Forearm Beta Adrenergic Receptor–mediated Vasodilation Is Impaired, without Alteration of Forearm Norepinephrine Spillover, in Borderline Hypertension

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Abstract

Impaired beta adrenoceptor-mediated vasodilation associated with enhanced sympathetic activity has been reported in established hypertension. We examined whether altered beta adrenoceptor-mediated vasodilation occurs early in the disease process, when structural vascular changes are likely to be less marked, by measurement of forearm blood flow by strain gauge plethysmography after the intraarterial administration of increasing doses of a beta receptor agonist, isoproterenol, in eight subjects with borderline hypertension (BHT) and 13 normotensive (NT) controls. To determine the role of sympathetic activation in the regulation of responsiveness, we measured local sympathetic activity in the forearm by a radioisotope dilution technique. Vasodilation in response to isoproterenol, measured either as changes in forearm blood flow or forearm vascular resistance, was impaired in the BHT group so that flow at the highest dose of isoproterenol (400 ng/min) increased less (15.2±1.5 ml/100 ml per min) than in the NT group (24.4±2.4 ml/100 ml per minute) ($P < 0.001$). Although, systemic norepinephrine spillover was significantly greater in BHT, the difference in blood flow response to isoproterenol was not accounted for by increased local sympathetic activity since forearm norepinephrine spillover at baseline (BHT 1.0±0.4 ng/min vs. NT 0.64±0.13 ng/min) and after the administration of isoproterenol 60 ng/min (BHT 5.2±1.4 ng/min vs. NT 6.0±1.5 ng/min) and 400 ng/min (BHT 13.5±2.9 ng/min vs. NT 16.5±2.7 ng/min) did not differ between the two groups. We therefore conclude that vasodilation in response to isoproterenol is impaired in subjects with BHT and that this impairment is not explained by locally increased basal, or stimulated, sympathetic activity. (*J. Clin. Invest.* 1995. 96:579–585.) Key words: hypertension • vasodilation • isoproterenol • sympathetic • human

Introduction

Altered vascular smooth muscle responsiveness and increased sympathetic activity are thought to be major factors accounting for the increased peripheral resistance characteristic of hypertension. In patients with hypertension vascular responses mediated through alpha (1) and beta adrenergic receptors (2), as well as those mediated through nitric oxide (3), have been reported to be altered. Although many studies have examined alpha adrenoceptor-mediated vasoconstrictor responses in patients with hypertension, relatively few have examined beta adrenoceptor-mediated vasodilation.

Reduced vascular beta adrenergic responsiveness has been demonstrated in animal models of genetic and acquired hypertension (2). In vitro human studies have found reduced affinity for beta agonist, a reduction in the proportion of beta receptors binding agonist with high affinity, and a reduction in isoproterenol-stimulated adenylate cyclase activity in the lymphocyte beta receptors of hypertensive subjects (4). In vivo studies that have used the hemodynamic responses occurring after systemic infusion of agonist to measure postsynaptic beta adrenoceptor sensitivity in patients with hypertension have yielded inconsistent results, variously reporting altered (5, 6) or unaltered (7, 8) beta adrenoceptor responsiveness. However, the administration of systemic doses of an agonist does not allow a direct determination of vascular response. Ideally, to limit the confounding effects of reflex sympathetic activation and alterations in parasympathetic activity that occur after systemic administration of isoproterenol, the response to a $beta_2$ agonist should be examined by administering the agonist directly into the vascular bed of interest in doses that have negligible systemic effects. In such studies vascular response to a beta agonist was found to be decreased in subjects with established essential hypertension in both the dorsal hand vein (9) and in the forearm (10) after the administration of low doses of isoproterenol directly into vessel being studied, suggesting that decreased beta receptor-mediated vasodilation might be important in the pathogenesis of hypertension. These previous findings may reflect late changes due to structural vascular changes due to hypertension and also may be confounded by enhanced beta adrenoceptor-mediated norepinephrine (NE) release in subjects by hypertension.

There is considerable evidence that sympathetic activity is increased in hypertension but the data are not uniform. Elevated plasma NE concentrations (11) and increased NE release determined by a radiotracer technique, have been found in some (12), but not all (13) studies. Increased sympathetic nerve traffic measured in the peroneal nerve (14) has also been reported in hypertension. In the forearm local presynaptic beta adrenergic receptors modify sympathetic activity by stimulating the release of NE (15). Therefore, the overall effect of a beta agonist may be influenced by the response, not only of postsynaptic beta adrenoceptors (mediating vasodilation), but also that of presynaptic adrenoceptors (mediating NE release). Since the degree of sympathetic activation may influence vascular tone, simultaneous determination of vascular responsiveness and sympathetic activity allows the contribution of alterations in sympathetic activity to changes in vascular sensitivity to be determined.

To overcome the problems of the previous studies that have

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suggested that beta receptor function in vascular smooth muscle may be altered in hypertension, we studied patients earlier in the disease process, in whom structural vascular changes are less marked (16). In addition, the potential confounding effect of altered local sympathetic activity on observed alterations in blood flow response to a beta agonist was addressed by simultaneously measuring both postsynaptic beta receptor-mediated vasodilation and presynaptic beta receptor-mediated NE release in order to define the contribution of altered local sympathetic activity to the observed changes in blood flow.

Methods

Subjects. 13 white, normotensive, healthy nonsmoking male volunteers aged 32.9±1.9 yr and eight white, nonsmoking male subjects with borderline hypertension aged 33.4±1.9 yr were studied. All subjects provided written informed consent and the study protocol was approved by the Vanderbilt Committee for the Protection of Human Subjects. Borderline hypertension was defined as a diastolic blood pressure intermittently > 90 mmHg while receiving no antihypertensive therapy. Antihypertensive medications were discontinued 4 wk before the study in the four borderline hypertensive (BHT)[1] subjects who were receiving antihypertensive treatment. Blood pressure was monitored once or twice weekly in these subjects and if the diastolic blood pressure rose to ≥ 110 mmHg, subjects were to be excluded from the study. In no case did this occur. Apart from elevated blood pressure no subject had clinically significant abnormalities on history, physical examination, or routine laboratory tests including complete blood count, prothrombin and partial thromboplastin times, renal and liver function tests, and electrocardiogram. Subjects did not take any medications for ≥ 4 wk before the study and were maintained on a diet, provided by the metabolic kitchen of the Vanderbilt Clinical Research Center, that was free of caffeine and alcohol and provided 150 mmol Na^+/d and 70 mmol K^+/d, for 5 d before the study.

Experimental protocol. All experiments were performed in the morning with the subjects resting supine in bed, in the same temperature-controlled room. An intravenous canula was placed in an antecubital vein of both arms. After subdermal administration of 1% lidocaine an 18-gauge polyurethane catheter (Cook Inc., Bloomington, IN) was inserted into the brachial artery of the nondominant arm for local infusions and blood sampling. Arterial catheter patency was maintained with a 30-ml/h saline infusion. By altering the concentration of isoproterenol the total flow rate through the canula was always maintained constant at 30-ml/h. Arterial blood pressure was measured by means of a pressure transducer (Hewlett Packard Co., Waltham, MA) and heart rate was recorded from a continuous electrocardiograph monitor. After the arterial line and intravenous catheters had been placed, subjects rested quietly for 30 min. [^{3}H]NE (norepinephrine levo-[ring-2,5,6-^{3}H] 43.7–56.9 Ci/mmol; Du Pont/NEN, Wilmington, DE) was infused into the arm contralateral to the arterial line. An initial loading dose of [^{3}H]NE, 25 μCi, was administered over 2 min followed by a constant infusion of 0.9 μCi/min. The [^{3}H]NE was prepared for human administration by the Vanderbilt Hospital Radiopharmacy and appropriate sterility and pyrogen testing was performed. Immediately before use [^{3}H]NE was diluted to a concentration of 2 μCi/ml in normal saline with ascorbic acid, 1 mg/ml, added to the infusion solution. Forearm blood flow was measured and simultaneous arterial and venous blood samples were drawn for determination of baseline concentrations of endogenous and [^{3}H]NE after 30 and 40 min of the [^{3}H]NE infusion. Isoproterenol (Isuprel; Winthrop Pharmaceuticals, New York) was infused intraarterially in increasing doses by a Harvard infusion pump (Harvard Apparatus, South Natick, MA). Each dose of isoproterenol was infused for 7 min with blood flow recordings performed during the last 2 min. After measurement of forearm blood flow at isoproterenol doses of 60 and 400 ng/min, simultaneous arterial and venous blood samples were drawn for catecholamine determinations into cooled tubes with EGTA and reduced glutathione (Amersham Corp., Arlington Heights, IL), placed on ice, and centrifuged at 4°C. Samples of the [^{3}H]NE infusion solution were collected, stored, and later assayed, as described for the blood samples, to allow determination of the actual rate of [^{3}H]NE infusion.

Forearm blood flow. Forearm blood flow was measured in the arm into which intraarterial isoproterenol was infused using mercury-in-silastic strain gauge plethysmography (17). The wrist was supported in a sling to raise the level of the forearm to above that of the atrium. The hand was excluded from the measurement of blood flow by inflation of a pediatric sphygmomanometer cuff to 200 mmHg around the wrist before and during measurement of forearm blood flow. The volume of the forearm, excluding the hand and wrist, was measured by water displacement. A complete forearm blood flow dose–response to isoproterenol was not performed in one normotensive (NT) subject, and this subject has been excluded from analysis of the forearm blood flow data. The forearm blood flow response in this individual was similar to that of the other NT controls with flows of 3.1, 15.0, and 29.9 ml/100 ml per minute at baseline and after administration of isoproterenol, 60 and 400 ng/min, respectively. NE data for this individual at baseline and after the administration of isoproterenol, 60 and 400 ng/min, are included in the analysis. In addition forearm blood flow data were not available for two subjects at the isoproterenol, 40 and 100 ng/min doses, respectively, representing two missing data points out of a possible 180 data points. Forearm blood flow data at the isoproterenol, 40 and 100 ng/min doses, were not included in the repeated-measures analysis of variance (ANOVA) because of these missing data points.

Catecholamine assay. NE concentrations were measured by high-performance liquid chromatography (HPLC) using electrochemical detection with 3,4-dihydroxybenzylamine (DHBA) as the internal standard as we have described previously (18). The chromatographic retention times of norepinephrine (9.5 min), DHBA (15.7 min), and isoproterenol (39.7 min) allowed complete separation of their respective peaks without any cross-interference. The HPLC effluent coinciding with the NE peak was collected and counted by liquid scintillation. This allowed determination of plasma [^{3}H]NE concentration without interference from tritiated metabolites. The intra- and inter-day coefficients of variation were 7.8% and 7.6% respectively.

Data analysis. Prestimulation values obtained after 30 and 40 min of [^{3}H]NE infusion were similar, and their mean was used as the baseline measurement. Calculations for the determination of NE kinetics using the isotope dilution method (19, 20) were performed as follows: Fractional extraction (FE) of [^{3}H]NE in the forearm = $(A^* - V^*)/A^*$, where A* and V* were the arterial and venous concentrations of [^{3}H]NE, respectively; Forearm spillover of NE = $[(V - A) + (A \times FE)]$ Q, where A and V were the arterial and venous concentrations of endogenous NE, respectively, and Q was the forearm plasma flow derived from the hematocrit, the forearm blood flow, and the forearm volume; Forearm norepinephrine clearance = FE × Q; Forearm norepinephrine plasma appearance rate and intrinsic clearance were obtained by dividing forearm norepinephrine spillover and forearm NE clearance by 1 − FE (21); NE plasma clearance from the whole body (systemic clearance) = [^{3}H]NE infusion rate/A*; and the rate at which NE entered plasma for the whole body (systemic spillover) = systemic clearance × A. Data were analyzed by repeated-measures ANOVA to compare responses of NT and hypertensive subjects with respect to the effect of blood pressure (BP) category, dose of isoproterenol (DOSE), and the interaction between blood pressure category and response to isoproterenol (BP × DOSE). Baseline data were compared by a two-tailed Student's *t* test for unpaired data. The minimum level of statistical significance was $P < 0.05$. The data from the NT control subjects studied have been reported elsewhere (15, 22).

Results

NT and BHT subjects did not differ with regard to age, height, weight, forearm volume, forearm circumference, 24-h sodium

1. *Abbreviations used in this paper:* BHT, borderline hypertensive; BMI, body mass index; NT, normotensive.

Table I. Baseline Data in Normotensive and Borderline Hypertensive Subjects

Measurement	Normotensive (n = 13)	Hypertensive (n = 8)
Age (yr)	32.9±1.9	33.4±1.9
Height (in.)	72.2±0.5	71.8±1.1
Weight (lbs)	174.2±5.7	200.0±16.5
Body mass index (kg/m^2)	23.5±2.8	27.2±5.6
Forearm volume (ml)	1180.4±48.6	1392.5±107.1
Forearm circumference (cm)	25.2±0.44	24.8±1.2
24-h Na^+ excretion (mmol)	118.7±11.7	102.0±17.8

Values are means±SEM. No measurement differed significantly between the two groups. To convert inches to meters multiply by 0.0254 and to convert pounds to kilograms multiply by 0.454.

excretion (Table I), baseline heart rate, or baseline forearm blood flow (Table II). However, although the differences did not attain statistical significance, weight and body mass index (BMI) (wt (kg)/ht^2 (m)) was greater in the borderline hypertensive group than the normotensive controls (P = 0.10 and P = 0.06, respectively); findings representative of the general difference in body weight between hypertensives and normotensives in the population (23). Baseline blood pressure was higher in the BHT group (mean arterial pressure, 102.6±1.6 mmHg) compared with the NT group (85.1±1.5 mmHg) ($P < 0.0001$) (Table II).

The administration of intraarterial isoproterenol resulted in an increase in forearm blood flow in both normotensive and hypertensive subjects but the response was blunted in subjects with borderline hypertension ($P < 0.0001$) (Fig. 1). Similarly, forearm vascular resistance (mean arterial blood pressure/forearm blood flow) was not different at baseline in the two groups (BHT 54.9±8.0 mmHg/ml per min/100 ml vs. NT 40.8±6.2 mmHg/ml per min per 100 ml, P = NS) but the decrease in forearm vascular resistance that resulted from the administration of isoproterenol was blunted in subjects with borderline hypertension (BP × DOSE, P = 0.006) (Table II). Changes in conductance, the reciprocal of forearm vascular resistance, are shown in Fig. 2.

Baseline forearm norepinephrine spillover, reflecting local sympathetic activity in the forearm was not different in the two groups (BHT 1.0±0.4 ng/min vs. NT 0.64±0.13 ng/min, P = NS). As we have previously reported (15), isoproterenol administered into the brachial artery resulted in a marked increase in forearm norepinephrine spillover (Fig. 3, Table II) with a similar response observed in hypertensive and normotensive subjects after the administration of isoproterenol 60 ng/min (BHT 5.2±1.4 ng/min vs. NT 6.0±1.5 ng/min, P = NS)

Table II. Results of Intra-arterial Infusion of Isoproterenol in Normotensive and Borderline Hypertensive Subjects

	Baseline		Isoproterenol, 60 ng/min		Isoproterenol, 400 ng/min		Significance		
	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	BP	DOSE	BP × DOSE
Forearm blood flow (ml/100 ml/min)	2.1±0.29	2.7±0.40	7.9±1.1	14.6±2.1	15.2±1.5	24.4±2.4	*	‡	‡
Forearm vascular resistance (mmHg/ml/min/100 ml)	54.9±8.0	40.8±6.2	14.3±1.6	7.1±1.0	7.1±0.66	3.9±0.44	*	‡	*
Arterial NE (pg/ml)	189.0±21.5	124.6±11.1	193.8±24.3	127.1±12.5	215.3±23.4	153.1±10.5	*	‡	NS
Venous NE (pg/ml)	178.8±21.5	128.8±10.2	200.4±25.1	155.1±12.6	249.1±25.7	209.8±12.6	NS	‡	NS
Forearm NE spillover (ng/min)	1.0±0.4	0.64±0.13	5.2±1.4	6.0±1.5	13.5±2.9	16.5±2.7	NS	‡	NS
Forearm NE clearance (ml/min/100 ml)	6.0±1.3	4.8±0.83	22.3±4.2	25.8±4.8	40.9±5.8	49.0±7.0	NS	‡	NS
Plasma NE apperance rate (ng/min)	2.1±0.95	1.1±0.27	9.1±2.8	9.0±2.2	20.6±4.0	26.4±5.6	NS	‡	NS
Forearm NE intrinsic clearance (ml/min/100 ml)	11.0±3.0	8.5±1.9	39.2±8.5	43.4±10.6	64.2±8.5	79.2±15.7	NS	‡	NS
Systemic NE spillover (ng/min)	543.5±68.1	320.4±34.3	517.4±74.7	333.2±30.2	658.1±91.9	446.7±33.1	*	‡	NS
Systemic NE clearance (liters/min)	2.9±0.17	2.6±0.13	2.7±0.19	2.7±0.15	3.1±0.20	3.0±0.14	NS	*	NS
Systolic blood pressure (mmHg)	138.8±1.9	120.6±2.2	134.9±2.4	116.5±2.1	136.6±2.9	120.7±2.9	‡	‡	NS
Diastolic blood pressure (mmHg)	84.6±1.6	67.4±1.6	83.9±2.0	66.6±2.0	77.8±2.2	63.0±2.5	‡	‡	NS
Mean arterial blood pressure (mmHg)	102.6±1.6	85.1±1.5	100.9±1.9	83.2±1.7	97.4±2.0	82.2±2.4	‡	‡	NS
Heart rate (beats/min)	71.4±4.7	63.2±2.0	70.0±3.6	61.8±1.9	79.3±5.1	71.5±3.4	NS	*	NS

Values are means±SEM. Statistical significance of the effect of blood pressure category (BP), response to isoproterenol (DOSE), and the interaction between blood pressure category and response to isoproterenol (BP × DOSE) is expressed as $P > 0.05$ (NS), * $P < 0.05$, and ‡ $P < 0.001$. Conversion factor: To convert norepinephrine concentrations from pg/ml to nmol/liter divide by 169.2.

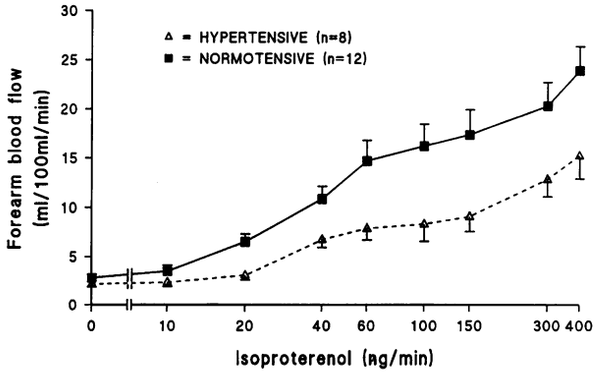

Figure 1. Forearm blood flow (ml/100 ml per min) at baseline and after the administration of increasing doses of intraarterial isoproterenol (10–400 ng/min) in normotensive controls (n = 12) and subjects with borderline hypertension (n = 8). Data are expressed as means±SEM. Statistical significance of the effect of blood pressure category (BP) was $P < 0.05$, response to isoproterenol (DOSE) $P < 0.001$, and the interaction between blood pressure category and response to isoproterenol (BP×DOSE) $P < 0.001$ (ANOVA).

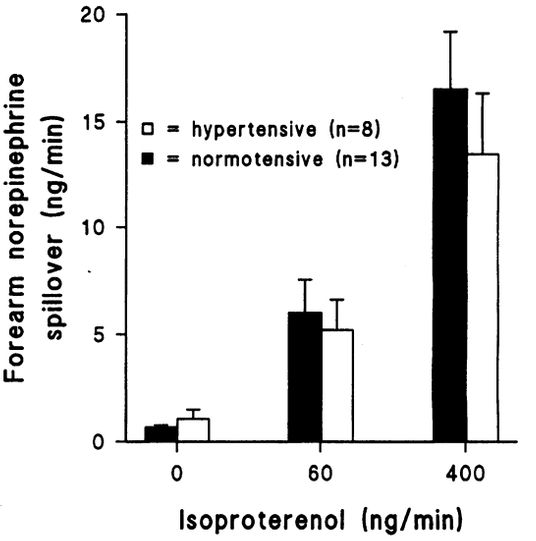

Figure 3. Forearm norepinephrine spillover (ng/min) at baseline and after the administration of intraarterial isoproterenol (60 and 400 ng/min) in normotensive controls (n = 13) and subjects with borderline hypertension (n = 8). Data are expressed as means±SEM. Statistical significance of the effect of blood pressure category (BP) was P = NS, response to isoproterenol (DOSE) $P < 0.001$, and the interaction between blood pressure category and response to isoproterenol (BP × DOSE) P = NS (ANOVA).

and 400 ng/min (BHT 13.5±2.9 ng/min vs. NT 16.5±2.7 ng/min, P = NS). Local norepinephrine spillover may be affected by blood flow and therefore forearm norepinephrine plasma appearance rate and intrinsic clearance, measures of local norepinephrine kinetics that have been reported to be independent of flow (21) were calculated. The norepinephrine plasma appearance rate, as was found for norepinephrine spillover, increased in both groups after the administration of isoproterenol, but did not differ between the hypertensive and normotensive groups either at baseline or after the administration of isoproterenol (Table II).

Subjects with borderline hypertension had higher baseline systemic norepinephrine spillover (BHT 543.5±68.1 ng/min vs. NT 320.4±34.3 ng/min; $P < 0.005$), reflecting overall sympathetic activity, as well as both baseline arterial (BHT 189.0±21.5 pg/ml vs. 124.6±11.1 pg/ml, $P < 0.01$) and venous (BHT 178.8±21.5 pg/ml vs. NT 128.8±10.2 pg/ml, $P < 0.05$) plasma norepinephrine concentrations (Table II, Fig. 4). Systemic norepinephrine spillover increased a small, but significant amount, after administration of the highest dose of isoproterenol in both groups (Fig. 4). Although the absolute systemic norepinephrine spillover after the administration of isoproterenol 400 ng/min was greater in the BHT group (658.1±91.9 ng/min vs. NT 446.7±33.1 ng/min, $P < 0.05$) (Table II), these reflect

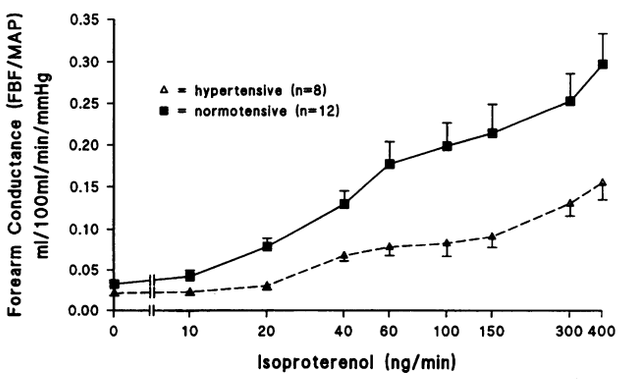

Figure 2. Forearm conductance [forearm blood flow (ml/100 ml per min)/mean arterial pressure (mmHg)] at baseline and after the administration of increasing doses of intraarterial isoproterenol (10–400 ng/min) in normotensive controls (n = 12) and subjects with borderline hypertension (n = 8). Data are expressed as means±SEM. Statistical significance of the effect of blood pressure category (BP) was P = 0.008, response to isoproterenol (DOSE) $P < 0.001$, and the interaction between blood pressure category and response to isoproterenol (BP×DOSE) $P < 0.001$ (ANOVA).

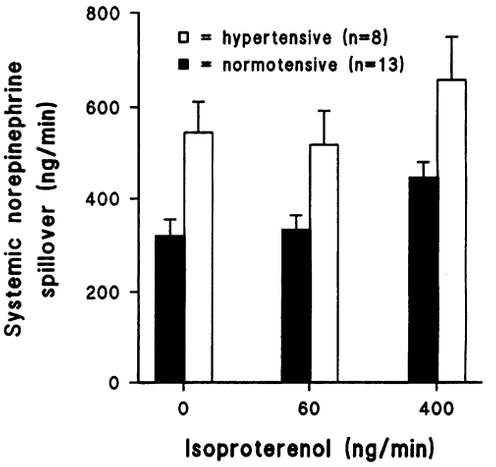

Figure 4. Systemic norepinephrine spillover (ng/min) at baseline and after the administration of intraarterial isoproterenol (60 and 400 ng/min) in normotensive controls (n = 13) and subjects with borderline hypertension (n = 8). Data are expressed as means±SEM. Statistical significance of the effect of blood pressure category (BP) was $P < 0.05$, response to isoproterenol (DOSE) $P < 0.001$, and the interaction between blood pressure category and response to isoproterenol (BP×DOSE) P = NS (ANOVA).

differences present at baseline (BHT 543.5±68.1 ng/min vs. NT 320.4±34.3, $P < 0.005$) and isoproterenol-induced increase in systemic norepinephrine spillover did not differ between BHT and NT subjects (BP × DOSE, P = NS) (Table II).

The doses of isoproterenol infused had minimal systemic effects with heart rate increasing from baseline (BHT 71.4±4.7 beats/min vs. NT 63.2±2.0 beats/min, P = NS) by approximately 8 beats/min in both groups after administration of the highest dose of isoproterenol (Table II). Similarly, small, but statistically significant, decrements in mean arterial pressure and diastolic blood pressure occurred in both groups after the administration of isoproterenol 400 ng/min but the response was similar in the two groups (BP × DOSE, P = NS) (Table II).

Discussion

Vasodilation in response to the intraarterial administration of isoproterenol, as determined by alterations in both forearm blood flow (Fig. 1) and forearm vascular resistance (Table I), was impaired in subjects with borderline hypertension, compared with a well-matched group of normotensive controls. These findings were not explained by increased local sympathetic activity in the BHT group since forearm norepinephrine spillover (and its flow-independent equivalent, forearm plasma norepinephrine appearance rate) were not different, either at baseline, or after stimulation of norepinephrine release by the intraarterial infusion of isoproterenol (Fig. 3, Table II).

In a previous study in which low doses of isoproterenol were infused into the brachial artery, it was found that in hypertensive subjects receiving a diet containing 250 mmol Na^+/d, the forearm blood flow response to isoproterenol was impaired and that this could be corrected by a low-sodium diet (10). Our study extends these findings by showing a similar impairment of the response to isoproterenol in subjects with borderline hypertension, in whom structural vascular alterations induced by hypertension are less likely to confound observations of vascular response and that these changes occurred while subjects were receiving a sodium intake more representative of the average sodium intake in the United States.

Several studies have indicated that sympathetic activity, particularly early in the disease process, is enhanced in subjects with hypertension (11, 12). Our study, which examined sympathetic activity in white normotensive and hypertensive subjects matched for sodium intake, confirms that systemic norepinephrine spillover is enhanced in subjects with borderline hypertension. Obesity and a higher BMI are associated with increased sympathetic activity (24). BMI was greater in the BHT group and may therefore have contributed to the finding of increased systemic NE spillover in this group. The difference in baseline forearm NE spillover between the BHT (1.0±0.4 ng/min) and NT (0.64±0.13) groups was not significant (P = 0.32), and the higher mean value was attributable to one BHT individual with a forearm NE spillover of 3.94 ng/min (more than twice the value obtained for any other BHT or NT individual). If the value for this individual is excluded from the comparison, then the baseline forearm NE spillover in the BHT group (0.63±0.13 ng/min) is similar to that of the NT group (0.64±0.13). Esler and colleagues (12) measured organ-specific norepinephrine spillover in hypertensive and normotensive subjects and found that the increase in systemic norepinephrine spillover observed in hypertensive subjects was largely accounted for by enhanced renal and cardiac NE spillover. Thus our findings that systemic norepinephrine spillover was increased but that local norepinephrine spillover in the forearm was unaltered in subjects with borderline hypertension is in keeping with that observation. However, the relatively small sample size in this and other studies examining overall and regional sympathetic activity in hypertension suggest that the power of these studies to exclude differences between groups is low and may account for differences in the literature (11–14).

Isoproterenol has effects mediated through both $beta_1$ and $beta_2$ adrenoceptors but its effects in human vasculature are thought to be mediated largely through $beta_2$ adrenoceptors (25, 26); therefore the observations in the present study are likely to largely be attributable to effects mediated through $beta_2$ adrenoceptors. Stimulation of presynaptic beta adrenoceptors by the administration of low doses of isoproterenol directly into the brachial artery in vivo in humans has been shown to increase the release of norepinephrine locally by ourselves (15) and confirmed recently by others (13). The overall effect of a beta agonist on forearm blood flow may therefore be influenced not only by postsynaptic beta adrenoceptors but also by presynaptic beta receptor response. In the present study the impaired vasodilation in response to isoproterenol in subjects with borderline hypertension occurred in spite of there being no difference in either basal or stimulated local sympathetic activity, measured either as forearm norepinephrine spillover, or its flow-independent equivalent—forearm norepinephrine plasma appearance rate, compared with normal controls. A possible explanation for the impaired isoproterenol-induced vasodilation in BHT subjects would be that isoproterenol-induced NE release, and consequently vasoconstriction, might have been greater in BHT subjects. In fact, however isoproterenol-stimulated forearm NE spillover was not significantly different in BHT and NT subjects and if anything tended to be lower in the BHT group. Therefore enhanced presynaptic beta adrenoceptor-mediated NE release in the BHT group does not explain the attenuated postsynaptic beta adrenoceptor–mediated vasodilation observed in this group. Furthermore, isoproterenol-stimulated norepinephrine release was maintained despite the impaired vasodilatory response in borderline hypertension, suggesting a differential sensitivity of these two isoproterenol-mediated responses as we have previously shown occurs in response to anesthesia (27). The unaltered sensitivity of presynaptic beta adrenergic receptors in hypertension is supported by a study performed by Chang and colleagues (13) that found that the increase in forearm norepinephrine spillover occurring after the administration of epinephrine (a mixed α and β receptor agonist) did not differ between subjects with longstanding hypertension and normal controls. Local NE spillover increases with increased flow but the calculation of NE plasma appearance rate has been reported to be a flow-independent measure of NE release (21), and we therefore have presented data for both NE spillover and plasma appearance rate. If plasma appearance rate does not fully correct for flow-mediated increases in NE spillover, it is possible that presynaptic beta receptor-mediated NE release may be increased in BHT but that this was masked by a lower flow-mediated increase in NE spillover in this group.

Most (3, 28), but not all (29), previous studies of vascular response in hypertensive subjects have found that responses to an endothelium-dependent agonist, such as acetylcholine, were impaired, whereas responses to an endothelium-independent agonist, such as sodium nitroprusside, were maintained. The preserved response to sodium nitroprusside in these studies of patients with established hypertension indicates that structural vas-

cular alterations, although present in subjects with borderline hypertension (16, 30), are unlikely to explain either the impaired responses to acetylcholine noted by others (3, 28) or the impaired response to isoproterenol found in the present study.

The administration of phentolamine, an alpha receptor antagonist, results in a greater reduction in forearm vascular resistance in hypertensive patients than in normal controls, suggesting increased alpha agonist activity in hypertension (1). However, the vasoconstrictor response following direct intraarterial administration of an alpha agonist was not enhanced in patients with hypertension in studies examining both arterial (1, 10) and venous (31) responses, suggesting that the enhanced response to phentolamine may have reflected increased basal sympathetic activity rather than true increased vascular sensitivity to alpha agonists. Enhanced alpha receptor-mediated vasoconstriction therefore does not appear to be a likely explanation for the impaired beta receptor-mediated vasodilation.

Prolonged exposure of beta receptors to agonist has been shown, both in vitro (32–34) and in vivo (35), to lead to a decrease in beta receptor-mediated responses, a process known as desensitization. Sympathetic activity, as determined by systemic norepinephrine spillover, was significantly higher at baseline in the subjects with borderline hypertension. Therefore, it is possible that catecholamine-induced desensitization of beta adrenoceptors in the borderline hypertensive subjects explains the decreased vasodilation in response to isoproterenol. However, since local norepinephrine release after the administration of intraarterial isoproterenol, thought to be mediated through presynaptic beta adrenoceptors (15), was not altered in subjects with BHT, it would imply that presynaptic beta adrenoceptors (mediating norepinephrine release) and postsynaptic beta adrenoceptors (mediating vasodilation) are regulated in a differential fashion. An argument against catecholamine-induced desensitization being important in this process is the observation that a low-sodium diet, a diet that results in sympathetic activation and a rise in plasma norepinephrine concentrations (36), has previously been reported to correct the impaired vasodilation in response to isoproterenol in hypertensive subjects (9, 10) when the increased catecholamines would be expected to increase desensitization.

Impaired responses to the endothelium-dependent vasodilator, acetylcholine, in subjects with hypertension have been reported (3, 28). It is unlikely that the same mechanisms thought to account for the impaired vascular responses of hypertensive subjects to acetylcholine explain the impaired responses to isoproterenol since isoproterenol is though to produce vasodilation by an endothelium-independent mechanism that does not involve nitric oxide or guanylate cyclase (37). However, studies suggesting that prolonged infusion of isoproterenol may have resulted in the release of an endogenous vasodilator (38) and that the effects of isoproterenol in rat aortic rings may be partially mediated through an endothelium-dependent, nitric oxide–mediated mechanism (39) raise the possibility that vascular responses to isoproterenol, and to agonists acting through nitric oxide, may not be totally independent. Altered endothelium-dependent isoproterenol-induced vasodilation, a phenomenon not known to occur in humans, appears to be an unlikely explanation for the blunted vasodilatory response to isoproterenol in BHT subjects.

The technique used in this study allowed the local intra-arterial infusion of the beta agonist isoproterenol to stimulate both presynaptic and postsynaptic beta adrenoceptors in the forearm and determination of their response. The dose of isoproterenol used (400 ng/min) has previously been shown by ourselves (10, 15) and others (40) to have minimal systemic effects and to produce no change in the blood flow in the contralateral forearm when infused intra-arterially in the same fashion as used in the present study. The effects of isoproterenol in the present study were largely limited to the forearm. The 10–20-fold increase in forearm NE spillover was accompanied by a much smaller increase ($< 50\%$) in systemic norepinephrine spillover and small systemic hemodynamic changes. This increase in systemic norepinephrine spillover may reflect either stimulation of presynaptic receptors at tissue sites outside the forearm, or reflex sympathetic stimulation due to baroreceptor stimulation. Systemic norepinephrine spillover increased by $22.3 \pm 8.8\%$ in the BHT group and $49.1 \pm 10.0\%$ in the NT group. This difference was not statistically significant ($P = 0.08$) but shows the same directional change as in the forearm in keeping with impairment of systemic vasodilation in BHT subjects. However, a study with a larger sample size and greater statistical power would be required to specifically determine this.

Impaired vasodilation of forearm vasculature was observed after the administration of intra-arterial isoproterenol in white subjects with borderline hypertension receiving a moderate sodium diet. Although systemic measures of sympathetic activity were increased in BHT, the impaired vasodilatory response to isoproterenol was not explained by locally increased sympathetic activity and suggests that impaired $beta_2$ receptor-mediated vasodilation occurs early in the course of hypertension and may be important in its pathogenesis.

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