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Research Article

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Responsiveness of Superficial Hand Veins to Phenylephrine in Essential Hypertension

Alpha Adrenergic Blockade during Prazosin Therapy

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Abstract

Patients with essential hypertension show an increase in vascular resistance. It is unclear whether this is caused by structural changes in the arterial wall or by hyperresponsiveness of vascular smooth muscle to endogenous alpha adrenergic agonists.

Using the dorsal hand vein compliance technique we compared the changes in diameter of superficial veins in response to phenylephrine, an alpha$_1$ adrenergic receptor agonist, and to nitroglycerin, a venorelaxant, in patients with essential hypertension and in normotensive subjects. The dose of phenylephrine that produced 50% of maximal venoconstriction (ED_{50}) in the hypertensive subjects was 257 ng/min (geometric mean; log mean±SD was 2.41±0.54). In the control subjects the ED_{50} was 269 ng/min (geometric mean; log mean was 2.43±0.43). Maximal response (E_{max}) for phenylephrine was 84±13% in the hypertensive subjects and 90±6% in the control subjects. Differences in the group means of the ED_{50} ($P = 0.92$) or the E_{max} ($P = 0.27$) were not significant. There were no significant differences in the ED_{50} ($P = 0.54$) or the E_{max} ($P = 0.08$) for nitroglycerin between the two groups.

These results show no evidence for a generalized change in alpha adrenergic responsiveness in hypertension and support the concept that increased blood pressure responses to alpha adrenergic stimulation in hypertensives are due to structural and geometric changes in the arterial wall rather than to an increased responsiveness of postsynaptic alpha adrenergic receptors.

The phenylephrine studies were repeated in seven hypertensive patients during treatment with prazosin, an alpha$_1$ adrenergic antagonist. The mean dose ratio of the shift in phenylephrine ED_{50} (ED_{50} during prazosin therapy/ED_{50} before prazosin therapy) was 6.1. This indicates that small doses of prazosin (1–2 mg) cause significant in vivo shifts in the dose-response relationship of alpha adrenergic agonists. The dorsal hand vein compliance technique is useful in detecting systemic effects of alpha adrenergic antagonists.

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Introduction

Increased peripheral resistance is the basic hemodynamic abnormality in most patients with essential hypertension. Hyperresponsiveness of vascular smooth muscle to alpha adrenergic receptor–mediated vasoconstriction has been proposed as a factor involved in maintaining this increase in vascular resistance (1). Platelets from hypertensive patients exhibit a defect in the ability of norepinephrine to desensitize the alpha$_2$ receptor (1). This suggests that there may be an alpha adrenergic receptor defect in hypertension, although findings from circulating cells are not necessarily applicable to vascular adrenergic receptors (2). Another possible explanation is that the responsiveness of resistance vessels to endogenous vasodilating substances is impaired in essential hypertension.

Several studies have shown an increased blood pressure response in hypertensive as compared with normotensive subjects to exogenous norepinephrine (3, 4) and phenylephrine (5); these pressor amines act predominantly on vascular alpha adrenergic receptors. This observed increase in blood pressure response to alpha adrenergic agonists in hypertensive patients need not reflect an increased responsiveness of alpha adrenergic receptors, since thickening of the arterial media, often associated with hypertension, may, for purely geometric reasons, give rise to exaggerated luminal changes for given shifts in smooth muscle activity (6). These geometric changes could result in vascular hyperactivity without necessitating any altered functional responsiveness of the smooth muscle cells. When isolated artery strips are compared, a procedure that eliminates the geometrically based hyperactivity in hypertensive vessels, there is no clear difference in the response to norepinephrine between hypertensive and normotensive arteries (7, 8).

To test the hypothesis that vascular alpha adrenergic responsiveness is increased in essential hypertension, we compared the diameter changes in superficial veins in response to phenylephrine, an alpha adrenergic receptor agonist, in untreated patients with mild to moderate essential hypertension and in normotensive subjects. Veins were studied because they are not exposed to the increased blood pressure, and therefore media hypertrophy and thickening of the wall, which occur in resistance vessels, do not play a role in reactivity. The dorsal hand vein compliance technique (9) was used because it permits complete dose-response studies of vascular relaxation without confounding reflex alterations. To test the hypothesis that impaired vascular relaxation is present in essential hypertension we compared the venorelaxant effect of nitroglycerin in both hypertensive and control subjects.

The study of hand vein responsiveness to phenylephrine in untreated hypertensive patients presented the opportunity to

examine the effect of systemic therapy with an alpha adrenergic antagonist on vascular responsiveness to alpha adrenergic agonists. Alpha adrenergic antagonists are believed to exert their antihypertensive action by reducing the vasoconstrictor effect of endogenous catecholamines with a subsequent decrease in peripheral resistance. Prazosin is a selective antagonist at alpha$_1$ adrenergic receptor sites (10). While the interaction of prazosin with alpha adrenergic agonists is well characterized in vitro (11), there are few data describing the prazosin-mediated shift in the dose-response curve in vivo. One study examined pressor responses to phenylephrine before and during prazosin therapy (12), but interpretation of such studies is difficult because of confounding homeostatic reflexes. With the hand vein technique agonist-antagonist interaction at vascular receptors can be more directly assessed. Phenylephrine studies were therefore repeated in seven hypertensive patients treated with prazosin to determine the magnitude of the shift of the phenylephrine dose-response curve in an in vivo setting.

Methods

Subject population. Studies were conducted in two groups of male subjects. Group 1 contained patients with stable, mild to moderate essential hypertension, age 33–71 yr (mean±SD: 51±12 yr; n = 10). Hypertension was defined as diastolic blood pressure readings on at least three different occasions above 95 mmHg. Most secondary causes of hypertension were excluded on the basis of history, physical examination, normal serum electrolyte and creatinine levels, and normal urinalysis. None of the subjects had been taking antihypertensive drugs for at least 12 wk before the study. The duration of hypertension ranged from 3 to 23 yr (mean±SD: 10±6 yr). Group 2 (control) was composed of drug-free, healthy, normotensive males age 29–74 yr (mean±SD: 50±16 yr; n = 10). The results from six subjects in the control group had previously been used for the control group of another study (13). Written informed consent was obtained before the study. All subjects were nonsmokers in good health. Subjects were asked to refrain from caffeine and alcohol for at least 12 h before the study.

Dorsal hand vein technique. The dorsal hand vein compliance technique, as modified by Aellig (9), was used as previously described in detail (13, 14). Briefly, the subjects were supine with one arm placed on a support sloping upwards at an angle of 30° from the horizontal to ensure complete emptying of the superficial hand veins. A 23-gauge needle was inserted into a suitable dorsal hand vein and a continuous infusion of physiological saline was started (rate: 0.36 ml/min). After ~ 30 min a linear variable differential transducer (LVDT)[1] was mounted onto the back of the hand. The LVDT (model 100 MHR; Schaevitz Engineering, Pennsauken, NJ) was mounted on the hand by means of a tripod and the LVDT's freely movable core, weighing 0.5 g, was placed over the center of the vein under study ~ 10 mm downstream from the tip of the needle. When the core was properly centered within the transformer there was a linear relationship over the range used between the vertical movement of the core and voltage output, which was recorded on a strip chart recorder. Recordings of the position of the core situated on the top of the vein were made both before and after inflation of a sphygmomanometer cuff on the same arm to 45 mmHg. This baseline vasodilation during saline infusion with the cuff inflated was defined as 100% relaxation, the recording obtained with the cuff not inflated (and the vein emptied) was defined as 100% constriction. The difference between the two positions of the core gave a measure of the diameter changes of the vein under the congestion pressure. All local drug infusions lasted for at least 7 min; the cuff was inflated for 2 min at intervals during each infusion period. Increasing concentrations of a drug were infused sequentially.

Phenylephrine, an alpha$_1$ selective adrenoceptor agonist, was used to produce vasoconstriction of the hand vein. A dose-response curve to phenylephrine was performed in each subject (dose range: 14–6,900 ng/min); in this way the dose of phenylephrine that produced 80% of maximal venous constriction was determined. This dose was then infused at a constant rate (preconstriction dose) during the subsequent performance of a nitroglycerin dose-response curve (dose range: 0.1–49 ng/min), which took ~ 80–120 min. Preliminary experiments indicated that phenylephrine-induced venoconstriction was stable during this time period.

Blood pressure and pulse were monitored at frequent intervals on the opposite arm; in no case did the infused drugs cause a change in heart rate or blood pressure.

The phenylephrine dose-response curve was repeated in the seven hypertensive patients treated with oral prazosin when satisfactory control of hypertension had been achieved with a constant dose for 2–4 wk. The dose response curves were begun 1 h after the last prazosin dose to study response when peak plasma levels of prazosin would probably be present (15).

Data analysis. Individual dose-response curves were analyzed using a sigmoid E_{max} model using the computer program MKMODEL (16) on an IBM PC AT microcomputer. This iterative nonlinear curve-fitting program provides an estimate of the maximal response (E_{max}) and the dose producing a half-maximal response. A log transformation was performed on individual ED_{50} values to obtain the geometric means. An unpaired two-tailed t test was used to compare the ED_{50} (after log transformation) and E_{max} values of the two groups. A paired one-tailed t test was used to compare the ED_{50} (after log transformation), E_{max}, and shape of the dose-response curve before and during treatment with prazosin. $P < 0.05$ was considered significant. A power calculation was done according to Stolley et al. (17) to estimate the level of type II error regarding the intergroup differences in the ED_{50} of phenylephrine and nitroglycerin.

Results

Blood pressures in the hypertensive patients ranged from 140 to 198 mmHg (systolic) and from 96 to 115 mmHg (diastolic) (mean±SD: 153±18/100±5 mmHg). Blood pressures in the control group ranged from 96 to 132 mmHg (systolic) and from 60 to 88 mmHg (diastolic) (mean±SD: 120±13/75±9 mmHg). The results from the dose-response studies with phen-

Table I. Responsiveness of the Hand Vein to Phenylephrine and Nitroglycerin in Hypertensive Patients and Control Subjects

	Hypertensives	Controls	P
Phenylephrine			
ED_{50} (geometric mean)	257	269	
(*ng/min*)	(43–1364)	(45–1106)	
Log ED_{50}	2.41±0.54	2.43±0.43	0.93
E_{max}	84±13	90±8	0.27
(% vasoconstriction)	(65–100)	(77–100)	
Nitroglycerin			
ED_{50} (geometric mean)	2.63	1.95	
(*ng/min*)	(1.01–10.10)	(0.16–10.90)	
Log ED_{50}	0.42±0.37	0.29±0.54	0.54
E_{max}	172±95	111±38	0.08
(% vasodilation)	(67–354)	(62–177)	

Data are presented as group means±1 SD; numbers in parentheses are minimum and maximum values in each group. There were 10 subjects in each group.

1. *Abbreviations used in this paper:* E_{max}, maximal response; LVDT, linear variable differential transducer.

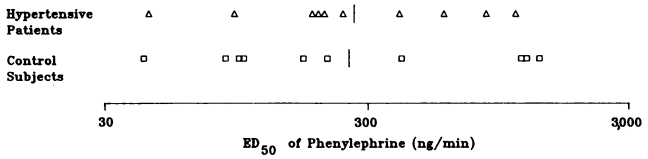

Figure 1. The phenylephrine ED_{50} in individual hypertensive (n = 10) and normotensive control subjects (n = 10) as determined by the dorsal hand vein compliance technique. The vertical lines represent the geometric means.

ylephrine and nitroglycerin are summarized in Table I. The dose of phenylephrine that produced 50% of maximal venoconstriction was 257 ng/min (geometric mean) in the hypertensive subjects and 269 ng/min in the control subjects. The means of the log ED_{50} in the two groups were 2.41±0.54 (mean±SD) and 2.43±0.43, respectively. The individual ED_{50} values for phenylephrine are presented in Fig. 1. E_{max} for phenylephrine was 84±13% in the hypertensive subjects and 90±6% in the control subjects. There were no statistically significant differences in the ED_{50} (P = 0.92) or the E_{max} (P = 0.27) between the group means.

In several subjects the highest doses of nitroglycerin caused a marked vasodilation with a diameter of the vein greater than that obtained under baseline conditions (i.e., during saline infusion). This accounts for the E_{max} values above 100% (Table I). As with phenylephrine there were no statistically significant differences in the ED_{50} (P = 0.54) or the E_{max} (P = 0.08) for nitroglycerin between the two groups.

In the hypertensive group there was no correlation between the log ED_{50} of phenylephrine and systolic blood pressure (r = 0.45, P = 0.14), or diastolic blood pressure (r = 0.22, P = 0.51), or duration of hypertension (r = 0.44, P = 0.14).

A power calculation estimates that with the given number of subjects in each group (n = 10), a 30% difference in the ED_{50} of phenylephrine could be detected with a power of 80% (alpha = 0.05, beta = 0.2).

Results for the seven hypertensive subjects restudied after treatment with prazosin are summarized in Table II. Dose-response curves from one patient are shown in Fig. 2 and the shifts in ED_{50} for all the subjects in Fig. 3. There was a significant increase in the ED_{50} for phenylephrine during prazosin therapy, from a geometric mean of 154 ng/min before prazosin therapy to a geometric mean of 721 ng/min during prazosin therapy. A paired t test of the log ED_{50} for phenylephrine before and during prazosin therapy showed that the ED_{50} was significantly increased (P = 0.003). The mean dose ratio (ED_{50} during prazosin therapy/ED_{50} before prazosin therapy) was 6.1±4.3 (P = 0.02). Prazosin had no effect on the slope of the dose-response curve (2.1±1.4 vs. 2.5±1.4, respectively). There was no statistically significant change in the E_{max} during prazosin therapy (81 vs. 79%, P = 0.44).

Table II. Results from the Phenylephrine Dose-Response Curves in Seven Hypertensive Patients before and during Prazosin Therapy

Patient (prazosin dose bid)	ED_{50} (ng/min)		Dose ratio	E_{max} (%)		BP (mmHg)	
	Before	During		Before	During	Before	During
P.D. (2 mg)	103	1,486	14.4	85	78	140/98	130/81
L.P. (1 mg)	88	587	6.7	96	68	155/105	140/80
H.P. (1 mg)	1,163	2,650	2.3	100	70	198/115	133/81
R.F. (2 mg)	43	290	6.7	64	89	140/98	141/91
R.L. (2 mg)	173	890	5.1	67	78	166/100	136/69
H.C. (2 mg)	408	2,489	6.1	100	80	140/96	140/72
A.L. (5 mg)	64	68	1.1	53	91	161/97	154/85

The last prazosin dose was given 1 h before the start of the dose-response curve. The blood pressures indicated were taken immediately before the phenylephrine infusions were started. Dose ratio = ED_{50} during prazosin therapy/ED_{50} in control period.

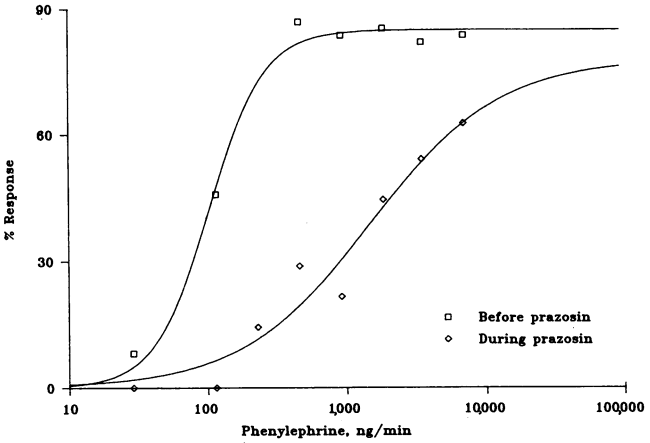

Figure 2. Dose-response curves for phenylephrine on dorsal hand veins from one hypertensive patient (P.D.) without treatment and 1 h after taking 2 mg prazosin orally. This subject had been taking prazosin (2 mg bid) for 6 wk. Constriction of the vein is expressed as percentage of baseline (predrug) vein diameter.

Discussion

The objectives of this study were to compare the venous responsiveness to phenylephrine, an $alpha_1$ adrenergic agonist, in patients with essential hypertension and normotensive subjects, and to determine the effect of systemic $alpha_1$ adrenergic antagonist antihypertensive therapy with prazosin on such responsiveness.

There was considerable intersubject variability in the phenylephrine responses of both study groups. Martin et al. (18)

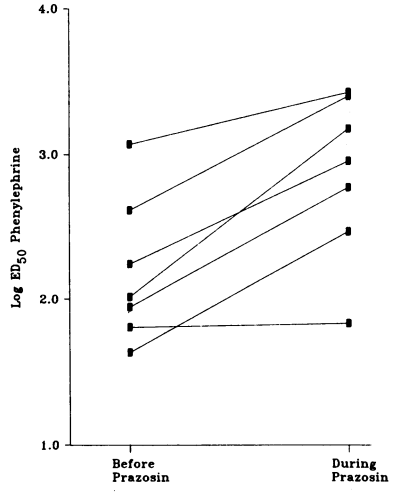

Figure 3. Change in phenylephrine ED_{50} before and during prazosin therapy in seven hypertensive subjects.

reported a range in ED_{50} of about two log cycles when norepinephrine was infused. We have previously found similar wide ranges for the ED_{50} of norepinephrine, isoproterenol, and nitroglycerin (13, 14). The reasons for this wide variability in vascular responsiveness (even in a healthy control group) are not clear, but may be attributed to genetic and/or environmental population factors rather than to the technique itself, since there seems to be little diurnal, day-to-day, or within-subject variability with the dorsal hand vein technique (19). There was no difference in the ED_{50} or the E_{max} of phenylephrine between hypertensive patients and the control group. In view of the wide intersubject variability of almost two log cycles for the ED_{50} values within the groups, a change in ED_{50} of $< 30\%$ difference between groups is unlikely to be significant in the pathophysiology of essential hypertension. The 80% power of our study to detect such a difference can be considered adequate in excluding any significant difference in $alpha_1$ adrenergic venous responsiveness between the groups.

How relevant are our findings in medium-sized veins in relation to changes in essential hypertension that primarily involve resistance vessels, i.e., arteries and arterioles? Contraction of resistance vessels appears to be mediated mainly through the $alpha_1$ receptor subtype (10, 20), whereas some human veins contain both $alpha_1$- and $alpha_2$ receptors on postsynaptic sites that mediate constriction (21). Phenylephrine acts preferentially on $alpha_1$ adrenergic receptors, and the results from our dose-response curves therefore primarily reflect vascular responsiveness mediated through the $alpha_1$ receptor subtype. While results in the dorsal hand vein cannot be directly extrapolated to reflect the responsiveness of resistance vessels, our results indicate that there is no generalized increase in responsiveness to stimulation of postsynaptic vascular $alpha_1$ adrenergic receptors in essential hypertension.

These results are in agreement with in vitro findings that show no increased alpha receptor responsiveness in isolated arteries from hypertensive patients (6, 7) and agree with a recent in vivo study of vascular alpha adrenergic responsiveness in young hypertensive and normotensive subjects that examined forearm vascular response to intraarterial norepinephrine and demonstrated that there was no change in alpha receptor sensitivity (22). The hypertensive subjects showed a greater reduction in forearm vascular resistance with phentolamine indicating increased sympathetic drive. At high doses of intraarterial norepinephrine a nonspecific enhancement of arterial vascular reactivity occurred, probably due to structural vascular changes. Our findings support the concept that increased blood pressure responses to alpha adrenergic stimulation in hypertensives are due to such structural and geometric changes in the arterial wall, rather than to an increased responsiveness of postsynaptic alpha adrenergic receptors (5).

The shift in the phenylephrine dose-response curves to the right with prazosin treatment was a consistent finding in all but one of the subjects studied. These changes in vascular responsiveness are unlikely to be due to intrasubject day-to-day variability because the coefficient of variation of the ED_{50} with this technique is in the order of 5–15% when studies are repeated on different occasions in different veins (19). Plasma concentrations of prazosin were not measured, so the observed shift in the phenylephrine ED_{50} cannot be related to prazosin concentrations. The sixfold shift in the dose-response curve is in broad agreement with the two- to threefold shift of the dose-response curve for pressor response to systemic phenylephrine seen after single 1-mg doses of prazosin (23). An estimate of the K_d for prazosin can be made using the equation $(DR - 1) \times K_d = [\text{prazosin}]$, where DR is the dose ratio of agonist, and [prazosin] the concentration of prazosin at $alpha_1$ adrenoreceptors in the dorsal hand vein. Using an estimate of 10 ng/ml as the usual approximate effective plasma prazosin concentration in the treatment of hypertension (23) and the value of 6.1 for the dose ratio estimates K_d to be in the region of 5×10^{-9} M. This estimate is in good agreement with the expected potency of prazosin at $alpha_1$ adrenergic receptors (11).

These results indicate that small doses of prazosin, effective in controlling blood pressure (Table II), cause detectable and substantial shifts in the dose-response relationship of alpha adrenergic agonists with vascular smooth muscle. This finding is in contrast to our experience with transdermally administered nitroglycerin, where no detectable shift in the phenylephrine dose-response relationship was found in the dorsal hand vein (Hiremath, A., B. B. Hoffman, and T. F. Blaschke, manuscript submitted for publication). The dorsal hand vein compliance technique is useful in detecting systemic effects of $alpha_1$ adrenergic antagonists and offers the opportunity to study the systemic effects of other vasoactive drugs, such as other direct-acting vasodilators and calcium channel blockers, on adrenergic-mediated vasoconstriction. Such an approach could be useful in elucidating the in vivo mechanisms of action of peripherally acting hypotensive drugs in man.

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