Brachial Vascular Reactivity in Blacks

Daniel Perregaux, Ajay Chaudhuri, Suresh Rao, Anshul Airen, Michael Wilson, Bong-Hee Sung, Paresh Dandona

Abstract—Endothelial function was studied ultrasonographically in a healthy subset of African Americans (blacks) because they have an increased risk of hypertension and vascular disease. Twenty-four healthy black and 28 well-matched white subjects were investigated. Ischemia was induced by inflating a cuff over the forearm to 40 mm Hg higher than systolic pressure for 5 minutes. Brachial artery diameter and blood flow velocity were measured at baseline and at 15, 45, and 60 seconds after deflation by use of an Acuson 128XP10 ultrasonograph with a 7.5 MHz transducer. Mean postischemic dilatation, an index of endothelial function, was 1.76±0.56% in blacks and 8.79±1.22% in whites (P<0.001). Median postischemic vasodilatation in black men [0% (0% to 2.86%)] was not significantly different to that in black women [0.82% (0% to 3.14%)], whereas white women [11.48% (8.70% to 14.29%)] dilated significantly more than white men [4.20% (2.13% to 5.56%)] (P<0.05). Both groups dilated significantly over baseline diameter to sublingual nitroglycerin administration 18.7±2.5% (blacks) and 20.2±3.2% (whites; P=NS). Mean hyperemic responses did not differ significantly between the 2 subject groups, nor did they differ between men and women of both ethnic groups. We conclude that endothelium-dependent vasodilatation is significantly impaired in healthy, young blacks compared with whites, and that gender differences are not seen in blacks with regard to this phenomenon. An impairment in endothelium-dependent NO generation may be a contributing factor to future hypertension and vascular disease in healthy blacks. (Hypertension. 2000;36:866-871.)

Key Words: blacks ■ vascular reactivity ■ ultrasonography ■ endothelium ■ vasodilation ■ nitric oxide

It has been shown previously that blacks of sub-Saharan descent exhibit a much higher frequency of hypertensive disease than whites of European descent or American Indians, with the greatest worldwide hypertensive frequency found in blacks. These data point to a basic pathophysiological mechanism of elevated BP that has yet to be identified but remains a significant public health problem. The high cardiovascular mortality and morbidity associated with essential hypertension and stroke in blacks has been a subject of increased study. Recent evidence has shown that blacks have a higher forearm vascular resistance than whites, which begins to explain a possible mechanism for this disease state.2–1 Investigators have also shown that blacks have platelets that exhibit increased intracellular calcium stores and turnover, possibly linking calcium regulation in smooth muscle as a source of hypertension in this population.4 Additionally, microneurographic and stress studies have shown a role of heightened sympathetic responses in blacks to be a source of increased vascular resistance.5–6 Finally, our group has shown that insulin-induced venodilation after intravenous norepinephrine administration observed in normal subjects7 is markedly diminished in blacks.8 However, these subjects demonstrate substantial venodilation after sodium nitroprusside infusion, which indicates that endothelium-mediated venous reactivity is altered in this ethnic group, whereas responsiveness to NO is maintained.8

A novel mechanism to noninvasively measure reactivity of the arterial vasculature has been developed to study the NO-mediated event of postischemic vasodilation.9 Use of high-frequency ultrasound allows investigators to accurately visualize and measure small changes in structure, diameter, and blood flow of a single conduit vessel. The brachial artery is ultrasonographically imaged in a longitudinal section to measure changes in the diameter of the artery and blood flow after an ischemic episode in the forearm. This technique has been studied extensively and found to be accurate and reproducible in terms of measurement of changes in diameter. Evidence has shown that the effect of postischemic vasodilatation measured by ultrasound, plethysmography, and femoral artery probes is an endothelium-dependent NO–mediated event.10,11 In certain disease states associated with increased risk of atherosclerosis, a measurable decrease in vascular reactivity through ultrasound has been shown. Some of these conditions include smoking, diabetes mellitus, hypercholesterolemia, and peripheral vascular disease.12–17

After considering the compelling research mentioned above, we began a study using this ultrasound technique to examine the effect of ischemia on the forearm arterial system

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in a healthy subset of black and white populations. We hypothesized that the study of these 2 groups would show a higher relative vascular reactivity in whites compared with blacks. We also expected to show that after sublingual nitroglycerin was administered to them, patients in both groups would dilate equally, indicating that the NO response is intact but that the NO-producing mechanism is somehow disrupted in blacks, thus leading to reduced postischemic response.

**Methods**

The Institutional Review Board of Millard Fillmore Hospital at the State University of New York at Buffalo approved all protocols of the present study. All participants were given a clear explanation of the study, and informed consent was obtained for the ultrasound study and blood tests in accordance with institutional guidelines.

**Subjects**

Twenty-four healthy blacks (age range, 20 to 47 years) and 28 healthy, age-matched whites were examined for postischemic vaso-reactivity of the brachial artery and may be overestimated compared with absolute flow, but relative flow values before and after cuff deflation are accurate.10

**Statistics**

All statistics were calculated with the SigmaStat statistical package, with a level of significance set at P<0.05. Data are represented as mean±SE for parametric and median (interquartile range) for nonparametric data. All analyses were performed by Student’s t tests for unpaired and paired parametric data or Mann-Whitney rank sum and Wilcoxon signed rank tests for nonparametric data. Graphic representations were prepared with the aid of SigmaPlot.

**Results**

Mean resting arterial diameter for the black group was 3.78±0.2 mm, dilating to a mean value of 3.84±0.2 mm after cuff deflation (P<0.03), whereas the age-matched whites had a mean resting diameter of 3.57±0.1 mm, dilating to a mean of 3.85±0.1 mm (P=0.0001). Mean change in absolute diameter for blacks and whites was 0.06±0.0 and 0.29±0.0 mm, respectively (P<0.05). Mean postischemic percentage dilatation was 1.76±0.56% in blacks, whereas that of age-matched whites was 8.79±1.22% (P<0.05). Although a significant difference existed between baseline and reactive diameters in both groups, absolute changes and percentage increases over baseline differed, with whites dilating significantly more (Figure 1A).

Baseline diameter of black men was 4.23±0.18 mm and increased to 4.30±0.17 mm after ischemia (P=NS), whereas baseline diameter of black women was 3.32±0.14 mm and increased to 3.37±0.14 mm after ischemia (P<0.05). Absolute change in diameter was 0.07±0.04 mm in black men and 0.05±0.02 mm in black women (P=NS). In white men, diameter increased from 4.16±0.15 to 4.35±0.14 mm (P<0.05), whereas it increased from 2.98±0.09 to 3.36±0.12 mm (P<0.05) in white women. Absolute change in diameter was 0.19±0.15 and 0.38±0.05 mm in white men and women, respectively (P<0.05). Median postischemic vasodilatation (interquartile range) was significantly greater in white men [4.20% (2.13% to 5.56%)] and women [11.48% (8.70% to 14.29%)] than black men [0% (0% to 2.86%)] and women [0.82% (0% to 3.14%)] (P<0.05), respectively (Figure 1B). Baseline diameters differed significantly between men and women of both ethnic groups. Whites demonstrated a significant gender difference in absolute diameter change and flow-mediated dilatation (FMD), with women dilating more at reperfusion, whereas blacks showed no such response between the sexes.

Eleven blacks (46%) and 11 whites (39%) agreed to a single sublingual dose (0.4 mg) of GTN. In this subgroup of blacks, baseline diameter was 3.58±0.29 mm and increased to 3.63±0.29 mm after ischemia (P=NS); however, with GTN, the diameter increased significantly, to 4.26±0.30 mm (P<0.01). In the whites taking GTN, baseline diameter
increased significantly, from 3.94 ± 0.24 to 4.12 ± 0.21 and 4.68 ± 0.22 mm after ischemia and GTN, respectively (P < 0.01). Response to nitroglycerin yielded a percentage change in arterial diameter of 18.7 ± 2.5% and 20.2 ± 3.2% (P = NS) in blacks and whites, respectively. Thus, nitroglycerin-induced response was equivalent in the 2 groups, with similar and significant change from baseline in each group (P < 0.05; Figure 2).

Hyperemic responses did not differ between ethnic groups, with blacks showing a mean increase in flow of 355 ± 42% and whites showing a 355 ± 40% increase (P = NS). No difference existed between the hyperemic responses of white men (333 ± 54%) and white women (378 ± 65%; P = NS) or between black men (337 ± 39%) and black women (372 ± 72%; P = NS). The increase in blood flow was also similar among ethnic gender subgroups.

Although most of the demographic values were not significantly different, triglyceride levels differed between the black and white groups. However, forward stepwise regression analysis of the laboratory data (F-to-enter = 4.000) indicated that no independent variables affected FMD. Additionally, triglyceride levels were all within normal limits for both groups, and no evidence exists to support that such differences within normal ranges would affect postischemic arterial dilation.

**Discussion**

Our data clearly demonstrate that postischemic vasodilatation in blacks is reduced compared with that in white controls, given that absolute and percentage changes from baseline differ significantly between ethnic groups, with mean absolute vasodilatory change in whites being almost 5 times that of blacks. Previous studies that used the same methodology showed that in patients with atherosclerosis and atherosclerotic risk factors such as hypertension, diabetes mellitus, menopause, and hypercholesterolemia, postischemic vasodilatation, which is dependent on endothelial function, is
This suggests that the propensity of blacks to develop hypertension and atherosclerosis may be related to an endothelial dysfunction.

Previous research in our laboratory has shown unique gender differences in postischemic vasodilatation, with women dilating significantly more than men in white subgroups. We thus proceeded to examine the effects of gender within the present study. When gender groups were compared, only whites showed a significant increase in postischemic diameter for both men and women. White women showed a significantly greater change in absolute diameter and FMD compared with white men, whereas no difference was seen in these parameters between black men and women. Postischemic dilatation in white men and women was also significantly higher than in blacks of the same gender. Thus, gender differences seen in whites, with women vasodilating more than men, an effect attributed primarily to estrogen, was not observed in blacks. The reasons for this finding are unclear from the present study; however, this observation raises the possibility that the beneficial effect of estrogen may be absent or impaired in this population. The effect of estrogen on endothelium-dependent vasodilatation has not been studied in blacks. This ethnic group has been poorly represented in observational and randomized clinical trials that assess the effect of hormone-replacement therapy on cardiovascular end points, precluding any subgroup analysis on the basis of ethnicity. Thus, in the current literature, evidence of the presence or absence of the beneficial effect of estrogen in blacks is lacking. Black women are known to have a higher incidence of hypertension, diabetes mellitus, and cardiovascular disease. Young black girls have a higher BP level and exhibit abnormal cardiovascular reactivity to stress compared with whites. The absence or impairment of the beneficial effect of estrogen in blacks may provide an explanation for the higher incidence of cardiovascular risk factors in this ethnic group, and further studies need to be done to investigate this possibility. Interestingly, white men dilated significantly more than black women and men, which indicates that ethnicity-mediated effects in this race supersede gender effects.

Postischemic vasodilatation is believed to be dependent on endothelial function, including NO. In pathological states in which postischemic vasodilatation is impaired, the balance between endothelial vasodilators such as NO and vasoconstrictors such as endothelin-1, both produced by the endothelium, may become crucial. Interplay between these factors may allow for increased or decreased response to ischemic episodes on the basis of the relative production of these compounds by the endothelium. Thus, it is prudent to question whether this reduced dilatory effect in blacks is due to inadequate bioavailability of NO or inability to respond to appropriate levels of NO.

We further studied the effect of sublingual nitroglycerin, which showed a significant and equal vasodilatory response in both ethnic groups, thus indicating that the NO response mechanism may be intact in blacks, although the bioavailability of endothelium-derived NO may be deficient in this group. These arterial data are consistent with similar data we previously demonstrated on venous reactivity. Although, the number of blacks and whites who agreed to take GTN were similar and GTN-induced vasodilatation did not show a statistical ethnic difference, a limitation of our study is the small sample size of black and white subjects voluntarily willing to take GTN. Black subjects who took GTN showed a vasodilatory response to nitroglycerin but did not respond to an endothelium-dependent NO-mediated stimulus, in contrast to whites, who responded significantly to both endothelium-dependent and endothelium-independent vasodilatory stimuli. Thus, the present study conclusively shows that endothelium-dependent vasodilatation is impaired in the conduit arteries of blacks.

Recent reports in which a method that measures forearm blood flow in response to acetylcholine and sodium nitroprusside was used have indicated a measurable attenuation of cyclic nucleotide–mediated vascular smooth muscle relaxation in blacks that leads to impaired endothelium-dependent and endothelium-independent NO-mediated vasodilatation. However, another study has shown that the response to sodium nitroprusside is normal in blacks similar in age to those in the present study and younger than the population examined by other authors when vasodilatation is assessed by measurement of forearm vascular resistance. To try to explain this discrepancy in the endothelium-independent NO-mediated vasodilatory response of blacks when assessed by different methods, we reviewed existing literature on assessment of endothelial function. In most of the studies, the findings regarding the endothelium-dependent and endothelium-independent NO mediated vasodilatory responses in a population were consistent, irrespective of the methodology used to assess endothelial function. However, in subjects with type 2 diabetes mellitus, although endothelium-dependent vasodilatation was impaired in all studies, endothelium-independent NO-mediated vasodilatory responses were found to be either normal or impaired. Therefore, except in subjects with type 2 diabetes mellitus, no inconsistency is seen among vasodilatory responses of whites when assessed by different methods. However, it is difficult to extrapolate observations in whites to the black population. Apart from the method used, studies (including the present study) in blacks who show normal endothelium-independent NO-mediated response were conducted on a younger population than that of studies showing impaired endothelium-independent NO-mediated vasodilatation. Thus, the discrepancy between our observation and those of other authors could also be the result of the difference in the age groups studied. Our method is based on measurement of diameter of a conduit artery, whereas others have measured forearm blood flow, which is modulated by the arterioles. It is possible that the smooth muscle tissue of conduit arteries is normal when compared with that in arterioles. It is also possible that the NO-responsive end-organ (arteriolar and arterial smooth muscle) dysfunction progresses with age in blacks (ie, arterioles are affected earlier than arteries). The present study is the first to assess endothelial function in the conduit arteries of blacks by the forearm ischemia model, and further investigations to explore the above possibilities are warranted in this ethnic group.
The difference in triglyceride levels between the 2 ethnic groups initially was a concern. However, forward stepwise regression analyses indicate no independent variables, including triglyceride levels, that could predict postischemic dilatation. Additionally, triglyceride levels were all within normal limits for both groups, and no evidence exists to suggest that such differences within normal ranges would affect postischemic arterial dilatation.

We measured the percentage increase in blood flow after cuff deflation (hyperemia) in all subjects. These flow data did not differ significantly between either group or between any of the gender subgroups indicating that vascular shear stress and thus the stimulus for endothelium-dependent vasodilatation was equal in all groups. Additionally, no correlation existed between hyperemia and baseline diameters or FMD in any group.

Recent evidence has dealt extensively with the role of insulin in the regulation of endothelium-mediated vasodilatation. As previously mentioned, our laboratory has shown through ultrasonographic venous studies that insulin reverses vasoconstrictive effects of norepinephrine in whites and that through ultrasonographic venous studies that insulin reverses vasoconstrictive effects of norepinephrine in blacks, that the vasoconstrictive effects of norepinephrine in African Americans—particularly evidence that directly links the vasoconstrictive effects of norepinephrine in whites and that of insulin-mediated skeletal muscle vasodilation is nitric oxide dependent. 11,34 As previously mentioned, our laboratory has shown for the first time that postischemic vasodilatation of the brachial arterial bed in young, healthy blacks compared with whites, it seems logical that a connection may be made between these epidemiological trends and that of recent vascular data, particularly evidence that directly links insulin-induced vasodilatation to endothelium-dependent NO-mediated mechanisms. 11,22,34–36

Although further study is required, the issue of insulin resistance in the black population may be relevant to the impairment of postischemic dilatation. Studies to analyze this issue currently are underway in our laboratory.

In conclusion, we have ultrasonographically demonstrated for the first time that postischemic vasodilatation of the brachial arterial bed is significantly impaired in young, healthy blacks compared with age-matched, healthy whites. Furthermore, no gender difference is observed in postischemic vasodilatory response of blacks, unlike that observed in whites. Because postischemic vasodilatation is endothelium mediated, blacks may have an endothelial deficit, which may be relevant to the pathogenesis of atherosclerosis and vascular disease in the black population.

References


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