Hemodynamic and Neuroendocrine Responses to Acute and Chronic Alpha-adrenergic Blockade with Prazosin and Phenoxybenzamine

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SUMMARY We investigated the relevance of the selective α₁-adrenergic receptor blockade produced by prazosin to its blood pressure-lowering efficacy in man. The hemodynamic and neuroendocrine responses to the acute and chronic oral administration of prazosin and phenoxybenzamine were compared in a randomized, double-blind, placebo-controlled, crossover study of 11 patients with essential hypertension. These responses were also evaluated during lower body negative pressure and dynamic bicycle exercise, which produce potent but diversified activation of the sympathetic nervous system. In the acute studies, arterial blood pressure decreased to similar levels with prazosin or phenoxybenzamine; however, hemodynamic and neuroendocrine responses differed both before and during sympathetic nervous system activation. Prazosin lowered arterial blood pressure by reducing total peripheral resistance (p < 0.05). In contrast, phenoxybenzamine produced a modest reduction in cardiac output (8%, p < 0.05) with little change in total peripheral resistance, forearm vascular resistance or forearm blood flow. Additionally, plasma norepinephrine concentration and heart rate rose to significantly higher levels with prazosin (p < 0.02) than with phenoxybenzamine, a difference that was most evident with lower body negative pressure or dynamic exercise. Baroreceptor control of arterial pressure homeostasis was preserved with both agents, except during marked degrees of cardiovascular stress. With chronic therapy, the circulatory responses adapted to the α₁-adrenergic antagonists, and both drugs produced similar hemodynamic and neuroendocrine profiles. The differences with acute administration may be the result of a more rapid onset of action and a more marked degree of α₁-adrenergic blockade with prazosin than with phenoxybenzamine therapy, rather than to any difference in their α₁- and α₂-adrenergic receptor blocking properties. Moreover, the findings of the present study suggest that the prejunctional α₂-receptor, autoinhibitory to sympathetic neuronal norepinephrine release, is of no functional significance in patients with essential hypertension.

SINCE their introduction in the 1950s, α₁-adrenergic antagonists have fallen into disrepute as therapeutic agents for the treatment of essential hypertension because of intolerable side effects such as tachycardia, postural hypotension and impotence and because of their weak antihypertensive effects. Prazosin, a recently developed α₁-adrenergic antagonist, is an effective antihypertensive agent that chronically produces little change in heart rate, cardiac output and renin release. The absence of reflexogenic effects with this agent may be explained by the finding in animal studies that prazosin blocks only α₁-adrenergic receptors, which mediate vasoconstriction, and not α₂-adrenergic receptors, which control stimulus-induced norepinephrine release from sympathetic nerve terminals. Thus, with prazosin, it has been postulated that prejunctional α₂-adrenergic receptors remain functional and prevent the disproportionate increase in norepinephrine release, heart rate, cardiac output and renin release that counteract the antihypertensive effects of less selective antagonists, such as phenoxybenzamine and phentolamine. However, the hemodynamic and neuroendocrine effects of prazosin and those of conventional α₁-adrenergic antagonists have not been compared in man.

In the present study, the hemodynamic and neuroendocrine responses to the acute and chronic administration of prazosin and phenoxybenzamine were compared using a randomized, placebo-controlled, double-blind, crossover design. Although phentolamine blocks α₂-adrenergic receptors more potently...
than phenoxybenzamine, the latter agent was selected for comparison with prazosin because phentolamine has a very short duration of action and in the usual clinical doses produces only moderately effective α-adrenergic receptor blockade, and because animal studies clearly indicate that phenoxybenzamine is a less selective α₁-adrenergic antagonist than prazosin, and in doses that inhibit vasoconstrictor responses, it also blocks prejunctional α₂-adrenergic receptors. The antihypertensive and neuroendocrine effects of prazosin and phenoxybenzamine, evaluated on an outpatient basis, have been reported. In this report, we describe the hemodynamic and neuroendocrine responses associated with the acute and chronic administration of these α-adrenergic antagonists. These responses were evaluated in a cardiovascular laboratory before and during two forms of cardiac stress: lower body negative pressure (LBNP) and dynamic bicycle exercise.

Patients and Methods

Eleven patients (five females and six males), ages 25–63 years, with mild essential hypertension (World Health Organization hypertension grades I or II; diastolic arterial pressures 95–115 mm Hg on three separate occasions) were studied. Criteria for selection, baseline investigations and patient characteristics were as described previously. All subjects gave written, informed consent. The study was approved by the Human Research Review Committee, University of Texas Health Science Center at Dallas.

Protocol

The study consisted of four 4-week periods (fig. 1). After an initial placebo period, the patients were randomly allocated to receive either prazosin or phenoxybenzamine. After a second placebo period, the patients received the alternate medication. Prazosin was commenced at 1 mg three times daily and phenoxybenzamine at 10 mg/day. These doses were increased at weekly intervals to 6, 12 and 15 mg/day or 20, 30 and 40 mg/day, respectively, until the average of the supine and standing diastolic arterial pressures was < 90 mm Hg, or until side effects developed. Two placebo capsules were dispensed during both placebo periods. One of these placebos was continued along with the active drug in periods 2 and 4. Doses of prazosin and phenoxybenzamine after 4 weeks of therapy were 11.5 ± 0.8 and 32.5 ± 3.3 mg/day, respectively.

The hemodynamic and neuroendocrine responses to placebo and to the acute administration of one or the other of the active drugs (prazosin, 1 mg; phenoxybenzamine, 10 mg) were evaluated at the end of the first placebo period. The responses to the acute administration of the alternate active medication were evaluated at the end of the second placebo period. The chronic hemodynamic and neuroendocrine responses to the α-adrenergic antagonists were assessed at the end of the respective periods of active medications.

Plasma volume was measured at the end of each placebo and active medication period using Evans blue dye. Blood volume was calculated from the plasma volume and a simultaneously determined hematocrit.

![Figure 1](http://circ.ahajournals.org/)

**FIGURE 1.** Study protocol. PNE = plasma norepinephrine; PE = plasma epinephrine; PRA = plasma renin activity; LBNP = lower body negative pressure; CO = cardiac output; BP = blood pressure; HR = heart rate; TPR = total peripheral resistance.
using the equation \[ BV = PV/1 - (Hct \cdot 0.96 \cdot 0.91/100), \] where \( BV \) = blood volume, \( PV \) = plasma volume and \( Hct \) = peripheral venous hematocrit.

**Hemodynamic Studies**

Two forms of cardiovascular stress were examined: LBNP, which provides a controlled degree of venous pooling into the legs with reduced cardiac output and stroke volume and stimulation of both carotid and cardiopulmonary baroreceptors; and dynamic exercise, which provides a more generalized activation of the sympathetic nervous system.

LBNP was produced with an airtight tank sealed at the level of the iliac crests. Dynamic exercise was performed on a mechanically braked bicycle ergometer (Monark). Intermediate and maximal work loads were determined for each patient from a maximal stress test performed before entry into the study. For these stress tests, 3-4-minute stages of graded bicycle exercise were carried out until the patient could not continue because of fatigue.

The patients were familiarized with the laboratory procedures to minimize the influence of psychological stress. Each study was performed between 9:30 a.m. and noon. After an indwelling heparin lock was inserted into an antecubital vein, the patient was positioned in the LBNP tank and hemodynamic variables were allowed to stabilize for 30 minutes. With the acute studies, a placebo or active medication was then administered and LBNP commenced 30 minutes thereafter. LBNP was induced to levels of \(-8, -16, -32\) and \(-40\) mm Hg, according to standard NASA protocol. With the chronic studies LBNP was commenced 30 minutes after the patient was positioned in the tank.

After LBNP, an interval of 30 minutes was allowed to elapse before the dynamic exercise studies were commenced. Preexercise cardiac output, blood pressure and heart rate were recorded with the subject sitting on the bicycle. Exercise was then performed until the predetermined intermediate and maximal work loads were achieved. These work loads produced heart rates of approximately 120 and 160 beats/min, respectively, during the presudy stress test.

**Hemodynamic and Neuroendocrine Measurements**

Indirect arterial blood pressure was determined semiautomatically every 5 minutes throughout the studies (Narco Bio-Systems Electro-Sphygmonanometer PE-300) and beat-to-beat heart rate (Quinton Cardiotachometer, model 611) and ECG (Frank orthogonal leads) were recorded and displayed continuously. Mean arterial blood pressure was determined by adding the diastolic blood pressure to one-third of the pulse pressure. Cardiac output was determined before and at the \(-16\) and \(-40\) mm Hg levels of LBNP, and before and at the intermediate and maximal work loads with dynamic exercise, using an acetylene rebreathing technique as previously described. Oxygen consumption was also measured during the cardiac output studies. Total peripheral resistance was calculated by dividing the mean arterial pressure by the cardiac output and multiplying by 80 to convert to dyn-sec-cm\(^{-5}\). Forearm blood flow was measured by venous occlusion plethysmography with a specially designed air-filled latex cuff. Forearm vascular resistance was calculated in units by dividing the mean arterial pressure by forearm blood flow (ml/100 ml/min). Calf volume changes were determined by a mercury-in-Silastic Whitney strain gauge placed around the calf at its maximal girth. Changes in calf circumference were converted to the equivalent volume change in the section of calf under the strain gauge. Leg-volume changes were calculated as total leg volume multiplied by the percent change in calf volume. Multiple circumferences and a modified Simpson's rule were used to obtain total leg volume.

Plasma norepinephrine concentration and plasma renin activity were determined by radioenzymatic assay and radioimmunoassay, respectively, as previously described.

**Statistical Analyses**

Results are expressed as the mean ± SEM. Data were analyzed using computer programs for parametric analysis of variance and Duncan's multiple-range test for differences between groups, and analysis of variance and Newman-Keul's multiple comparisons for differences between linear regression analyses.

**Results**

**Lower Body Negative Pressure**

**Placebo**

Mean arterial pressure, cardiac output, heart rate and total peripheral resistance remained unchanged during the 30-minute stabilization period after placebo (table 1). Graded increases in LBNP resulted in progressive pooling of blood into the lower limbs, as evidenced by the increases in leg volume (fig. 2). At \(-40\) mm Hg LBNP, leg volume had increased by 4\%, from \(16.2 ± 0.9\) to \(16.9 ± 1.01\) (\(p < 0.01\)) (fig. 2). The central hypovolemia resulting from the induction of negative pressure was associated with progressive decreases in cardiac output and stroke volume from \(5.0 ± 0.4\) ml and \(73 ± 6\) at rest to \(3.4 ± 0.2\) l/min (\(p < 0.01\)) and \(42 ± 4\) ml (\(p < 0.025\)) at \(-40\) mm Hg.

**Table 1. Hemodynamic Responses to Placebo Administration in Patients Resting in the Supine Position for 30 Minutes Before the Induction of Lower Body Negative Pressure**

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Time (min)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-30</td>
<td>-15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>108 ± 4</td>
<td>107 ± 4</td>
<td>106 ± 3</td>
<td></td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>4.8 ± 0.5</td>
<td>5.2 ± 0.6</td>
<td>5.0 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Total peripheral resistance (dyn-sec-cm(^{-5}))</td>
<td>1802 ± 179</td>
<td>1713 ± 141</td>
<td>1785 ± 155</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71 ± 4</td>
<td>68 ± 3</td>
<td>70 ± 3</td>
<td></td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>69 ± 7</td>
<td>75 ± 4</td>
<td>73 ± 6</td>
<td></td>
</tr>
</tbody>
</table>

*Values are means ± SEM; temporal differences are not significant for any of the variables.
LBNP, respectively. When LBNP was reduced to −32 mm Hg, mean arterial pressure remained stable (fig. 2) due to a compensatory increase in sympathetic nerve activity, as evidenced by the increases in plasma norepinephrine concentration, heart rate and total peripheral resistance, from 320 ± 26, 70 ± 3 and 1785 ± 155 at rest to 467 ± 28 pg/ml (p < 0.05), 83 ± 4 beats/min (p < 0.05) and 2517 ± 183 dyn-sec-cm⁻² (p < 0.01) at −40 mm Hg, respectively (figs. 2 and 3). Forearm vascular resistance increased by 43% (p < 0.001) and forearm blood flow decreased by 32% (p < 0.05) (fig. 2). Despite these compensatory changes, mean arterial pressure fell by 4% at −40 mm Hg, from 106 ± 3 to 101 ± 3 mm Hg (p < 0.05). Plasma renin activity was 0.97 ± 0.33 ng A₁/ml/hour at rest and 1.24 ± 0.4 ng A₁/ml/hour at −40 mm Hg LBNP (p > 0.1).

**Prazosin and Phenoxybenzamine**

**Acute.** Mean arterial pressure decreased from 106 ± 3 to 95 ± 3 mm Hg 30 minutes after prazosin (p < 0.002) and from 106 ± 3 to 97 ± 3 mm Hg 30 minutes after phenoxybenzamine (p < 0.005).

When LBNP was reduced to −32 mm Hg, mean arterial pressure did not change in the phenoxybenzamine-treated patients, but decreased 18% at −40 mm Hg LBNP, to 80 ± 6 mm Hg (p < 0.02), a significantly greater reduction than that with the same degree of LBNP after placebo (4%, p < 0.02). After prazosin, mean arterial pressure fell progressively with increasing LBNP to 80 ± 5 mm Hg (16%, p < 0.002) at −40 mm Hg LBNP. The hemodynamic and neuroendocrine responses associated with these changes in arterial pressure differed for prazosin and phenoxybenzamine.

Prazosin decreased total peripheral resistance (p < 0.05) and forearm vascular resistance (p < 0.05) at rest and attenuated the LBNP-induced increases in these values (fig. 2). Forearm blood flow at rest in-
increased after prazosin and was maintained at higher levels after the induction of LBNP than after placebo (F = 0.31, NS, slopes; Q = 4.93, p < 0.005 for the intercepts of the linear regression lines relating forearm blood flow to levels of LBNP). These hemodynamic changes were associated with activation of the sympathetic nervous system, as evidenced by the higher plasma norepinephrine concentration (p < 0.02) and heart rate after prazosin than after placebo (figs. 2 and 3), although the increases in heart rate were of marginal significance (0.05 < p < 0.1). The plasma norepinephrine concentration after prazosin was also higher than that after phenoxybenzamine (p < 0.05, at each level), and at −40 mm Hg LBNP, the difference between the drug-induced changes in heart rate was significant (p < 0.05). The prazosin-induced changes in cardiac output, stroke volume and leg volume before and during LBNP were similar to those after placebo (fig. 2). The values for plasma renin activity at rest and at −40 mm Hg LBNP were also not different after prazosin (1.0 ± 0.4 and 1.5 ± 0.5 ng A/ml/hour, respectively) than after placebo (p > 0.1).

In contrast to the responses to prazosin, total peripheral resistance, forearm vascular resistance and forearm blood flow were unchanged from placebo after phenoxybenzamine (fig. 2). With LBNP, the increase in total peripheral resistance was attenuated marginally (by 7% and 10% at −16 and −40 mm Hg LBNP, respectively), although the values for this measurement and for forearm vascular resistance and forearm blood flow at −40 mm Hg LBNP were not significantly different from those with the same degree of LBNP after placebo. Similarly, the phenoxybenzamine-induced changes in heart rate, stroke volume and plasma norepinephrine concentration before and after LBNP were similar to those after placebo. Phenoxybenzamine, however, reduced cardiac output by 8% (compared with the placebo value), which persisted with LBNP (fig. 2). At −40 mm Hg LBNP, cardiac output was significantly lower after phenoxybenzamine (3.1 ± 0.3 l/min) than after prazosin (3.8 ± 0.3 l/min, p < 0.05). With LBNP at −32 mm Hg, leg volume increased similarly after phenoxybenzamine, prazosin and placebo. At −40 mm Hg, the increase in leg volume (0.93 ± 0.19 l) was greater after phenoxybenzamine than after prazosin (0.67 ± 0.17 l, p < 0.05), but was not significantly different from the placebo response (0.74 ± 0.15 l). Plasma renin activity after phenoxybenzamine increased from 0.74 ± 0.2 at rest, to 1.12 ± 0.4 ng A/ml/hour at −40 mm Hg LBNP. These values were not significantly different from those for prazosin or placebo.

Chronic. The hemodynamic and neuroendocrine responses after 4 weeks of therapy with prazosin or phenoxybenzamine are compared with the placebo responses in figures 3 and 4. The responses after the chronic administration or prazosin were qualitatively similar to those after acute administration; although the changes in forearm blood flow and heart rate were now similar to the placebo effects, and forearm vascular resistance was significantly attenuated (p < 0.05) only at −40 mm Hg LBNP (fig. 4). Before LBNP, mean arterial pressure was reduced (p < 0.05) in all but one patient to 98 ± 4 mm Hg, a level similar to that after the acute administration of prazosin (95 ± 3 mm Hg). With LBNP, mean arterial pressure fell progressively to 85 ± 4 mm Hg (13%, p < 0.01). This reduction in mean arterial pressure was due to a 8% fall in total peripheral resistance at rest, relative to the placebo response, which increased to 19% (p < 0.01) at −40 mm Hg LBNP. Acute and chronic prazosin therapy induced similar changes in cardiac output, stroke volume, leg volume and plasma norepinephrine concentration before and during LBNP. Plasma renin activity was 1.1 ± 0.4 at rest and 1.2 ± 0.5 ng A/ml/hour (NS) at −40 mm Hg LBNP.

With chronic phenoxybenzamine therapy, mean arterial pressure was not significantly lower than the level after placebo (104 ± 5 vs 106 ± 3 mm Hg, respectively). This finding is consistent with the antihypertensive effects of this agent, as evaluated on an
outpatient basis; phenoxybenzamine, in contrast to prazosin, was ineffective in lowering the supine arterial pressure. In keeping with these changes in mean arterial pressure, total peripheral resistance and cardiac output at rest did not change during chronic phenoxybenzamine therapy. However, plasma norepinephrine concentration increased to 746 ± 129 pg/ml, a level significantly higher than that after placebo (330 ± 26 pg/ml, p < 0.001) or acute phenoxybenzamine (326 ± 27 pg/ml, p < 0.001). With LBNP, there was a slight, insignificant decrease in mean arterial pressure of 4% at 32 mm Hg and a more marked reduction of 18% (p < 0.001) at 40 mm Hg. These changes were associated with an attenuation of the LBNP-induced increases in total peripheral resistance (p < 0.05). Moreover, with chronic phenoxybenzamine therapy, the LBNP-induced increases in leg volume and plasma norepinephrine concentration were now similar to those after prazosin (figs. 3 and 4). Plasma renin activity was 0.7 ± 0.3 at rest and 0.8 ± 0.4 ng A/ ml/hour (NS) at 40 mm Hg LBNP with chronic phenoxybenzamine treatment.

Exercise

Placebo

The hemodynamic and neuroendocrine responses at rest, sitting and with intermediate and maximal upright bicycle exercise (average work loads of 150 and 450 kpm, respectively), after placebo administration, are shown in figure 5. Compared with the values at rest, dynamic exercise to intermediate and maximal levels resulted in 10% and 23% increases in mean arterial pressure (p < 0.005 in each case), 95% and 170% increases in cardiac output (p < 0.001) and 39% and 51% decreases in total peripheral resistance (p < 0.005), respectively. These hemodynamic changes were associated with progressive increases in oxygen consumption by 194% (p < 0.001) and 351% (p < 0.001), and activation of the sympathetic nervous system, as evidenced by 51% and 103% increases in heart rate (p < 0.001), and 200% and 377% increases in plasma norepinephrine concentration (p < 0.001). Plasma renin activity rose from 0.97 ± 0.3 to 2.01 ± 0.08 ng A/ ml/hour (p < 0.02) with maximal exercise. Increases in stroke volume of 28% (p < 0.05) and 31% (p < 0.01) were also observed with exercise to intermediate and maximal levels, respectively.

Prazosin and Phenoxybenzamine

Acute. After the acute administration of prazosin or phenoxybenzamine, the patients were subjected to degrees of exercise-stress similar to those induced after placebo. Thus, the exercise-induced changes in oxygen consumption during drug treatment with prazosin and phenoxybenzamine were similar to the placebo responses (fig. 5). The exercise-induced changes in cardiac output and stroke volume and in the neuroendocrine measurements were qualitatively similar to those observed after placebo. However, both drugs induced changes in mean arterial pressure that differed quantitatively from those after placebo. Thus, parallel shifts to the right were noted in the regression lines relating mean arterial pressure and work load (slopes, F = 0.41 (NS); intercepts, Q = 6.15, p < 0.005, prazosin vs placebo; Q = 4.19, p < 0.005, phenoxybenzamine vs placebo). These lower mean arterial pressure levels were a result of similar drug-induced reductions in total peripheral resistance (slopes of the regressions lines relating total peripheral resistance and work load, F = 0.95, NS; intercepts, Q = 3.92, p < 0.05, prazosin vs placebo; Q = 2.91, p < 0.05, phenoxybenzamine vs placebo), and not to changes in cardiac output or stroke volume (fig. 5).

The effects of prazosin and phenoxybenzamine on heart rate and plasma norepinephrine concentration differed. After prazosin, heart rate at rest and with exercise was higher than that after placebo or phenoxybenzamine, as evidenced by the parallel shift to the left of the regression lines relating work load and heart rate (slopes, F = 0.76, NS; intercepts, Q = 3.4, p < 0.05, prazosin vs placebo; Q = 2.9, p < 0.05, prazosin vs phenoxybenzamine). Similarly, plasma norepinephrine concentration after prazosin was higher at rest (56%, p < 0.05, placebo; 60%, p < 0.05, phenoxybenzamine) and with exercise to intermediate (52%, p < 0.05, placebo; 60%, p < 0.01, phenoxybenzamine) and maximal (103%, p < 0.01, placebo; 120%, p < 0.01, phenoxybenzamine) levels. The plasma renin activity at rest after prazosin or after phenoxybenzamine was not significantly different from that after placebo. However, with maximal exercise, plasma renin activity after prazosin increased to 3.6 ± 1.1 ng A/ ml/hour, a value significantly higher than that observed after phenoxybenzamine or placebo (1.4 ± 0.4 ng A/ ml/hour, p < 0.05 and 2.0 ± 0.8 ng A/ ml/hour, p < 0.05, respectively).

Chronic. As with the acute exercise studies, similar oxygen consumption values at rest and with exercise were observed after the chronic administration of prazosin or phenoxybenzamine (fig. 6). However, mean arterial pressure at rest was significantly lower after prazosin or phenoxybenzamine (105 ± 3, p < 0.05 and 100 ± 4 mm Hg, p < 0.05, respectively) than after placebo (112 ± 3 mm Hg), and remained below the placebo value (137 ± 3 mm Hg) with maximal exercise (127 ± 5, p < 0.05, prazosin; 117 ± 5 mm Hg, p < 0.01, phenoxybenzamine). These changes were due to a reduction in total peripheral resistance, as cardiac output and stroke volume at rest and with exercise were not significantly different after the α-adrenergic antagonists than after placebo (fig. 6). These chronic, drug-induced changes in total peripheral resistance, however, were less marked than in the acute studies and were of marginal statistical significance (0.05 < p < 0.1). Differences in the prazosin- and phenoxybenzamine-induced changes in heart rate, plasma norepinephrine concentration and plasma renin activity were also not evident in the chronic exercise studies. However, higher plasma norepinephrine values were observed at rest with the chronic administration of the α-adrenergic antagonists than with placebo (p < 0.01). These values remained elevated with exercise to intermediate (p < 0.01, with each drug) and maximal (p < 0.01) levels (fig. 6).
Plasma and blood volume (fig. 7) and body weight did not change with the chronic administration of prazosin or phenoxybenzamine.

**Discussion**

The hypothesis to be tested by these studies was that with comparable reductions in arterial pressure, phenoxybenzamine should result in greater increments in norepinephrine release and thus in heart rate, cardiac output and plasma renin activity, due to blockade of prejunctional \( \alpha_1 \)-receptors as well as postjunctional \( \alpha_2 \)-receptors, than prazosin. Moreover, with increased sympathetic activity, this difference between prazosin and phenoxybenzamine may be more apparent (table 2).

Clearly, these expected responses were not observed with either the acute or chronic administration of the \( \alpha \)-adrenergic antagonists, at rest or with activation of the sympathetic nervous system by LBNP or dynamic exercise. These findings, therefore, strongly suggest that \( \alpha_2 \)-receptor-mediated prejunctional control of sympathetic neurotransmission does not play a major role in circulatory homeostasis in patients with essential hypertension. Nevertheless, in the presence of multiple intact regulatory reflexes, one cannot ascribe particular hemodynamic and neuroendocrine responses to an isolated receptor-mediated effect. However, factors apart from the differential prejunctional \( \alpha_2 \)-blocking effects of prazosin and phenoxybenzamine, such as the norepinephrine uptake blocking effects of phenoxybenzamine or direct actions of the \( \alpha \)-adrenergic antagonists at the level of the adrenal medulla, are unlikely to account for the present observations.

Whether similar hemodynamic and neuroendocrine profiles would be observed with prazosin- and phenoxybenzamine-induced reductions in arterial pressure in normotensive subjects is unknown. With acute i.v. administration of the \( \alpha \)-adrenergic antagonists to normotensive rats, greater increments in plasma norepinephrine concentration and heart rate are observed with phenoxybenzamine than with prazosin. These and other in vivo studies suggest that the \( \alpha_2 \)-receptor-mediated prejunctional control of sympathetic neurotransmission may indeed be of functional significance in normotensive animals, although some issues in this regard remain unresolved. Therefore, in some patients with hypertension, there may be a defect in the prejunctional control of norepinephrine release,
which contributes to the development or maintenance of their elevated blood pressure. However, no evidence is available to support or refute such a postulate.

In the acute studies with the patients in the supine position, the hemodynamic profile associated with prazosin suggested that its antihypertensive effect was due to a reduction in arteriolar resistance vessel tone. Thus, mean arterial pressure fell as a consequence of a reduction in total peripheral resistance. In addition, forearm vascular resistance was reduced and forearm flow increased. Cardiac output was maintained with prazosin therapy due to a reflex increase in sympathetic nerve activity, as evidenced by the rise in plasma norepinephrine concentration and heart rate. As stroke volume did not increase in this situation, despite the reduction in afterload (systolic pressure) and the in-

![Figure 6. Mean arterial pressure (MAP), cardiac output (CO), stroke volume (SV), plasma norepinephrine concentration (PNE), total peripheral resistance (TPR), heart rate (HR), oxygen consumption (VO₂) and plasma renin activity (PRA) responses to the chronic administration of phenoxybenzamine or prazosin before and during dynamic exercise to intermediate and maximal work loads. Placebo effects shown in figure 5 are also shown here for comparison with the active drug responses. Symbols are as in figure 2.](image)

![Figure 7. Plasma and blood volumes determined after 4 weeks of therapy with prazosin or phenoxybenzamine and at the end of their respective placebo periods.](image)

**TABLE 2. Summary of Hemodynamic and Neuroendocrine Responses to Lower Body Negative Pressure and Dynamic Bicycle Exercise Observed During Placebo Administration**

<table>
<thead>
<tr>
<th>Variable</th>
<th>LBNP</th>
<th>Dynamic exercise</th>
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</thead>
<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>0 or −</td>
<td>+ +</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>− −</td>
<td>+ +</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>+ + +</td>
<td>− − −</td>
</tr>
<tr>
<td>Heart rate</td>
<td>+</td>
<td>+ + +</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>− −</td>
<td>+ or 0</td>
</tr>
<tr>
<td>Plasma norepinephrine</td>
<td>+</td>
<td>+ +</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>0 or +</td>
<td>+ +</td>
</tr>
</tbody>
</table>

*0, no change; +, increase; −, decrease.
crease in contractility (heart rate and catecholamines), it is likely that prazosin additionally reduced venous capacitance tone and cardiac preload. A similar potent reduction in resistance vessel tone was also evident when the patients were in the sitting position before and during the exercise studies; mean arterial pressure and total peripheral resistance were reduced, whereas cardiac output was maintained by the reflex increase in heart rate. Again in this situation, the finding that stroke volume did not change despite a reduction in afterload and an increase in cardiac sympathetic drive implies that prazosin additionally reduced preload. In contrast, prominent arteriolar vasodilating and reflexogenic effects were not evident with phenoxybenzamine administration. In the supine position, total peripheral resistance did not fall and the LBNP-induced increases in this variable were only marginally attenuated. Forearm vascular resistance and forearm blood flow also remained unchanged with phenoxybenzamine and in the absence of a compensatory increase in heart rate, cardiac output fell. In the sitting position, an arteriolar vasodilating effect was more evident. Thus, total peripheral resistance was reduced. However, increases in plasma norepinephrine concentration, heart rate and plasma renin activity to values above those observed with placebo, were not present.

These findings suggest that acutely, at dosages producing similar reductions in arterial pressure, prazosin potently antagonizes sympathetically mediated arteriolar vasoconstriction as well as reducing cardiac preload, whereas phenoxybenzamine induces only a modest reduction in arteriolar and venous tone. What causes these disparate effects is not known. Nevertheless, it is difficult to reconcile them on the basis of the differing α1- and α2-blocking potentials of prazosin and phenoxybenzamine. Rather, it seems likely that despite the comparable decreases in arterial blood pressure, prazosin, which is rapidly absorbed, produced a prompt and marked degree of α-adrenergic blockade and a brisk reflexogenic response. With phenoxybenzamine, which has a slow onset of action, the extent of α blockade was less complete. Such a mechanism could also explain why similar hemodynamic and neuroendocrine profiles were observed with the chronic administration of the α-adrenergic antagonists. Thus, with long-term therapy and the attainment of higher drug concentrations or the development of nonequilibrium blockade, phenoxybenzamine as well as prazosin may have produced a marked degree of α-adrenergic blockade. Indeed, with chronic therapy, both agents attenuated the LBNP-induced increases in total peripheral resistance and forearm vascular resistance and produced similar increases in plasma norepinephrine concentration.

Acute administration of equipotent antihypertensive doses of the two α-adrenergic antagonists produced different neuroendocrine and blood flow responses; with chronic administration, the responses were similar. Moreover, chronically, the reflex increase in heart rate with phenoxybenzamine was not greater than that with prazosin. Nevertheless, because of the differing acute responses, one may argue that the degree of α-adrenergic blockade produced by prazosin and phenoxybenzamine should have been quantitated by evaluating the potential for the α-adrenergic blockers to antagonize α-agonist-induced pressor responses. Such studies were not performed for we considered it unreasonable to burden the study subjects with these additional investigations. In addition, recent pharmacologic studies indicate that apart from autoinhibitory prejunctional α2 receptors, in some tissues there are postjunctional α2 receptors. In vascular tissue these α2 receptors, like α1 receptors, mediate vasoconstriction. Whether postjunctional α2 receptors are also present in human vascular tissue and the role of these receptors in circulatory homeostasis is unknown. In addition, animal studies indicate that postjunctional α2 receptors are intrasynaptic and respond to norepinephrine released by sympathetic nerve stimulation, whereas α1 receptors are extrasynaptic and respond to exogenously administered catecholamines. Therefore, quantitating the degree of α blockade by the administration of α-adrenergic agonists is difficult in vivo, even if selective α1- and α2-agonists are used.

Hemodynamic and neuroendocrine responses were similar in the acute and chronic studies with prazosin. Nevertheless, the tendency for heart rate and plasma renin activity to increase with acute prazosin administration was not sustained in the chronic studies, despite persistent large increases in plasma norepinephrine concentration and a sustained decrease in arterial blood pressure. The explanation for these responses and for the smaller reduction in forearm vascular tone with chronic prazosin therapy is unclear, but is consistent with the findings of clinical studies that compared the first-dose effects of prazosin with prolonged therapy. Semplicini et al. reported that plasma volume expansion reduces the first-dose effects of prazosin, whereas Koshy et al. reported increases in plasma volume in some, but not all, patients treated with prazosin. On the basis of these findings and previous investigations, we felt that the cardiovascular adaptation with prolonged prazosin therapy may be due to plasma volume expansion. However, plasma volume, blood volume (fig. 7) and body weight did not change significantly with either prazosin or phenoxybenzamine therapy.

Although prazosin and phenoxybenzamine produced differing hemodynamic and neuroendocrine profiles, particularly acutely, the pressor and cardiovascular effects of dynamic exercise were qualitatively unaltered by the α-adrenergic antagonists, despite a reduction in arterial pressure. Similarly, appropriate hemodynamic and neural responses were observed with all but the most marked degrees of LBNP. Both types of cardiovascular stress were accompanied by activation of the sympathetic nervous system and α-adrenergic receptors. This activation is of paramount importance in modulating peripheral vasomotor responses, either by causing vascular resistance to increase during LBNP or by modulating the systemic impact of metabolically induced vasodilation in skel-
et al muscle that occurs with dynamic exercise. The preservation of qualitatively normal cardiovascular responses with these potent cardiovascular stimuli, therefore, provides indirect evidence that neither prazosin nor phenoxybenzamine markedly interferes with the carotid or cardiopulmonary baroreceptor control of arterial pressure.

Mancia et al. described similar findings for prazosin. They noted that the maintenance of normal baroreceptor control mechanisms is of considerable therapeutic importance. Integrity of pressor responses with exercise means that circulatory homeostasis is preserved while arterial pressure, both at rest and with exertion, is nonetheless reduced. Moreover, the preservation of normal baroreceptor-mediated pressor responses ensures the maintenance of adequate arterial pressure on standing. Orthostatic hypotension has been described with prazosin, but is uncommon unless therapy is initiated with large doses or unless there is a preexisting impairment of baroreceptor function, as in the elderly.

In conclusion, acute administration of the \(\alpha_1\)-selective antagonist prazosin to patients with essential hypertension results in hemodynamic and neuroendocrine responses that differ from those observed with equihypotensive doses of the less selective antagonist phenoxybenzamine. This difference may be due to a more rapid onset of action with prazosin, which results in a more marked degree of arteriolar \(\alpha\)-adrenergic blockade, rather than to a difference in their \(\alpha_1\) and \(\alpha_2\)-adrenergic receptor blocking propensities. With chronic administration of the \(\alpha\)-adrenergic antagonists, as occurs clinically, the hemodynamic and neuroendocrine responses to both prazosin and phenoxybenzamine are similar.

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References

Origin of the Third Heart Sound
I. Studies in Dogs

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SUMMARY We studied 13 anesthetized dogs in which a third heart sound (S₃) was repeatedly induced by hypoxemia plus fluid overload. A miniature accelerometer with a mass of about 1.1 g was applied at three levels — intact chest wall over cardiac apex, on the pericardium and on the epicardium — to record motion of the structures under observation as well as sound. Intraventricular pressure and sound were monitored using a Millar catheter. Application of two accelerometers simultaneously over the epicardium permitted observation of the chronologic sequence of ventricular wall dynamics in early diastole. The S₃ at each level occurred simultaneously with the sudden onset of reduced acceleration, or negative jerk. These dynamic phenomena were maximal at or near the cardiac apex. We conclude that the event that triggers the S₃ is a sudden intrinsic limitation of longitudinal expansion of the left ventricular wall.

THE THIRD HEART SOUND (S₃) is an important physical sign which, when found in a patient with a failing heart, is regarded empirically as a poor prognostic sign. Early diastolic sounds are regularly found in normal children as well as in diastolic overload conditions and constrictive pericarditis.

The physiologic basis of the S₃ remains controversial. The sound is most widely attributed to a termination of rapid filling at the moment that the elastic limit of the ventricular chamber is reached.¹ ² Two other theories attribute the sound to a valvular event³ ⁴ or to extracardiac factors — the impact of the heart against the chest wall.⁵

The ventricular distention theory has been challenged by the observation of Prewitt et al.,⁶ who, using digitized measurements of the transverse diameter of the left ventricle as perceived by M-mode echocardiography, could not find any aspect of filling that could reproducibly and consistently be related to the appearance of an S₃.

Our studies⁷ using cineangiography have shown that in diastolic overload conditions, the achievement of maximum velocity and deceleration occurred later in the long axis than in the transverse or short axis, which was the only dimension that had been available to Prewitt et al.⁸ using M-mode echocardiography. Our cineangiographic studies indicate that in diastolic overload, long-axis filling movement may be paramount in genesis of the S₃.

The importance of valvular events in the genesis of the S₃ is controversial. Some authors have reported disappearance of the sound when the mitral valve is replaced by a prosthesis⁹,¹⁰ and others have noted persistence of the sound following this operation in cases where valvular incompetence has occurred.¹¹ ¹² The chest wall impact or tapping theory recently proposed by Reddy et al.⁷ is based on their observation that the intensity of the sound at the chest wall is much greater than any pressure vibration elicited from within the ventricular cavity.

We report a controlled canine experiment in which an S₃ was produced by a combination of hypoxemia and fluid overload. The sound was tracked from its manifestation on the chest wall through several layers to its source, which we believe is the wall of the left ventricle.

Materials and Methods

Thirteen mongrel dogs that weighed 23–35 kg were anesthetized with i.v. sodium pentobarbital. Respiration was controlled with a ventilator with intermittent positive pressure after endotracheal intubation. The

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