

Effects of Prazosin on Autonomic Control of Circulation in Essential Hypertension

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SUMMARY Prazosin, an antihypertensive agent that reduces blood pressure (BP) mainly through a blockade of alpha-adrenergic receptors, may, in theory, affect sympathetic control of circulation to an extent that impairs circulatory homeostasis. This possibility was studied in subjects with essential hypertension by examining the cardiovascular effects of several stimuli that induce a powerful and diversified activation of the sympathetic noradrenergic activity (dynamic and isometric exercise, cold exposure) and of stimuli that exert a powerful inhibitory influence upon the sympathetic nervous system (carotid baroreceptor reflex). Before and after 15 days of continuous administration of prazosin (2-5 mg), 3 times a day, measurements were made of BP (intraarterial catheter), heart rate, cardiac output (thermodilution), and peripheral resistance. Prazosin reduced mean arterial pressure (10%) and peripheral resistance (9%) at rest, and it did not affect heart rate and cardiac output. Neurally mediated changes in arterial pressure, cardiac output, and peripheral resistance during dynamic or isometric exercise and cold exposure were unaffected by the drug; also unaffected were the cardiovascular responses to increase and decrease in carotid baroreceptor activity obtained by varying carotid transmural pressure through a variable neck pressure chamber device. Thus, the hypotensive and vasodilating effect of prazosin in essential hypertension is not accompanied by an impaired response to neural excitation influences upon the cardiovascular system. Also, the inhibitory influences originating from the carotid baroreflex are unchanged. These data indicate that circulatory homeostasis is largely preserved during administration of prazosin at clinically effective doses. (*Hypertension* 2: 700-707, 1980)

KEY WORDS • prazosin • sympathetic nervous system • noradrenergic activity •
alpha-adrenergic blockade • carotid baroreflex • circulatory homeostasis

PRAZOSIN is a vasodilator drug employed in the treatment of arterial hypertension that acts both as a direct relaxant of vascular smooth muscle and as a blocker of alpha-adrenergic receptors.^{1, 2} Several studies in experimental animals, however, suggest that the latter action of the drug is the major mechanism of its antihypertensive effect.³⁻⁷ These results show that: 1) prazosin does not induce any vasodilatation in the hindlimb if this vascular area has been subjected to prior sympathetic denervation;^{4, 5} 2) pretreatment with ganglion-blocking or alpha-adrenergic blocking agents prevents any vasodilatory effect of this drug;^{6, 7} 3) prazosin abolishes the vasoconstrictor effect of norepinephrine, being much more powerful than another classical alpha-blocker, phentolamine.^{4, 6}

Such effective blockade of alpha-adrenergic receptors may have undesirable clinical consequences, however. It may reduce the sympathetic control of circulation, thereby impairing one of the main mechanisms that maintain circulatory homeostasis. Indeed, severe interference with autonomic circulatory control has been the reason that the clinical use of alpha-blocking agents has been drastically limited in the past.

The present investigation was planned to examine whether clinical use of prazosin in hypertensive patients affected the cardiovascular responses to various reflex and central neural influences; the excitatory influences studied were those operating during dynamic and isometric exercise as well as during cold exposure, while the inhibitory ones were those arising from the most important reflexogenic area for blood pressure (BP) homeostasis, the carotid sinuses.⁸

Methods

Our study was performed on seven hospitalized subjects with essential hypertension of mild-to-moderate degree: six were men, one a woman, who had a mean

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age of 43 ± 3 years. They were selected for the investigation only if no cardiac or renal failure was present, no symptoms of coronary or cerebral vascular insufficiency had ever occurred, no major disease other than the hypertension was diagnosed, and no treatment with antihypertensive drugs had been given during the 3 weeks preceding the beginning of the study. All subjects gave free consent to the procedure after having its nature and purpose fully explained.

Hemodynamic Measurements

Pulsatile arterial BP was measured by a catheter introduced percutaneously into a femoral artery (after local anesthesia with 2% lidocaine) and connected with a strain-gauge transducer. Mean arterial pressure was obtained from the pulsatile signal both by electric damping and by continuous integration over consecutive 10-second periods. Heart rate was measured by a cardiometer, the signal for which was derived from the R wave of a suitable electrocardiographic lead. Cardiac output was measured by the thermodilution technique, a Swan-Ganz catheter being introduced percutaneously into an antecubital vein both to inject cold saline into the right atrium and to sense alterations in blood temperature from a pulmonary artery.⁹ Total peripheral resistance was calculated in units by dividing mean arterial pressure (mm Hg) by cardiac output (liter/min).

In each patient, systemic plasma renin activity (PRA) was also measured, according to the radioimmunoassay method described in previous studies.^{10, 11} Blood samples for the renin measurements were taken from the pulmonary circulation via the thermodilution catheter.

Hemodynamic Tests

Cardiovascular responses to the following maneuvers were studied: 1) dynamic exercise; 2) isometric exercise; 3) exposure to cold; and 4) increase and decrease in activity of the carotid sinus baroreceptors. Dynamic exercise, isometric exercise, and cold exposure were selected because under these circumstances powerful and diversified sympathetic excitatory influences act upon the heart and systemic vessels through alpha- as well as beta-adrenergic receptors.¹²⁻¹⁵ The carotid baroreflex was selected because of its paramount importance in homeostasis control of BP, largely via modulation of peripheral circulation.⁸

Dynamic exercise consisted in steadily pedaling a cycle-ergometer for 5 minutes, the level of work being adjusted to be always 75 watts. Isometric exercise consisted in steadily gripping a spring with the right hand for 1½ minutes. The spring was connected with a dynamometer that allowed the strength of gripping to be measured. This exercise was always performed at 40% of the maximum strength, which was established by a short-lived gripping at the beginning of the study

and confirmed at the end of it. Exposure to cold was obtained according to the traditional method of immersing one hand into water in an ice bath. Immersion was maintained for 1 minute.

Alterations in carotid baroreceptor activity were induced by means of the neck chamber technique, a description of which has been given in previous studies.¹⁶⁻¹⁹ Positive and negative changes in pneumatic pressure were almost instantaneously induced within a collar applied to the patient's neck. As these changes are linearly transmitted to the carotid sinuses (although 14% of the positive and 36% of the negative pressure are lost through the neck tissues), their application results in decrease and increase in carotid sinus transmural pressure, and therefore in decrease and increase in the activity of the carotid sinus baroreceptors with respect to the level determined by the existing arterial BP.¹⁶ As in previous studies^{17, 18} the BP changes produced within the neck chamber were maintained stable for 2 minutes. Their magnitude was such that, once the pressure loss through the neck tissues was correct, pressure changes outside the carotid sinuses were approximately ± 30 mm Hg. Almost identical changes were produced before and during treatment with prazosin.

Protocol

The subjects were kept without antihypertensive therapy for at least 21 days. During the last 5 days of the pretreatment period, all subjects were in the hospital and showed constancy of arterial BP values from day to day (cuff method, measurements made twice daily in the supine and upright positions). They were then subjected to a first hemodynamic study performed supine, which was started at least 20 minutes after the positioning of the catheters to minimize possible emotional factors involved in the catheterization procedures. Initially, three cardiac output measurements were made at intervals of 10 minutes while the patient lay supine without being engaged in any test. Then exposure to cold, isometric and dynamic exercise were performed, followed by application of a positive and negative pressure within the neck chamber. During each test, cardiac output was measured immediately before and during the last 10 seconds of the stimulus application. An interval of 10 minutes was observed between the beginning of a test and the end of the preceding one.

After the first hemodynamic study, therapy with prazosin was started. The drug was administered orally at 8-hour intervals beginning with a daily dose of 3 mg (1 mg 3 times a day) which was increased every 3 days until a consistent reduction in arterial pressure became evident. The effective dose of the drug was maintained for 10-15 days, at the end of which a hemodynamic study identical to the first one was repeated. The subjects suffered no untoward effect from the administration of prazosin and showed no consistent variations in body weight from the values

measured before the beginning of the treatment (average and standard errors for the seven patients, 69 ± 4 and 70 ± 4 kg respectively).

Data Analysis

The results were analyzed in the following way. For each patient, the eight hemodynamic measurements obtained at rest (three in the initial period and five before the beginning of the various tests) were averaged to obtain mean values (\pm standard deviations) for this condition. These values were then averaged for all seven patients to obtain mean values (\pm standard errors) for the entire group of patients during the resting state.

Effects of dynamic exercise, isometric exercise, and cold were evaluated by comparing average hemodynamic values of the 10 seconds immediately preceding the stimulus with the average values of the last 10 seconds of its application. To evaluate the effects of increasing and decreasing neck pressure, the comparisons were made between average hemodynamic values occurring during the 30 seconds preceding these stimuli and average values occurring at two different times during the stimuli: between the 5th and the 15th second and during the last 30 seconds of their application. This was done because the hemodynamic responses to alterations in neck tissue pressure have an early and partly transient component and after 30 seconds reach steady-state which is maintained for the remaining duration of the stimulus.^{17, 18} Measurements of cardiac output were performed during the steady state. Also, for these various hemodynamic tests, data from single subjects were averaged to obtain means (\pm standard errors) for the entire group.

Statistical analysis of the data was made by the Students *t* test for paired observations, a comparison being made between mean values during hemodynamic tests and mean values during baseline, and another comparison between mean values before and during therapy. The differences were considered to be statistically significant when *p* was no greater than 5%.

Results

Hemodynamics at Rest

The results obtained when the patients were at rest are shown in table 1. It can be seen that treatment with prazosin induced a reduction in mean arterial pressure that was statistically significant in each patient and in the group as a whole. On the other hand, during the resting state prazosin did not cause any consistent change in heart rate and cardiac output. Heart rate was significantly reduced by prazosin in one patient, and cardiac output significantly increased in two patients; however, in the remaining ones as well as in the whole group, the drug had no effect on these two variables. Therefore, the significant reduction in arterial pressure during administration of prazosin was due to a reduction in total peripheral resistance;

this reduction was significant in six of the seven patients and was also significant in the whole group.

In the seven subjects, PRA measured in the resting supine condition was 0.22 ± 0.06 ng/ml/hr before and 0.29 ± 0.04 ng/ml/hr during treatment with prazosin. The difference between these two values was not statistically significant.

Hemodynamics During Dynamic Exercise, Isometric Exercise, and Cold Exposure

Dynamic exercise (fig. 1) caused a moderate but significant increase in mean arterial pressure ($p < 0.05$), a huge increase in cardiac output and heart rate ($p < 0.001$), and a very marked reduction in total peripheral resistance ($p < 0.001$). The extent of all changes induced by dynamic exercise was quite similar

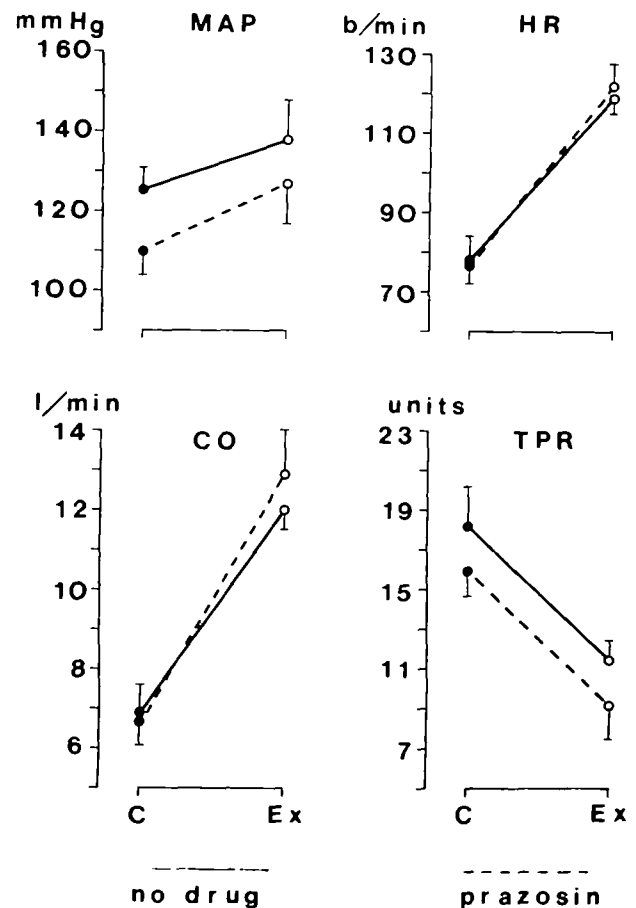


FIGURE 1. Hemodynamic effects of dynamic exercise before and during treatment with prazosin. Data are shown as means \pm SE of seven hypertensive subjects. C = data before exercise; Ex = data during the last 10 seconds of exercise; MAP = mean arterial pressure; HR = heart rate; CO = cardiac output; TPR = total peripheral resistance. Changes in MAP with exercise were significant at $p < 0.05$, and changes in CO, HR, and TPR at $p < 0.001$. Responses to exercise before and during prazosin were not significantly different.

before and during treatment with prazosin, no significant difference ever being found. However, the levels of mean arterial pressure and of total peripheral resistance, both at rest and at the end of the exercise test, remained significantly lower during than before prazosin ($p < 0.01$).

Isometric exercise (fig. 2) and exposure to cold (fig. 3) caused a significant and marked increase in mean arterial pressure ($p < 0.01$) and heart rate ($p < 0.001$). For isometric exercise, the rise in pressure was due to an increase in both cardiac output and total peripheral resistance (with a variable contribution of these two factors from subject to subject) while for cold exposure it was entirely due to an increase in total peripheral resistance (response significant at $p < 0.05$). Treatment with prazosin did not cause any significant alteration in the hemodynamic effects of all these maneuvers, but throughout both tests the levels of mean arterial pressure and of total peripheral resistance remained significantly lower during than before prazosin ($p < 0.01$).

Carotid Baroreceptor Reflex

As shown in figure 4, when the activity of the carotid baroreceptors was increased (by reducing neck tissue pressure around the carotid sinuses) there was a decrease in mean arterial pressure and heart rate during the early part of the stimulus and a less pronounced but significant steady hypotensive effect during the later phase of the test. When the activity of carotid baroreceptors was reduced (by increasing neck tissue pressure around the carotid sinuses), there was an early rise in mean arterial pressure and heart rate followed by a later pressor and tachycardiac effect of even greater magnitude. All responses (except the steady-state heart rate response to increased baroreceptor activity) were statistically significant at $p < 0.001$ for BP and < 0.01 for heart rate, and were almost identical before and during administration of prazosin.

Figure 5 shows the effects on cardiac output and total peripheral resistance. The pressor response to reduced baroreceptor activity was due entirely to a

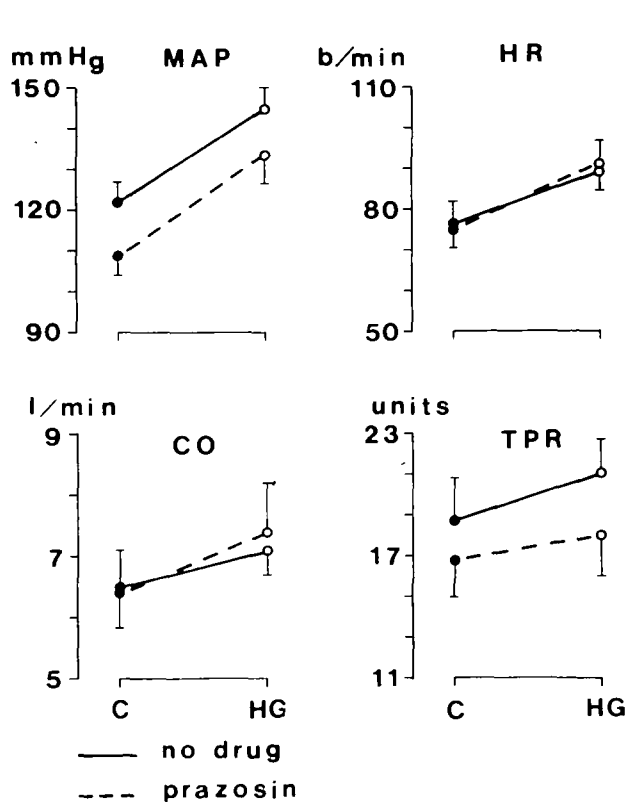


FIGURE 2. Hemodynamic effects of isometric exercise (handgrip) before and during treatment with prazosin. Data are shown as means \pm SE of the seven subjects of figure 1. C = data before exercise; HG = data during the last 10 seconds of exercise. Other symbols as in figure 1. Changes in MAP with exercise were significant at $p < 0.01$, changes in HR at $p < 0.001$, while changes in CO and TPR were not significant. Responses to exercise before and during prazosin were not significantly different.

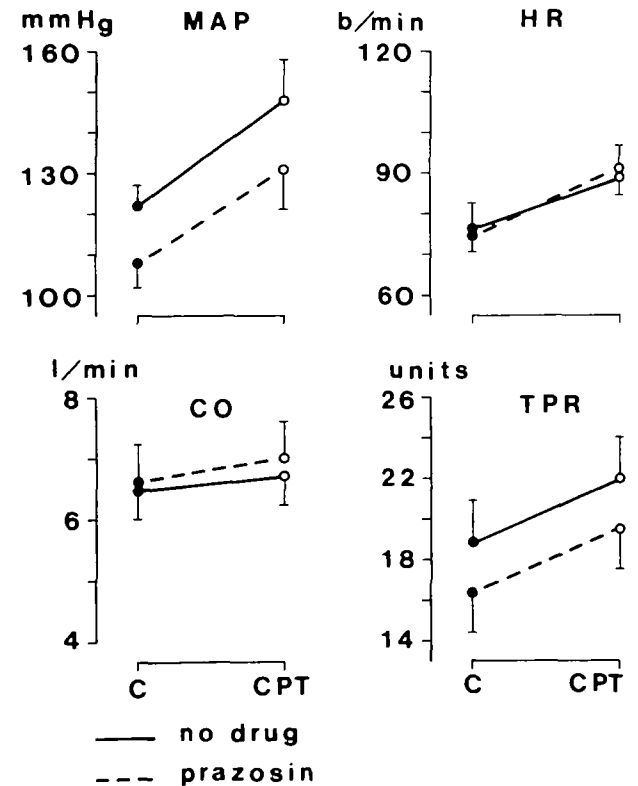


FIGURE 3. Hemodynamic effects of exposure to cold (cold pressor test) before and during treatment with prazosin. Data are shown as means \pm SE of the seven subjects of figure 1. C = data before cold exposure; CPT = data during the last 10 seconds of cold exposure. Symbols as in figure 1. Changes in MAP with cold were significant at $p < 0.01$ and changes in HR and TPR at $p < 0.001$. Changes in CO with cold were not significant. Responses to cold before and during prazosin were not significantly different.

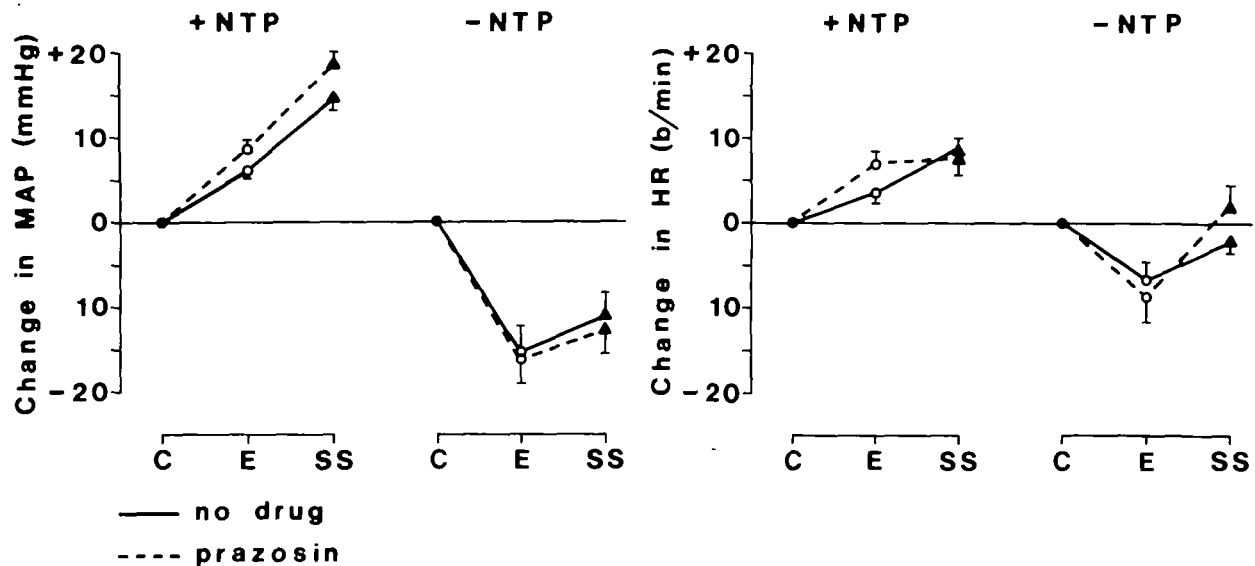


FIGURE 4. Effects of decreasing and increasing carotid baroreceptor activity on mean arterial pressure (MAP) and heart rate (HR) before and during treatment with prazosin in the seven subjects of figure 1. Data are shown as mean changes (\pm SE) from control values (C), E representing the early response, and SS the late or steady-state response to baroreceptor manipulation. Decrease in baroreceptor activity was obtained by increasing neck tissue pressure at the carotid sinuses (+NTP) by 28 ± 3 mm Hg before and by 28 ± 2 mm Hg during prazosin. Increase in baroreceptor activity was obtained by decreasing neck tissue pressure at the carotid sinuses (-NTP) by 35 ± 1 mm Hg before and by 34 ± 3 mm Hg during prazosin. MAP changes were all significant at $p < 0.001$, and heart rate changes at $p < 0.01$ (only the steady-state HR change was not significant). Responses to baroreceptor manipulation before and during prazosin were not significantly different.

rise in total peripheral resistance ($p < 0.01$) with no significant change in cardiac output, and this pattern was preserved during treatment with prazosin. The depressor response to increased baroreceptor activity was due to a reduction in both total peripheral resistance and cardiac output ($p < 0.02$ for either response). Also, this pattern was substantially preserved during prazosin, although there was a tendency for the reduction in total peripheral resistance to be more important and for the reduction in cardiac output to be less important in accounting for the depressor response.

Discussion

Our study has shown that in hypertensive subjects the pressor and cardiac effects of dynamic exercise, isometric exercise, and cold exposure are unchanged by prolonged administration of prazosin in spite of the fact that arterial pressure and peripheral resistance at rest were definitely lowered by the drug. Both types of exercise and exposure to cold are known to be accompanied by marked activation of the sympathetic nervous system and alpha-adrenergic receptors. This activation is of paramount importance in modulating the peripheral vasomotor responses, either by causing vascular resistance to increase during cold exposure or by limiting or counterbalancing the metabolically-induced vasodilatation during dynamic or static exercise.¹²⁻¹⁵

Also, the hemodynamic reflex responses to activation of the carotid sinus baroreceptors above and below the existing level have been found to be unaffected during treatment with prazosin. An important observation in this regard is that treatment with prazosin leaves unmodified not only the baroreceptor effects on heart rate but also the baroreceptor control of BP. This latter control is effected largely via a sympathetic modulation of peripheral resistance and again heavily depends on alpha-adrenergic receptors.^{19, 20}

Our observations that the hemodynamic responses, and in particular the changes in peripheral resistance, to all the stimuli above are similar before and during prazosin administration suggests that therapy with this drug does not impair the ability of alpha-adrenergic receptors to be modulated above or below their resting level of excitation by alterations in sympathetic activity. This might be interpreted as an indication that prazosin does not have a strong alpha-blocking effect and that its hypotensive activation depends on direct vasodilatation more than it is currently thought. However, this interpretation is in conflict with the experimental evidence that prazosin is a powerful blocking agent for postsynaptic alpha-receptors, its action being greater than other alpha-blocking drugs,^{4, 6} and the evidence that alpha-blockade can be achieved in man during chronic administration of prazosin at doses similar to those used in the present study.²¹

TABLE 1. Resting Hemodynamic Values Before (C) and During Treatment with Prazosin (T) in Seven Subjects with Essential Hypertension*

Patient	Age (yrs)	Sex	Prazosin (mg/day)	MAP (mm Hg)	HR (beats/min)	CO (liter/min)	TPR (mm Hg ÷ liter/min)
SG	42	M	9	C 102.7 ± 2.3	102.5 ± 2.0	9.40 ± 0.52	10.94 ± 0.59
				T 88.5 ± 1.3	89.9 ± 4.1	9.28 ± 0.51	9.54 ± 0.50
				P <0.001	<0.001	ns	<0.01
TP	31	M	15	C 114.9 ± 4.7	72.3 ± 3.8	6.41 ± 0.48	18.03 ± 2.08
				T 109.0 ± 4.7	72.0 ± 2.1	6.04 ± 0.47	18.12 ± 1.51
				P <0.001	ns	ns	ns
MV	42	M	15	C 127.3 ± 4.4	63.0 ± 4.4	4.90 ± 0.40	26.40 ± 1.80
				T 118.5 ± 3.6	63.1 ± 2.6	4.95 ± 0.01	23.90 ± 0.63
				P <0.001	ns	ns	<0.01
LL	42	M	15	C 138.9 ± 2.5	69.3 ± 1.8	6.01 ± 0.37	23.19 ± 1.94
				T 127.6 ± 2.2	73.0 ± 5.9	5.73 ± 0.40	22.35 ± 1.63
				P <0.001	ns	ns	<0.05
RM	46	F	3	C 124.8 ± 3.4	83.0 ± 2.9	6.64 ± 0.20	18.77 ± 0.70
				T 100.0 ± 2.8	87.1 ± 1.7	7.10 ± 0.10	14.06 ± 0.65
				P <0.001	<0.001	<0.001	<0.001
PR	53	M	6	C 126.1 ± 1.8	74.6 ± 0.7	6.10 ± 0.36	20.68 ± 1.00
				T 111.1 ± 2.5	74.4 ± 3.5	6.55 ± 0.28	16.99 ± 1.09
				P <0.001	ns	<0.02	<0.001
RR	47	M	6	C 122.3 ± 2.3	76.6 ± 1.6	6.57 ± 0.24	18.62 ± 0.71
				T 109.3 ± 1.3	76.3 ± 1.7	6.60 ± 0.10	16.52 ± 0.36
				P <0.001	ns	ns	<0.001
Average				C 122.4 ± 4.7	77.3 ± 4.8	6.58 ± 0.52	19.52 ± 1.83
				T 109.1 ± 4.2	76.5 ± 3.5	6.61 ± 0.52	17.35 ± 1.82
				P <0.001	ns	ns	<0.02

*In each subject data represent means ± standard deviation of 8 measurements made before (C) and eight measurements made during treatment with prazosin (T). P refers to the difference between these two values. Average data (± standard errors) for the whole group of subjects are also shown. MAP = mean arterial pressure; HR = heart rate; CO = cardiac output; TPR = total peripheral resistance.

Therefore, a more likely explanation of our findings is that prazosin can block alpha-adrenergic receptors to effectively reduce arterial BP at rest but that the nature and the extent of this blockade is such that it does not interfere with the activation and deactivation of the alpha-receptors when sympathetic activity is increased or reduced by central or reflex neural influences. Why this occurs is a matter for speculation. We may suggest that what we observed with prazosin is what should occur with a competitive antagonist for alpha-adrenergic receptors. A competitive antagonist raises the threshold of activation of the receptors but it does not modify the slope of the stimulus-response curve once the activation is obtained. Thus, variations in the stimuli intensity (the sympathetic activity) above the level of activation should induce the same alpha-adrenergic receptor response in presence or in absence of the antagonist. Alternatively, it may be that the doses of prazosin that are clinically effective

exert their alpha-adrenergic blocking action only on a limited number of the alpha-receptor population. The unaffected receptors would remain under the influence of the sympathetic nerves and may be sufficient for mediating normal cardiovascular responses when sympathetic activity is either reduced or increased.

Our observations with prazosin have favorable implications for the clinical use of the drug. Preservation of normal pressor responses to excitatory stimuli such as exercise means that circulatory homeostasis is preserved while peak pressure values during exertion are nonetheless lower than before therapy, being superimposed upon a lower resting level. Also, preservation of the depressor response to baroreceptor stimulation points to the integrity of an important inhibitory influence on the sympathetic vasoconstrictor activity, which would protect subjects under prazosin treatment in the event of sudden rises in arterial BP. Finally, preservation of the pressor response to

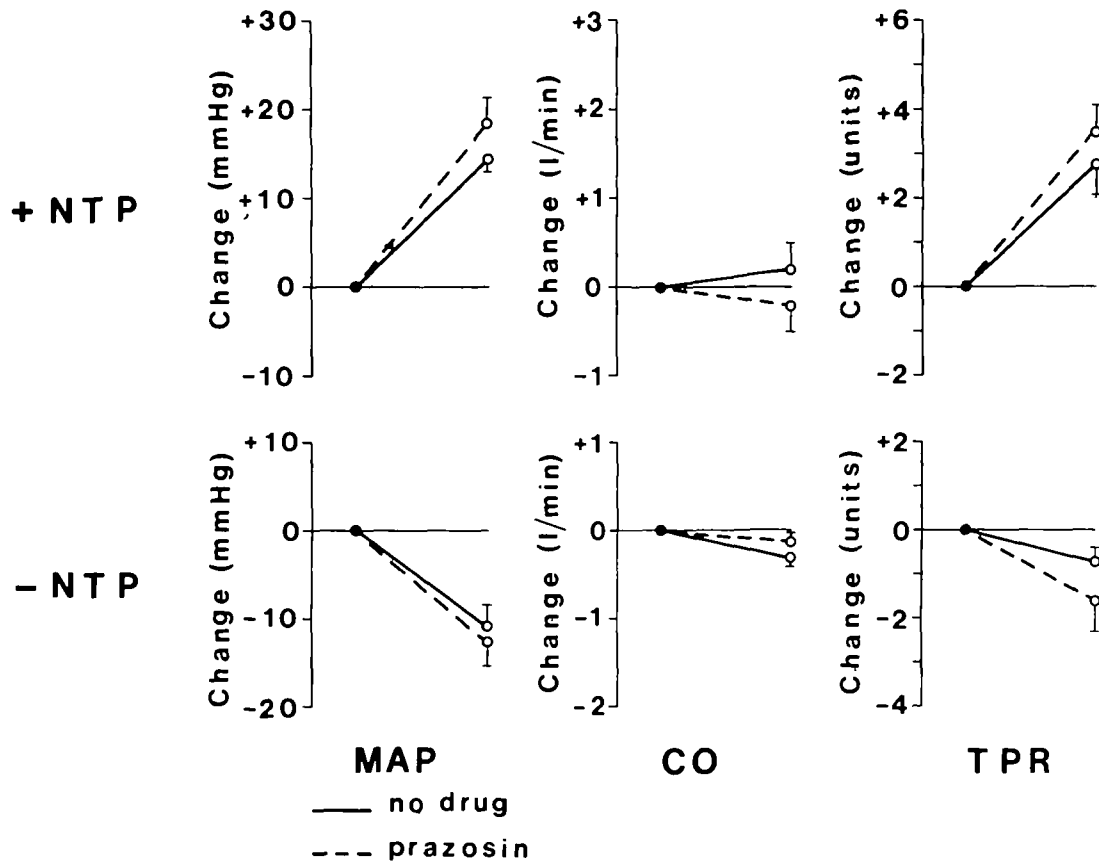


FIGURE 5. Effects of decreasing and increasing carotid baroreceptor activity on mean arterial pressure (MAP), cardiac output (CO), and total peripheral resistance (TPR). Data are shown as mean changes (\pm SE) from values and were collected by measurements performed in the last 10 seconds of the alterations in neck tissue pressure described in figure 4. Symbols as in figure 4. Increase in TPR with reduction in baroreceptor activity was significant at $p < 0.01$. Decreases in CO and TPR with increase in baroreceptor activity were significant at $p < 0.02$. Responses to baroreceptor manipulation before and during prazosin were not significantly different.

baroreceptor deactivation would be instrumental in maintaining a satisfactory BP homeostasis on standing. Indeed, in our patients under prazosin we have not found any significant fall in BP on the upright posture. Orthostatic reactions have been described in patients under prazosin but only early in the course of the treatment when too large initial doses were used (first dose effect²²).

A final comment concerns the effects of prazosin administration under resting conditions. Our data, based on a large number of measurements, show that the hypotensive effect of this drug is due to systemic vasodilatation and that there is no significant change in cardiac output. This confirms previous findings^{2, 23, 24} that have also shown that prazosin dilates an activation on the arterial and the venous side of the systemic circulation, and that this provides a balanced reduction in the preload and afterload of the heart, thus maintaining its output constant.²⁵⁻²⁹

Our findings also agree with previous studies that the hypotension induced by this drug is not accom-

panied by an increase in heart rate and renin release.^{2, 23-29} These are intriguing features of prazosin, as reduction in BP by vasodilatation and/or blockade of alpha-adrenergic receptors should induce a reflex increase in both these variables.³¹ Several possible explanations have been advanced: 1) prazosin enhances baroreceptor reflexes and keeps unaltered their inhibitory influence on the sinus node and the juxtaglomerular cells in spite of the lower BP;³² 2) prazosin blocks postsynaptic alpha-receptors and leaves unaltered presynaptic alpha-receptors, the function of which is to moderate the output of norepinephrine from the nerve terminals;³³ 3) prazosin exerts a negative chronotropic effect;³⁴ and 4) prazosin reduces the Bainbridge reflex, which is the influence of volume receptors located in the heart, the stimulation of which induces tachycardia in animals.³⁵ However, that prazosin enhances the baroreflexes is made unlikely by our results that the carotid sinus reflex is left unmodified by the drug. Also unlikely seems to us the explanation based upon preservation of presynaptic

alpha-receptors, as such preservation does not prevent heart rate and renin secretion from occurring with vasodilator agents such as hydralazine. Furthermore, one might expect that preservation of moderating presynaptic receptors during prazosin administration should reduce the pressor and tachycardiac responses to excretion and other excitatory stimuli, which is contrary to what we have observed. The possibilities that prazosin has a negative chronotropic effect or acts on the Bainbridge reflex are both attractive. It must be emphasized, however, that they might provide an explanation for the lack of tachycardia and not for the lack of renin stimulation during treatment with prazosin.

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