown whether significant biologic differences exist in coronary vasoreactivity on the basis of race. However, increased vasoconstrictor sensitivity to norepinephrine and serotonin and depressed vasodilator sensitivity to acetylcholine have been observed in forms of experimental hypertension. We hypothesized that intrinsic or acquired depression in coronary endothelial and vaso-motor dilator function might be disproportionately present among African Americans, possibly as part of a generalized defect in vascular relaxation or as a consequence of hypertension. Accordingly, we initiated a prospective, invasive study of endothelium-dependent and -independent coronary vasoreactivity in 1992, whose purpose was to determine whether African American race is independently associated with depressed coronary relaxation. We previously reported interim findings in 80 subjects, showing that African American race was not associated with excess intrinsic or acquired depression in maximum coronary vascular relaxation during peak effect of the endothelium-dependent and -independent agonists, acetylcholine and adenosine. However, the interim
Methods

The approved investigational study was conducted in 195 patients after clinical referral for cardiac catheterization. Informed consent was obtained, documenting the investigational nature of the protocol. The study was designed to examine the independent effects of African American ethnicity and LVH on coronary artery and arteriolar relaxation. Patients were excluded from the study because of CAD, valvular heart disease, marked obesity, severe LVH, and clinically significant LV systolic dysfunction or renal insufficiency. Normotensive subjects were defined as those with reproducible blood pressure measurements <140/90 mm Hg and normal indexed LV mass (LVM). Hypertensive subjects with LVH were defined as those with known hypertension or blood pressure measurements ≥140/90 mm Hg and indexed LVM exceeding established gender-specific, normal limits.26 Blood was collected in the fasting state for measurement of cholesterol panel, lipoprotein(a), and glucose.

LVM (g) was calculated by M-mode echocardiographic measurements made in accordance with the PENN convention, corrected to agree with necropsy data,21 and then indexed by height (m)2/3. Relative wall thickness (RWT) was defined as twice the posterior wall thickness divided by LV end-diastolic dimension.

After diagnostic cardiac catheterization, a 0.018-in. Doppler-tipped guide wire was advanced into the left coronary artery. Instantaneous coronary pressure and coronary blood flow (CBF) velocity were continuously recorded. Adenosine was administered by graded intracoronary bolus into the left main artery (8, 16, and 20 μg). Graded infusions of acetylcholine were performed with concentrations of 10−7, 10−6, and 10−5 mol/L in all subjects. A final infusion, 2×10−6 mol/L, was performed in 77% of patients but was withheld for significant sinus bradycardia in 23%. Coronary arteriograms were obtained at baseline and after each infusion of acetylcholine. An optimal end-diastolic frame was selected, and diameter measurements were performed by a single investigator, utilizing electronic digital calipers and without knowledge of patient characteristics or test results, at the site of velocity measurements. We have previously shown that intraobserver variability was minimal with excellent reproducibility.22 Percent change in coronary artery diameter was calculated in response to infusions of acetylcholine. Arteriography was not repeated after adenosine infusions because of minimal expected diameter change.25

CBF was defined as the product of mean CBF velocity and corresponding cross-sectional area. Percent change in CBF was calculated in response to drug infusions. Coronary microvascular resistance (CVR) was calculated as the quotient of instantaneous mean coronary perfusion pressure and CBF. CVR index was defined as the percentage of baseline CVR during each infusion of acetylcholine.

Demographic and research data are expressed as mean±SE. The unpaired t test, χ2 test, or Fisher exact test was used to assess group differences at baseline. Subjects were grouped by race and presence of LVH, and repeated-measures ANOVA, adjusted for characteristics found to differ by race, was performed to test for racial differences in CBF, diameter, and CVR dose-response curves. One-way ANOVA with Bonferroni correction was used to test for dose-specific racial differences; 95% confidence intervals were calculated for differences in means of response variables. Linear regression analysis was performed, where appropriate, to assess the presence of univariate relations between response variables and potential confounders. An expanded Methods section can be found in an online supplement available at http://www.hypertensionaha.org.

### Results

Patients

Study subjects included 98 men and 97 women, of whom 80 were normotensive (24 African American, 56 white) and 115 hypertensive with LVH (50 African American, 65 white). Table 1 demonstrates comparability among African Americans and whites with LVH for age, indexed LVM, body mass index, LV function, mean arterial pressure, LDL cholesterol, basal CBF before infusion of acetylcholine, endothelium-independent relaxation after adenosine, and presence of risk factors for atherosclerosis. Similarly, there were no significant racial differences among normotensive subjects in these parameters, with the exception of a slight increase in mean arterial pressure and a higher frequency of current tobacco use in African American normotensive subjects. However, there was no difference by race in frequency of normotensive subjects who had smoked for some portion of their lives (67% African American vs 57% white, P=0.6) or in cumulative pack-year consumption (15±4.5 vs 14.9±2.6, respectively, P=1.0). In addition, pack-per-day usage was less among normotensive African American smokers (0.84±0.14 vs 1.3±0.18, P=0.045). Though not reaching statistical significance, the frequency of tobacco use was slightly higher among African Americans when compared with whites with hypertensive LVH. However, similarly to normotensive subjects, there was no difference by race in frequency of those hypertensive subjects who had ever smoked (60% African-American vs 63% white, P=0.9) or in cumulative pack-year consumption.
consumption (12.0 ± 2.1 in African American vs 18.3 ± 2.5 in white subjects, P = 0.07). Pack-per-day usage was less among hypertensive African American smokers (0.82 ± 0.13 vs 1.4 ± 0.14, P = 0.003). In those with hypertension, 78% of African American and 74% of white subjects were aware of the diagnosis. Historical and medical record information revealed that hypertension duration was equal to 6.6 ± 1.2 years in African Americans and 7.8 ± 1.0 years in whites (P = 0.4).

As shown in Table 1, lipoprotein(a) was significantly greater and triglyceride level lower among African American versus white subjects. HDL cholesterol was significantly greater among hypertensive and nonsignificantly greater among normotensive African American subjects. RWT was similar among normotensive African American and white subjects (0.4 ± 0.02 vs 0.39 ± 0.01, P = 0.35) but significantly increased among hypertensive African American subjects versus whites with LVH (0.46 ± 0.01 vs 0.41 ± 0.01, P = 0.004). By linear regression analysis, there was no significant correlation between CBF response to acetylcholine and the independent variables lipoprotein(a) (P = 0.6, r = 0.06), triglyceride level (P = 0.8, r = 0.022), HDL cholesterol (P = 0.18, r = 0.13), and RWT (P = 0.85, r = −0.02) among all study subjects and specifically among those with hypertension LVH. Dose-response curves relating percent increase in CBF to acetylcholine dose were similar among those with either eccentric (RWT < 0.45) or concentric (RWT ≥ 0.45) LVH among the entire hypertensive group and after partitioning by race.

Of African American and white subjects with hypertension and LVH, 38 (76%) and 56 (86%), respectively, were taking vasoactive medications, defined as the following drug classes: calcium channel blockers, β-receptor blockers, nitrates, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, and α-receptor blockers. In all but 7 (14%) and 9 (14%), respectively, these were discontinued for >12 hours before the research procedure. Of normotensive African American and white subjects, 12 (50%) and 36 (64%), respectively, were taking vasoactive medications for chest pain syndromes, including β-receptor blockers, calcium channel blockers, and nitrate drugs. In all but 2 (8%) and 3 (5%), respectively, these were similarly withheld for >12 hours. Use of angiotensin-converting-enzyme inhibitors was similar among hypertensive African American and white subjects (20% vs 25%, P = 0.7). Both angiotensin-receptor blockers and statin drugs were infrequently but similarly prescribed among hypertensive African American and white subjects (2% vs 1.5% and 4% vs 8%, respectively). Of normotensive African American and white women, 5 (63%) and 17 (65%) and of African American and white women with hypertensive LVH, 18 (56%) and 20 (61%), respectively, were premenopausal or postmenopausal and on hormone replacement therapy.

**Indicators of Socioeconomic Status**
We collected information on 3 indicators of socioeconomic status: years of formal education, employment status, and medical insurance status. Years of education was similar among normotensive African American and white subjects (12.6 ± 0.7 vs 12.8 ± 0.3 years, P = 0.8), but significantly less among African Americans with LVH (10.9 ± 0.5 vs 13.1 ± 0.4 years, P = 0.0005). Employment status (employed or previously employed, now retired) was significantly different on the basis of race whether normotensive (54% in African Americans vs 86% in whites, P = 0.004) or hypertensive (62% in African Americans vs 82% in whites, P = 0.03). Possession of private medical insurance was also markedly different on the basis of race (25% in African American vs 86% in white normotensives, P < 0.0001, and 52% in African American vs 86% in white hypertensives, P = 0.0003). There was no significant correlation between response to acetylcholine and years of education (P = 0.73, r = 0.03). Furthermore, dose-response curves relating percent increase in CBF to acetylcholine infusions were similar among those who were employed versus unemployed among the entire group and after partitioning by race. The same held true with regard to insurance status.

**Noninvasive Evidence of Myocardial Ischemia**
Stress testing using exercise only in 25, exercise ± dipyridamole nuclear perfusion imaging in 152 (44% exercise alone), and exercise echocardiographic imaging in 5 were conducted in 69 of 74 (93%) African American subjects and in 113 of 121 (93%) whites. These tests were abnormal in 26% of normotensive and 41% of hypertensive African American subjects and in 43% and 47%, respectively, of whites. CBF responses after adenosine were significantly depressed among African Americans when exercise tests were abnormal versus normal (173 ± 14% vs 218 ± 12%, P = 0.016). A similar analysis with regard to peak acetylcholine responses revealed depression in CBF among African Americans with abnormal stress tests, which did not reach statistical significance (125 ± 21% vs 153 ± 18%, P = 0.34). Among white subjects, CBF responses to adenosine and acetylcholine were not appreciably different among those with abnormal versus normal stress tests (188 ± 9% vs 197 ± 10%, P = 0.5, and 166 ± 17% vs 172 ± 16%, P = 0.8). For the 152 nuclear perfusion stress tests alone, the same type of analyses revealed similar findings.

**Endothelium-Independent Coronary Microvascular Relaxation**
In response to infusion of adenosine, peak increase in CBF above baseline was similar among normotensive African American and white subjects (226 ± 16% vs 205 ± 9%, P = 0.24). Among African American and white subjects with hypertensive LVH, adenosine responses were mildly but similarly reduced (194 ± 10% vs 184 ± 9%, P = 0.5).

**Endothelium-Dependent Coronary Microvascular Relaxation**
Figure 1 displays the relation between percent increase in CBF and graded infusion of intracoronary acetylcholine among African American and white subjects. The highest infusion rate was administered in 79% of normotensive and in 76% of hypertensive subjects and was independent of race. Baseline CBF before agonist testing was similar among African American and white normotensive groups (86 ± 8 vs
96±7 mL/min, \( P=0.4 \)), and responses during acetylcholine infusions were very similar (Figure 1, left). Baseline CBF before testing was also similar among African American and white groups with LVH (121±8 vs 110±9 mL/min, \( P=0.4 \)), but the CBF dose-response curve (Figure 1, right) was significantly depressed among hypertensive African Americans (\( P<0.03 \)). These results were unchanged after adjusting for possible confounding factors, including gender, tobacco use, lipoprotein(a), HDL cholesterol, triglyceride level, and residual effect of vasoactive drugs. As shown in Figure 1 and Table 2, African American subjects with LVH also demonstrated significantly reduced submaximal responses. Racial differences persisted at higher doses but were estimated with less precision. Though more profound among African Americans, the presence of LVH was a marker for attenuation of coronary microvascular relaxation within each race. By repeated-measures ANOVA for comparison of curves and \( t \) tests for individual doses, hypertensive compared with normotensive African Americans demonstrated marked depression in the CBF dose-response curve (\( P<0.006 \)), with significant differences also for each of the 4 individual doses. By the same type of analyses, hypertensive compared with normotensive whites exhibited significant depression in CBF responses during the 2 highest acetylcholine doses only and consequently, insignificant depression in the overall dose-response curve (\( P=0.11 \)). Analyses of resistance and diameter responses yielded similar differences when the effect of LVH within race was compared.

### Coronary Microvascular Resistance

In Figure 2, CVR as a percentage of baseline is displayed for each acetylcholine infusion. Baseline CVR among normoten-

sive African American and white groups was 1.4±0.2 and 1.4±0.1 mm Hg·mL\(^{-1}\)·min, respectively (\( P=0.9 \)). Baseline CVR among African American and white hypertensive groups was 1.1±0.1 and 1.3±0.1 mm Hg·mL\(^{-1}\)·min (\( P=0.17 \)). There was no significant difference in CVR responses among normotensive African American and white subjects (Figure 2, left), but dose-response curves revealed significantly greater decreases in CVR (Figure 2, right) in white when compared with African American subjects with LVH (\( P<0.002 \)) in response to graded infusion of acetylcholine. This finding was unchanged after adjusting for possible confounding factors as described in the preceding section.

### Endothelium-Dependent Coronary Epicardial Relaxation

Figure 3 demonstrates epicardial coronary artery diameter changes during acetylcholine infusions. This figure shows a similar pattern of vasodilation in normotensive African American and white subjects (left) and a pattern of decreasing dilation and/or constriction in hypertensive subjects (right). In response to all infusions of acetylcholine including the maximal, epicardial vessels undergoing study dilated in white subjects with LVH. Conversely, in response to all infusions in African Americans with LVH, the epicardial vessels undergoing study constricted. Although a greater constrictor response was suggested among hypertensive African Americans, the probability value obtained from repeated-measures ANOVA did not achieve statistical significance (\( P=0.13 \)). There was no change in this finding after adjusting for possible confounding factors.

### TABLE 2. Confidence Intervals (95%) for Difference in Means of White and African American Subjects with LVH for CBF, Resistance, and Diameter Responses (% Increase) to Infused Acetylcholine

<table>
<thead>
<tr>
<th>Response</th>
<th>ACh1</th>
<th>ACh2</th>
<th>ACh3</th>
<th>ACh4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF</td>
<td>11.5 (1.6, 21.4)</td>
<td>23.5 (1.6, 45.4)</td>
<td>33.2 (−17.5, 84)</td>
<td>22.7 (−37.5, 82.9)</td>
</tr>
<tr>
<td>CVR</td>
<td>−9.1 (−16.1, −2.1)</td>
<td>−13.3 (−22.9, −3.3)</td>
<td>−9 (−19.9, 1.9)</td>
<td>−7.1 (−19.3, 5.1)</td>
</tr>
<tr>
<td>D</td>
<td>2.1 (−0.3, 4.5)</td>
<td>2.1 (−1.5, 5.7)</td>
<td>2.1 (−3.3, 7.5)</td>
<td>1.9 (−4.0, 7.8)</td>
</tr>
</tbody>
</table>

ACh1=0.15 μg/min; ACh2=1.5 μg/min; ACh3=15 μg/min; ACh4=30 μg/min (performed in 76%). CVR indicates coronary vascular resistance; D, coronary artery diameter. Data in each cell is arranged as the difference in means followed by 95% confidence intervals in parentheses.
Discussion

Our study addresses the issue of intrinsic and acquired racial differences in coronary vasoreactivity in patients with normal coronary arteriograms clinically referred for cardiac catheterization. As previously reported in an interim publication, we found no significant racial differences in conduit- and resistance-vessel vasoreactivity among normotensive subjects. The smaller number of normotensive study subjects (particularly among African Americans) reduces the statistical power of analyses in this subgroup, but the available data do not suggest racial differences in coronary vasoreactivity in normotensives. In contrast, we have shown for the first time that there are significant racial differences in sensitivity to stimulated relaxation of the coronary microcirculation among subjects with LVH. When compared with whites with similar LVH, African American subjects demonstrated markedly depressed augmentation of CBF during graded infusions of the endothelium-dependent agonist acetylcholine. This finding was independent of the geometric pattern of hypertrophy and was unrelated to differences in the indicators of socioeconomic status: years of formal education, employment, and possession of private medical insurance. Statistical adjustment for possible confounding variables, including gender, tobacco use, HDL cholesterol, lipoprotein(a), triglyceride level, and residual effect of vasoactive drugs, did not change the results. The proximate mechanism for our findings was a lesser reduction in CVR among African Americans with LVH during acetylcholine infusions. Qualitatively similar racial differences were found with respect to diameter changes in conduit vessels during graded acetylcholine infusions. When the effect of LVH within race was compared, whites demonstrated significantly less attenuation of microvascular relaxation, despite a similar degree of LVH, when compared with African Americans. This suggests a greater physiologic burden imposed by LVH among African Americans. Of potential importance, abnormal stress tests were associated with significant depression in peak endothelium-independent responses among African Americans, suggesting that microvascular dysfunction might be a source of ischemia in this group. It has previously been shown that hypertension and LVH are associated with exercise-induced myocardial ischemia in the absence of obstructive CAD, and in some studies, in association with depressed coronary vasodilator reserve. Impaired endothelium-dependent vasodilation of the coronary microcirculation has been demonstrated in the setting of exercise-induced myocardial ischemia. Increases in CBF during exercise are postulated to be due to both endothelium-independent and dependent mechanisms. In our study, dipyridamole exercise imaging stress tests were performed in the majority of patients. Dipyridamole infusion causes endothelium-independent vasodilatation of the microcirculation by blocking adenosine reuptake by vascular...
smooth muscle cells. This might explain why adenosine, but not acetylcholine, responses were significantly depressed among African Americans with abnormal stress tests.

Although current tobacco use was significantly increased among normotensive African Americans when compared with similar whites, further analysis showed similar proportions with a history of tobacco use and equivalent cumulative pack-year history. No subject smoked within 8 hours of the research procedure per protocol, and in fact, there were no racial differences found in vasoreactivity among the normotensive subjects. Epicardial coronary artery vasoconstriction after smoking one cigarette was previously shown to peak at 5 minutes and to resolve within 30 minutes. Among hypertensives, there was a slight but nonsignificant increase in current tobacco use among African American compared with white subjects. Further analysis showed nearly identical proportions with a history of tobacco use and a greater cumulative pack-year consumption among hypertensive white subjects. Finally, results from the ANOVA models were unchanged with the addition of a variable for smoking. Thus, it is unlikely that differences in tobacco usage affected our results. Although duration and severity of hypertensive disease are frequently difficult to ascertain, we found a similar reported frequency of diagnosed hypertension, similar duration of hypertension, and similar degree of LVH among hypertensive African American and white subjects. Given these, it seems unlikely that unappreciated differences in duration and degree of hypertension significantly affected our results.

Acetylcholine, the drug used in our study to evaluate endothelium-dependent relaxation, is the prototypical drug used to study endothelial function in the coronary circulation. It is a complex drug that causes direct contraction of vascular smooth muscle in addition to relaxation through endothelium-derived relaxing factors, nitric oxide and hyperpolarizing factor. The nitric oxide effect is mediated through the second messenger cGMP. Constrictor responses in the epicardial coronary arteries elicited during intracoronary infusion of acetylcholine have been shown to be correlated with those paradoxically found during supine bicycle exercise and during phenylephrine infusion. Impaired vasodilator response occurs when coronary relaxation after stimulated release of nitric oxide is significantly attenuated or exceeded by constriction mediated through direct stimulation of muscarinic receptors on vascular smooth muscle cells. This occurs in the setting of endothelial dysfunction, where there is decreased bioactivity of nitric oxide, shifting the balance away from dilation and toward constriction. Other possibilities include increased release or bioactivity of endothelium-derived contracting factors and increased sensitivity of vascular smooth muscle to the direct constricting effects of acetylcholine.

Although the exact mechanism remains unknown in our study, depressed bioactivity of nitric oxide related to release of vasoconstrictor agonists and/or competitive antagonists of nitric oxide synthase merit particular attention. Complex relations are known to exist among race, salt-sensitive hypertension, LVH, renal regulation of salt and water, sympathetic nervous system reactivity, and circulating concentrations of certain vasoactive peptides and amino acids. Among normotensives, the frequency of salt sensitivity is similar in African American and white subjects (36% vs 29%). However, among African Americans, salt-sensitive hypertension, which is characterized by low renin levels, predominates and is significantly more prevalent than in hypertensive whites. LVH is more prevalent among African Americans and in experimental models of salt-sensitive hypertension. Endothelin-1 (ET-1), a potent vasoconstrictor and mitogen produced by the endothelium, is overexpressed in the vasculature of salt-sensitive animal models of hypertension. Furthermore, plasma ET-1 levels were shown to be significantly elevated among African American compared with white hypertensives, in addition to its direct vasoconstrictor effect, also augments the contractile response to other vasoactive agonists, including norepinephrine and serotonin. Finally, the naturally occurring nitric oxide synthase inhibitor, asymmetric dimethylarginine, is increased and nitric oxide metabolites decreased after salt loading in salt-sensitive hypertensives. Thus, attenuation of nitric oxide bioactivity through one or more pathways related to salt-sensitive hypertension is a plausible explanation for depressed coronary sensitivity to the vasodilator effect of infused acetylcholine among African Americans with LVH. However, this reasoning remains speculative, because our study was designed neither to measure ET-1 or asymmetric dimethylarginine nor to test for the presence of salt-sensitive hypertension.

There is a clinical basis for suspecting increased coronary contractile sensitivity (or equivalently depressed vasodilator sensitivity) among African Americans. A consistent observation in previous studies is that African Americans exhibit increased peripheral vasoconstriction in response to stimuli that activate the sympathetic nervous system. These stressors include exercise, mental arithmetic and other forms of behavioral coping challenge, and cold pressor stimuli. Studies in the forearm circulation have found important racial differences in vasoreactivity, including a higher minimum forearm vascular resistance, depressed vasodilation in response to β-adrenergic stimulation, attenuation in cyclic nucleotide-mediated vascular smooth muscle relaxation, depressed postischemic vasodilation, and an increased median effective concentration in response to acetylcholine among African American subjects. These studies were all performed in healthy, young or middle-aged volunteer subjects. Our study differs because of its performance in the coronary circulation in subjects with angiographically normal arteries referred because of symptoms suggestive of coronary insufficiency. Second, adenosine vasodilator responses, predominately mediated through the second messenger cAMP, were not significantly different on the basis of race in either of our comparison groups. This suggests that the mechanism is not due to generalized attenuation of cyclic nucleotide activity, as found in the forearm circulation. Finally, the minimum CVR index was not significantly different among the normotensive comparison groups on the basis of race, unlike reported findings in the forearm circulation.

Our study addresses the issue of racial differences in coronary vasoreactivity among a select group of individuals...
with normal coronary arteriograms but with symptoms that prompted clinical referral for cardiac catheterization. This differentiates them from a randomly selected sample of a defined population, thus raising the possibility of selection bias. It is unlikely, however, that subject recruitment or participation among African Americans compared with whites would be selectively different on the basis of responses to endothelium-dependent or -independent agents. Clinical referral for angiography was frequently motivated by results of stress testing. Progression to the research study occurred only when the diagnostic study demonstrated the absence of CAD. Thus, the high proportion of subjects with abnormal stress tests and no CAD was in part a by-product of the eligibility criteria for study participation. Because recruitment spanned 7.5 years, poor reproducibility and/or bias in performance of arterial measurements could have compromised study results. We do not believe this is likely, because arterial measurements were made after recruitment and without knowledge of individual subject characteristics or study results. Furthermore, quality of measurement was previously shown to be consistent throughout the study period.19 We acknowledge that angiographic assessment is insensitive for detection of atherosclerosis. However, patient groups such as ours with no angiographic CAD, yet endothelial dysfunction, are conjectured to represent an early stage in the natural history of CAD and/or cardiomyopathy, populations of enormous importance in preventive cardiology, where early diagnosis and individualized therapy might be especially efficacious. We recognize that the social and physical environment surrounding an individual’s lifespan as well as socioeconomic status and access to medical care are important factors in the complex relation between race and cardiovascular prognosis. These elements require further study in concert with vasoreactivity studies with noninvasive techniques to confirm and expand our findings. Finally, others have demonstrated an association between abnormal coronary endothelial function and long-term cardiovascular outcome among white subjects.52,53 Long-term follow-up of our cohort and other racially mixed populations, together with baseline invasive or noninvasive endothelial function studies, are needed to definitively prove the association between racial differences in endothelial function and adverse coronary heart disease prognosis.

Perspectives
We found that coronary microvascular relaxation is significantly reduced among African American compared with similar white subjects with hypertensive LVH during provocative endothelial function testing. This was due to depressed sensitivity of the coronary vasomotor apparatus to acetylcholine-mediated vasodilation, resulting in a shift of the dose-response curve to the right. By way of contrast, CBF dose-response curves were not significantly different among normotensive African American and white subjects. Vasodilator responses to adenosine were similar among African American and white subjects after partitioning for LVH, suggesting that the cGMP but not the cAMP pathway is involved in the mechanism. We conclude that there are racial differences in endothelium-dependent coronary vasoreactive-

ity that are associated with the presence of hypertensive LVH. Depressed capacity for coronary microvascular relaxation is one likely contributory element in the observed adverse coronary heart disease prognosis found among African Americans, a group in whom LVH is prevalent.

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