ATTENUATION OF ISOPROTERENOL-MEDIATED VASODILATATION IN BLACKS

Chim C. Lang, M.D., C. Michael Stein, M.B., Ch.B., R. Michael Brown, M.B., B.S.,
Robert Deegan, M.B., Ch.B., Richard Nelson, M.B., B.S., Huai B. He, Pharm.D.,
Margaret Wood, M.B., Ch.B., and Alastair J.J. Wood, M.B., Ch.B.

Abstract *Background.* The mechanism of enhanced vascular reactivity in young blacks, which may play a part in the development of hypertension, has not been defined. To determine the contribution of blunted vasodilatation mediated by β_2-adrenergic receptors to this phenomenon, we compared forearm blood-flow responses to isoproterenol in young black and white normotensive men.

Methods. We used venous-occlusion plethysmography to measure the responses of blood flow in the forearm to the intraarterial administration of isoproterenol (10 to 400 ng per minute) in 9 normotensive black men (mean [$\pm$SD] age, 31.3$\pm$8.0 years) and 13 normotensive white men (mean age, 32.9$\pm$5.6 years). Sympathetic activity in the forearm was measured simultaneously by isotope-dilution techniques.

Results. Base-line blood flow in the forearm was similar in blacks and whites, but the degree of vasodilatation in response to isoproterenol was markedly lower in blacks. Isoproterenol at an infusion rate of 400 ng per minute produced a 9-fold increase in blood flow in whites but only a 3.5-fold increase in blacks ($P<0.001$). The base-line rate of norepinephrine spillover in the forearm was higher in blacks (2.0$\pm$1.3 ng per minute [11.8$\pm$7.7 nmol per minute]) than in whites (0.6$\pm$0.5 ng per minute [3.5$\pm$3.0 nmol per minute], $P=0.002$), but there was no difference between the groups after isoproterenol stimulation.

Conclusions. Forearm blood-flow responses to isoproterenol were markedly attenuated in normotensive blacks, indicating a blunting of vasodilatation mediated by β_2-adrenergic receptors. Our findings suggest that the mechanisms responsible for blunted vasodilatation in response to the administration of isoproterenol may contribute to enhanced vascular reactivity in blacks and may play a part in the pathogenesis of hypertension in blacks. (N Engl J Med 1995;333:155-60.)

THERE are racial and geographic differences in the incidence and severity of essential hypertension. In the United States, the prevalence of essential hypertension is greater among blacks than among whites at all ages after young adulthood[1,2]; the higher prevalence among blacks is associated with greater morbidity and mortality.[3]

A variety of genetic and environmental factors have been proposed to account for the racial differences in the prevalence and severity of hypertension.[4-6] Greater blood-pressure responses to mental and physical stress have been reported in normotensive blacks.[7-11] The heightened blood-pressure response generally occurs in conjunction with an increase in total peripheral vascular resistance that is unaccompanied by a change in cardiac output.[10,11] This enhanced vascular reactivity, perhaps coupled with higher levels of environmental stress, may result in sustained increases in peripheral vascular resistance and, consequently, elevated blood pressure.[12,13] The mechanism of enhanced vascular reactivity in blacks has not been defined.

An alteration in vascular responsiveness to sympathetic stimuli such as either increased vasoconstriction mediated by α-adrenergic receptors or decreased vasodilatation mediated by β_2-adrenergic receptors could contribute to increases in total peripheral vascular resistance.[14-16] A blunted β_2-adrenergic–mediated vascular response to isoproterenol, which may be involved in the pathogenesis and maintenance of the hypertensive state, has been demonstrated in whites with hypertension.[17-19] The possible relevance of this mechanism to the development of hypertension in blacks has not been explored. To test the hypothesis that vascular β_2-adrenergic responsiveness is attenuated in normotensive blacks, we examined blood-flow responses in the forearm after the infusion of isoproterenol into the brachial artery in normotensive black and white subjects matched for age and weight. The overall effect of an intrabrachial infusion of isoproterenol on forearm blood flow may be influenced not only by the activation of postsynaptic β_2-adrenergic receptors, which mediate vasodilatation, but also by the activation of presynaptic β_2-adrenergic receptors, which mediate norepinephrine release,[20] which in turn causes vasoconstriction. To determine the contribution of altered norepinephrine release to any changes in blood flow, we therefore simultaneously measured local sympathetic activity in the forearm, using an isotope-dilution technique,[21] and determined the forearm vascular response to the intraarterial infusion of isoproterenol.

METHODS

Subjects

Twenty-two healthy, nonsmoking, normotensive male volunteers provided written informed consent to their participation in the study, which was approved by the Vanderbilt University Committee for the Protection of Human Subjects. No clinically important abnormalities were evident in any subject in the history, physical examination, or hematologic or biochemical laboratory tests. Thirteen subjects were white (mean [$\pm$SD] age, 32.9$\pm$5.6 years), and nine were black (mean age, 31.3$\pm$8.0 years); all were from the United States. Four black and four white subjects reported a history of hypertension in a first-degree relative, and one subject in each group reported a family history of diabetes mellitus. The subjects followed a diet, provided by the metabolic kitchen at the Vanderbilt University Clinical Research Center, that was free of caffeine and alcohol and provided 150 mmol of so-

dium and 70 mmol of potassium per day for five days before the study. The subjects did not take any medications for at least two weeks before the study.

Experimental Protocol

All experiments were performed in the morning, with the subjects resting in the supine position in a quiet room maintained at a temperature of 22 to 23°C. A cannula was inserted into a large antecubital vein in the nondominant arm to sample blood draining the vascular bed of the forearm, including the forearm muscles and subcutaneous tissues.[22] Another intravenous cannula was inserted in the dominant arm for the infusion of tritiated norepinephrine. After subdermal local anesthesia, an 18-gauge catheter was inserted into the brachial artery of the nondominant arm (study arm) for the infusion of drugs, blood sampling, and intraarterial blood-pressure monitoring with a pressure transducer (HP 1295C, Hewlett–Packard, Andover, Mass.). The heart rate was determined by continuous electrocardiography. The patency of the arterial catheter was maintained with a normal saline infusion (30 ml per hour); during the intraarterial administration of isoproterenol, the total flow rate through the cannula was maintained at 30 ml per hour by varying the concentration of isoproterenol.

After placement of the catheters and a 30-minute equilibration period, we administered a loading dose of 25 μCi of tritiated norepinephrine (norepinephrine levo-[ring-2,5,6-^{3}H], 70.1 Ci per millimole; New England Nuclear, Wilmington, Del., prepared for administration to humans by the Vanderbilt Hospital Radiopharmacy) in normal saline containing 1 mg of ascorbic acid per milliliter over 2 minutes; the loading dose was followed by a constant infusion of 0.9 μCi per minute into the arm opposite that with the arterial catheter. This infusion regimen has been shown to achieve a constant plasma concentration of tritiated norepinephrine within 30 minutes.[20]

Base-line flow measurements were made after 30 and 40 minutes of the tritiated norepinephrine infusion. Forearm blood flow was measured by venous-occlusion plethysmography with a mercury-in-Silastic strain-gauge plethysmograph as previously described.[20] Forearm blood flow was expressed in milliliters per minute per deciliter of forearm tissue. The volume of the forearm, excluding the hand and wrist, was measured by water displacement. Immediately after the blood-flow measurements, arterial and venous blood samples were drawn simultaneously for the measurement of plasma norepinephrine and tritiated norepinephrine.

After these base-line measurements had been made, isoproterenol (Isuprel, Winthrop Pharmaceuticals, New York) was infused into the artery in increasing doses (from 10 to 400 ng per minute); each dose was infused for seven minutes by a Harvard infusion pump, with forearm blood flow recorded during the last two minutes of each dose. The doses used have been shown to have minimal systemic effects[20] and to produce no change in blood flow in the contralateral forearm.[17] Arterial and venous blood samples for the determination of norepinephrine kinetics were obtained simultaneously after the measurement of forearm blood flow at base line and after the infusion of isoproterenol at rates of 60 ng per minute and 400 ng per minute.

Blood Collection and Analysis

Blood was collected in cooled tubes with ethylene glycol tetraacetic acid and reduced glutathione (Amersham, Arlington Heights, Ill.) and centrifuged at 3000 revolutions per minute at 4°C; the plasma was stored at −20°C until assayed. Samples of the tritiated norepinephrine solution were also collected. Both endogenous norepinephrine and tritiated norepinephrine were measured by high-performance liquid chromatography.[23]

Determination of Norepinephrine Kinetics

Values obtained before isoproterenol stimulation 30 and 40 minutes after the start of the tritiated norepinephrine infusion were similar, and their mean was therefore used as the base-line measurement. Norepinephrine kinetics were calculated by the method of Esler et al.,[21] as follows. The fractional extraction of tritiated norepinephrine in the forearm was calculated as $(A^* - V^*) \div A^*$, where A^* was the arterial concentration of tritiated norepinephrine and V^* the venous concentration. Forearm norepinephrine spillover was calculat-

ed as $[(V - A) + (A \times \text{the fractional extraction of tritiated norepinephrine})] \div Q$, where A was the arterial concentration of endogenous norepinephrine, V the venous concentration, and Q the forearm plasma flow derived from the hematocrit, the forearm blood flow, and the forearm volume. Forearm norepinephrine clearance was calculated as the fractional extraction of tritiated norepinephrine multiplied by forearm plasma flow (Q). The rate of appearance of norepinephrine in the forearm plasma and its intrinsic clearance have been proposed by Chang et al.[24] as measurements of spillover and clearance, respectively, that are independent of flow. These values were obtained by dividing forearm norepinephrine spillover and forearm norepinephrine clearance by 1 minus the fractional extraction of tritiated norepinephrine. Systemic norepinephrine clearance was defined as the rate of infusion of tritiated norepinephrine divided by A^*. Systemic norepinephrine spillover was calculated as systemic clearance times A.

Statistical Analysis

Forearm blood flow was measured during the last two minutes of each seven-minute infusion of isoproterenol, and an average of 8 to 10 flow curves were obtained. Data on norepinephrine kinetics represent the averages for samples of venous and arterial blood, assayed in duplicate. Statistical analyses were performed with repeated-measures analysis of variance, the unpaired t-test, and Fisher's exact test (with SPSS for Windows Release 6, SPSS, Chicago). Because a complete test of the response of forearm blood flow to various doses of isoproterenol was not performed in one white subject, data on this subject were excluded from the analysis of forearm blood flow. Data on norepinephrine levels for this subject were included in the analysis. When base-line values differed significantly between blacks and whites (as was the case with forearm arterial norepinephrine levels, venous norepinephrine levels, norepinephrine spillover, and the rate of appearance of norepinephrine in plasma), data were analyzed both as absolute values and as changes from the base-line values. All results are expressed as means ±SD. A two-tailed P value of less than 0.05 was the criterion for statistical significance. The white subjects served as controls in studies that have been reported previously.[19,20]

RESULTS

The two study groups were well matched in terms of age, body weight, forearm volume, 24-hour urinary sodium excretion, and plasma glucose and serum cholesterol levels (Table 1).

Base-Line Hemodynamic and Norepinephrine Measurements

Base-line hemodynamic values and forearm blood-flow measurements were similar in the two groups (Table 2). The arterial plasma norepinephrine concentration was significantly higher in the black subjects (209±118 pg per milliliter [1.24±0.69 nmol per liter]) than in the whites (125±40 pg per milliliter [0.74±0.24 nmol per liter], P = 0.03). Systemic norepinephrine spillover also tended to be higher in the blacks (493±316 ng per minute [2914±1868 nmol per minute]) than in the whites (320±124 ng per minute [1892±733 nmol per minute], P = 0.09). Both forearm norepinephrine spillover and the appearance rate of norepinephrine in plasma in the forearm were higher in blacks than whites (P = 0.002 and P = 0.003, respectively).

Hemodynamic and Forearm Blood-Flow Responses to Isoproterenol

The intraarterial administration of isoproterenol resulted in an increase in forearm blood flow in both blacks and whites, but the response was significantly

Table 1. Demographic Characteristics of the Subjects.*

CHARACTERISTIC	WHITES (N = 13)	BLACKS (N = 9)
Age (yr)	32.9±5.6	31.3±8.0
Weight (kg)	79.2±9.4	84.9±15.3
Height (cm)	183.4±4.3	176.8±5.6
Plasma glucose (mg/dl)	99.8±18.7	100.4±14.8
Serum cholesterol (mg/dl)	166±32	159±76
Urinary sodium excretion (mmol/liter/24 hr)	119±42	113±59
Systolic blood pressure (mm Hg)	121±8	119±9
Diastolic blood pressure (mm Hg)	67±6	71±7
Mean arterial pressure (mm Hg)	85±6	87±8
Forearm volume (ml)	1180±175	1358±362
Forearm circumference (cm)	64.0±4.1	69.8±7.6
Family history of essential hypertension (no.)	4	4
Family history of diabetes mellitus (no.)	1	1

*Plus−minus values are means ±SD. To convert plasma glucose values to millimoles per liter, multiply by 0.055; to convert cholesterol values to millimoles per liter, multiply by 0.02586. There were no significant differences between the groups.

blunted in blacks (P<0.001) (Fig. 1 and Table 2). The decrease in forearm vascular resistance that resulted from the administration of isoproterenol was also blunted in blacks (a decrease from 41.5±8.6 to 14.6±6.7 mm Hg per milliliter per minute per deciliter of forearm volume at an infusion rate of 400 ng of isoproterenol per minute), as compared with that in whites (from 41.7±23.0 to 4.0±1.6 mm Hg per milliliter per minute per deciliter, P<0.001) (Table 2). The doses of isoproterenol administered in this study produced no systemic effects, except for the highest dose of isoproterenol, which increased the heart rate equally in both races, with no significant change in the mean arterial pressure in either group (Table 2).

Systemic and Forearm Sympathetic Responses to Isoproterenol

The intrabrachial infusion of isoproterenol increased forearm norepinephrine spillover and the rate of appearance of norepinephrine in plasma in the forearm in both blacks and whites. The groups did not differ significantly in either absolute forearm norepinephrine spillover or in the change from the base-line value after the administration of isoproterenol (Fig. 2). Similarly, the rate of appearance of norepinephrine in forearm plasma was increased equally by isoproterenol in blacks and whites (Table 2). Isoproterenol at an infusion rate of 400 ng per minute resulted in a significant increase in systemic norepinephrine spillover in both groups (P=0.01), with no difference between the two (Table 2).

Isoproterenol increased forearm norepinephrine clearance in both groups (Table 2). The blunted forearm vasodilatation in blacks was accompanied by lower forearm clearance of norepinephrine (Table 2). The flow-independent variable of the intrinsic rate of clearance of norepinephrine in the forearm tended to be

Table 2. Forearm Blood Flow and Hemodynamic and Sympathetic Values at Base Line and after the Intraarterial Administration of Isoproterenol in Normotensive Black and White Men.*

VARIABLE	BASE LINE		AFTER ISOPROTERENOL (400 ng/min)		P VALUE†	
	WHITES	BLACKS	WHITES	BLACKS	DOSE	DOSE × RACE
Forearm blood flow (ml/min/dl)	2.7±1.4	2.2±0.6	24.4±8.7	7.8±5.5	<0.001	<0.001
Forearm vascular resistance (mm Hg/ml/min/dl)	41.7±23.0	41.5±8.6	4.0±1.6	14.6±6.7	<0.001	<0.001
Forearm norepinephrine spillover (ng/min)	0.6±0.5	2.0±1.3‡	16.5±9.6	20.4±14.5	<0.001 (<0.001)	0.80 (0.78)
Forearm norepinephrine appearance rate (ng/min)	1.1±1.0	3.7±2.4‡	26.4±20.0	33.9±27.9	<0.001 (<0.001)	0.72 (0.99)
Forearm norepinephrine clearance (ml/min/dl)	4.8±3.0	6.8±3.4	49.0±25.3	28.6±15.5	<0.001	0.03
Intrinsic norepinephrine clearance from forearm (ml/min/dl)	8.5±6.7	12.8±8.8	79.2±56.7	46.4±29.9	0.001	0.14
Systemic norepinephrine spillover (ng/min)	320±124	493±316	447±119	557±314	0.01	0.59
Systemic norepinephrine clearance (liters/min)	2.6±0.5	2.5±1.1	3.0±0.5	2.5±0.3	0.22	0.37
Arterial norepinephrine (pg/ml)	125±40	209±118§	153±38	223±125	0.04 (0.002)	0.61 (0.89)
Venous norepinephrine (pg/ml)	129±37	245±96‡	210±45	397±121	<0.001 (0.002)	0.02 (0.65)
Heart rate (beats/min)	63±7	59±8	71±12	65±9	<0.001	0.43
Mean arterial pressure (mm Hg)	85±6	87±3	83±9	86±6	0.02	0.46

*Plus−minus values are means ±SD. To convert values for plasma norepinephrine to nanomoles per liter, multiply by 0.005911.

†By repeated-measures analysis of variance, showing the statistical significance of the response to isoproterenol (dose) and the interaction between race and the response to isoproterenol (dose × race). When base-line values differed significantly between blacks and whites (forearm arterial norepinephrine concentration, venous norepinephrine concentration, norepinephrine spillover, and norepinephrine appearance rate), data were analyzed both as absolute values and as changes from base line; the P values for the comparisons of the changes from base line are shown in parentheses.

‡P<0.01 by unpaired t-test for the comparison between blacks and whites.

§P<0.05 by unpaired t-test for the comparison between blacks and whites.

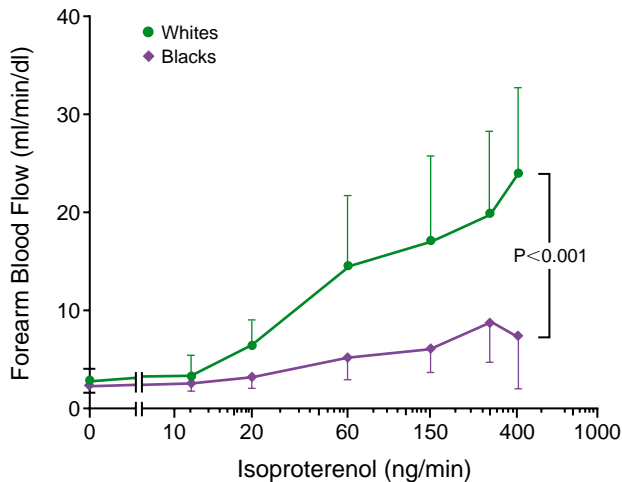**Figure 1. Forearm Blood-Flow Responses to Isoproterenol Administered by Intrabrachial Infusion in Normotensive Blacks (N = 9) and Whites (N = 12), Plotted on a Log Scale.**

The rates of infusion ranged from 10 to 400 ng per minute. The values shown are means ±SD. The increase in the forearm blood flow in response to isoproterenol was significantly blunted in blacks (P<0.001 by repeated-measures analysis of variance).

lower in blacks than in whites, but this difference did not reach statistical significance (Table 2). Systemic norepinephrine clearance was not altered by isoproterenol in either group. Venous and arterial plasma norepinephrine concentrations were increased by isoproterenol in both groups (Table 2). The absolute increase in the venous plasma norepinephrine concentration af-

ter the administration of isoproterenol was greater in blacks than whites. When the degree of change from base line was analyzed, however, there was no difference between the groups (Table 2). There was no difference between blacks and whites in the degree of change in the arterial plasma norepinephrine concentration in the forearm in response to isoproterenol.

DISCUSSION

The principal finding of this study is that, although base-line forearm blood flow was similar in normotensive black and white men, vasodilatation in response to the infusion of isoproterenol, a β-adrenergic agonist, into the brachial artery was markedly blunted in the black subjects. Although base-line forearm norepinephrine spillover was higher in blacks than in whites, the increase in forearm norepinephrine spillover after the stimulation of presynaptic β_2-adrenergic receptors by isoproterenol did not differ between blacks and whites. Thus, the attenuation of isoproterenol-mediated vasodilatation in blacks cannot be accounted for by an enhanced presynaptic β_2-adrenoceptor–mediated release of norepinephrine.

Blunted β_2-adrenergic vasodilatation has been demonstrated in white patients with hypertension,[17-19] and it has been suggested that this alteration in vascular adrenergic responsiveness may contribute to the increase in total peripheral vascular resistance in patients with essential hypertension. In this study, we observed a blunted response to isoproterenol in normotensive blacks as compared with whites. This blunted β_2-adre-
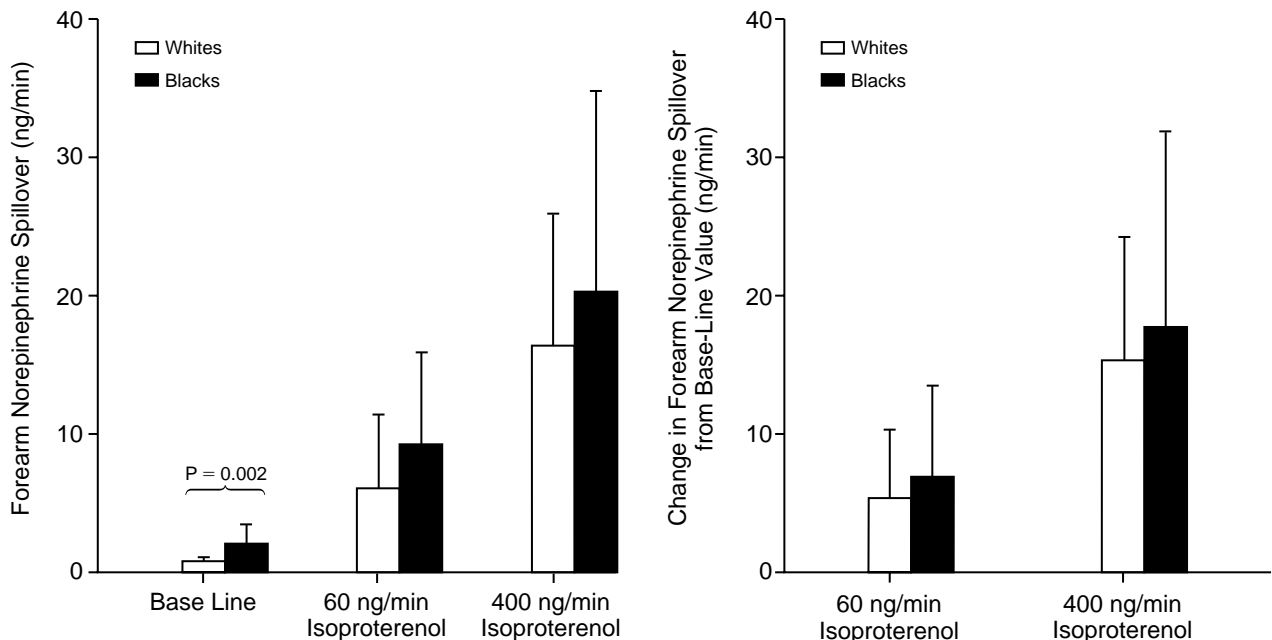

Figure 2. Norepinephrine Spillover in the Forearm in Response to the Intrabrachial Infusion of Isoproterenol in Normotensive Blacks (N = 9) and Whites (N = 13).

The values shown are means +SD. Both absolute values (left-hand panel) and changes from base-line values (right-hand panel) are shown. There was no significant difference between blacks and whites in forearm norepinephrine spillover after the infusion of isoproterenol. To convert values for forearm norepinephrine spillover to nanomoles per minute, multiply by 5.911.

nergic vasodilatation may play a part in the enhanced vascular response to stress seen in blacks and perhaps in the pathogenesis of early hypertension in this group. Our observations in this study of the forearm contrast with the lack of difference between the races in the response in the superficial dorsal hand vein to the local infusion of isoproterenol.[25] The responsiveness of forearm resistance arteries is probably more important than that of dorsal hand veins in the regulation of peripheral vascular resistance.

The attenuated vasodilatation in response to isoproterenol in blacks remains to be explained. Studies of human lymphocytes have examined racial differences in the density of β_2-adrenergic receptors and cyclic AMP (cAMP) responses. Receptor density has been reported to be similar in whites and blacks[26] or lower in normotensive blacks than in whites.[27] Results regarding lymphocyte cAMP production in response to β_2-adrenergic stimulation have been similarly conflicting. An early study showed higher β_2-adrenergic–stimulated cAMP production in vitro by lymphocytes obtained from blacks,[28] but others have found lower basal concentrations of cAMP in lymphocytes and lower isoproterenol-stimulated accumulation of cAMP in blacks.[26] No racial differences have been found in forskolin-stimulated cAMP production,[29] which would suggest that any racial difference in β-adrenoceptor sensitivity must involve the recognition site or the coupling between the receptor and stimulatory G protein, since the postreceptor activation of adenylate cyclase by forskolin appears normal. Most of these earlier studies have used mixed peripheral lymphocytes. In an effort to control for possible effects of race on white-cell subpopulations, Mills and coworkers[29] recently examined β_2-adrenergic receptors on suppressor–cytotoxic T lymphocytes and subgroups of natural killer lymphocytes (which were similar in blacks and whites) in a group of hypertensive and normotensive black and white men fed a controlled-sodium diet. Normotensive white and black subjects were found to have a similar density of β-adrenergic receptors and similar responses. However, black men with hypertension had greater β-adrenoceptor sensitivity and density than white men with hypertension. Whether there are similar racial differences in β-adrenoceptor sensitivity that are apparent in the vascular responses of patients with hypertension remains to be determined.

It is not known whether the decreased vasodilative response in blacks is specific to isoproterenol. However, a reduction in maximal forearm vasodilatation in response to ischemic exercise has been reported in normotensive blacks.[30] The mechanisms producing reactive hyperemia are complex, involving mediators such as prostaglandins and adenosine.[31] The specific effects on vascular responsiveness to these and other mediators in blacks will need to be examined in further studies.

The role of racial and ethnic differences in sympathetic outflow as a potential explanation for enhanced cardiovascular reactivity to stress, and consequently

hypertension, remains controversial, partly because of the methodologic inadequacies of previous studies, most of which relied on the measurement of plasma norepinephrine concentrations and found no difference between blacks and whites without hypertension.[32-34] However, the absence of racial differences in plasma norepinephrine concentrations does not rule out differences in sympathetic activity. Plasma norepinephrine concentrations represent the release of norepinephrine into plasma and its clearance from plasma.[35] Therefore, an increase in sympathetic activity and norepinephrine release may be masked by a compensatory increase in norepinephrine clearance, with the result that the plasma norepinephrine concentration is unchanged.

A potential explanation for the attenuated forearm blood-flow response to isoproterenol in the black subjects is enhanced release of norepinephrine in the forearm in response to isoproterenol. Although base-line forearm norepinephrine spillover was higher in blacks than whites, however, there was no difference in the degree of increase in norepinephrine spillover in response to isoproterenol; this finding raises the possibility that alterations in β_2-adrenergic responses in blacks may not affect all β_2-adrenoceptor sites.

Several factors, such as socioeconomic status, dietary sodium levels, and family history of hypertension and diabetes, are related to the regulation of sympathetic activity and vascular tone. In this study, we attempted to control for these factors. Subjects had similar educational backgrounds and similar family histories of hypertension and diabetes. By controlling dietary sodium levels for five days before the study and on the study days, we ensured that the subjects' sodium intake was similar.

In summary, the increase in forearm blood flow in response to the infusion of isoproterenol is markedly blunted in normotensive blacks. Whether this blunting of vasodilatation in blacks in response to isoproterenol is specific to the β_2-adrenoceptor or might occur with other vasodilators remains to be determined. Our findings suggest, however, that attenuated vasodilatation may contribute to enhanced vascular reactivity and may perhaps play a part in the pathogenesis of hypertension in blacks.

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