α₁-Adrenergic Blockade and Cardiovascular Pressor Responses in Essential Hypertension

CARLO BERETTA-PICCOLI, CLAUDIA FERRIER, AND PETER WEIDMANN

SUMMARY The effects of selective α₁-adrenergic blockade with terazosin on blood pressure and cardiovascular pressor responsiveness were assessed in 17 subjects with mild to moderate essential hypertension (mean age, 48 ± 2 [SEM] years). As compared with a 2-week placebo period, 8 weeks of terazosin treatment (mean dose, 10.5 ± 1.7 mg/day) caused a fall of supine (from 153/103 ± 3/2 to 143/96 ± 4/2 mm Hg; p < 0.025) and upright (from 145/106 ± 4/2 to 131/94 ± 5/3 mm Hg; p < 0.01) arterial pressure; a marked blunting of cardiovascular pressor responsiveness to norepinephrine, as judged from the pressor dose (from 73 ± 9 to 2156 ± 496 ng/kg/min; p < 0.02) and from the rightward shift (p < 0.01) of the plasma concentration–blood pressure response curve; and a slight increase in plasma norepinephrine concentration (from 37.7 ± 3.3 to 52.2 ± 7.8 ng/dl; p < 0.01). Heart rate, body weight, exchangeable sodium, blood volume, and norepinephrine plasma clearance; plasma epinephrine, renin, angiotensin II, and aldosterone levels; the relationships between angiotensin II-induced increases in arterial pressure or plasma aldosterone and the concomitant increments of plasma angiotensin II; and heart rate responsiveness to isoproterenol did not change significantly after terazosin treatment. These findings suggest that the fall of arterial pressure induced by selective α₁-adrenergic blockade in subjects with essential hypertension is associated with, and probably explained by, inhibition of α₁-mediated, noradrenergic-dependent vasoconstriction. α₁-Adrenergic receptor antagonism did not modify body sodium concentration, the adrenomedullary component of the sympathetic nervous system, angiotensin II levels, or ß-adrenergic dependent mechanisms.

KEY WORDS • terazosin • essential hypertension • α₁-adrenergic receptors • norepinephrine • cardiovascular pressor responsiveness • body sodium • plasma renin activity • aldosterone • cardiac ß-adrenergic receptor response

TERAZOSIN is a new quinazoline compound with sympatholytic activity mediated by selective postsynaptic α₁-adrenergic blockade1,2 and with a long-lasting hypotensive effect.3 Given in one daily dose, this agent exhibited marked hypotensive efficacy over 24 hours in five patients with mild to moderate essential hypertension.4 This long-lasting action may represent an important advantage over established α₁-antagonists.5

Although α₁-adrenergic blockade is a well-established pharmacological tool in the treatment of hypertension, the effects of terazosin or related compounds on cardiovascular homeostasis under conditions of stable pharmacological intervention are not known. In experimental animals, α₁-adrenergic inhibition is associated with a marked decrease of vascular reactivity to norepinephrine (NE).6 In humans, the cardiovascular pressor responsiveness to norepinephrine is largely modulated by the endogenous sympathetic activity,7 but the impact of α₁-antagonists on this physiological relationship has not been investigated. This question could be relevant in patients with essential hypertension, in whom an exaggerated pressor responsiveness to norepinephrine relative to plasma norepinephrine concentration has been noted.7,8 Moreover, since the sympathetic nervous system participates in the control of multiple blood pressure regulating systems, such as body sodium–blood volume homeostasis9 and the renin-angiotensin-aldosterone axis,10 a concomitant evaluation of these parameters is important for a comprehensive assessment of cardiovascular effects.

To extend our knowledge of cardiovascular regulation during selective α₁-adrenergic inhibition, the influence of the new compound terazosin on endogenous sympathetic activity, cardiovascular pressor respon-
siveness to norepinephrine, β-adrenergic sensitivity, body sodium and blood volume, and pressor or aldosterone responsiveness to angiotensin II (ANG II) in relation to basal activity of the renin-angiotensin system was studied in subjects with essential hypertension.

Subjects and Methods

The study group comprised 22 subjects (9 women, 13 men), aged 31 to 62 years (mean age, 48 ± 2 [± SEM] years), with mild to moderate essential hypertension. The presence of hypertension was defined by obtaining repeated blood pressure measurements between 140/90 and 180/115 mm Hg under outpatient conditions. Secondary forms of hypertension were excluded by the usual tests; no subject had malignant hypertension (hypertensive retinopathy Stages III–IV), edema, arrhythmia, or heart failure. All antihypertensive drugs and potassium supplements were discontinued at least 4 weeks before the study began. None of the women were taking hormonal contraceptives. Informed consent was obtained from all subjects, and the study protocol was approved by the ethical committee of our institution.

The subjects were instructed to eat a normal diet, avoiding very high or low sodium intake. A placebo was given for 2 weeks and was then replaced by active terazosin, given once a day for 4 weeks at increasing doses of 2, 5, 10, and 20 mg; each increment was given for 1 week. Maximal doses were then continued for another 4 weeks. To evaluate dose-related efficacy, maximal doses were fixed at random and were 2 mg for four subjects and 5, 10, and 20 mg for six subjects each. Compliance was assessed by pill counts and was defined as ingestion of at least 90% of the prescribed tablets.

During terazosin therapy, subjects’ blood pressure and heart rate were measured after 10 minutes of rest in the supine position and after 2 minutes in the upright position at the end of Weeks 1, 2, 3, 4, and 6 of treatment; these measurements were performed at least 12 hours after the last terazosin dose. During the last 4 days of the placebo and terazosin treatments, the following measurements were performed. A 24-hour urine collection was made for determination of sodium, potassium, creatinine, NE, and epinephrine excretion rates. Blood pressure was obtained using a standard cuff and sphygmomanometer; each value was the mean of three readings. Heart rate, exchangeable sodium, blood volume, and plasma sodium, potassium, creatinine, renin activity, aldosterone, NE, and epinephrine levels were determined the morning after an overnight fast and after 1 hour of recumbency.

Blood pressure, heart rate, plasma renin activity, and aldosterone, NE, and epinephrine levels were remeasured after the subjects had spent 1 hour walking. After emptying the bladder, subjects rested in the supine position. A 5% dextrose solution was infused over 20 minutes, and an isoproterenol injection was calculated from the three shortest RR intervals.

To test subjects’ pressor or aldosterone responsiveness, NE and ANG II were infused intravenously 1 to 3 days after the isoproterenol sensitivity test. After an overnight fast, subjects took the usual morning dose of placebo or terazosin. A 60-minute equilibration period with low intravenous infusion of 5% dextrose with subjects in the supine position, blood samples were taken between 0800 and 0930 for the measurement of basal blood pressure, heart rate, and plasma NE and epinephrine levels. The dextrose solution was then replaced by a solution of J-NE bitartrate in 5% dextrose, which was infused at stepwise increasing dose rates of approximately 20, 40, 100, and 200 ng/kg/min lasting 20 minutes each. During the last 10 minutes of each infusion step, blood pressure and heart rate were recorded every minute using a cuff and the automatic recorder Sphygmodigital 4000 (Asulab S.A. Neuenburg, Switzerland). At the end of each infusion step, plasma NE and epinephrine levels were measured. The NE solution was then replaced by 5% dextrose, which was infused for 60 minutes at a constant rate of 6 ml/hr. At the end of this second equilibration period, basal blood pressure, heart rate, plasma renin activity, and ANG II and aldosterone levels were determined. The dextrose infusion then was replaced by a solution of ANG II (Hypertensin, Ciba-Geigy, Basle, Switzerland) in 5% dextrose, which was infused at increasing dose rates of 2, 4, 10, and 20 ng/kg/min lasting 20 minutes each. Blood pressure and heart rate were monitored as just described above, and plasma ANG II and aldosterone levels were determined at the end of each ANG II infusion step.

Plasma and urinary sodium and potassium concentrations were measured by flame photometer. Creatinine concentration was measured by autoanalyzer. Plasma renin activity, aldosterone, and ANG II were measured by radioimmunoassay, and plasma or urinary NE and epinephrine concentrations were obtained using a radioenzymatic method, as reported previously. Exchangeable sodium and blood volume were measured by isotope dilution technique using 24Na and 125I-human serum albumin, respectively.

Cardiovascular responsiveness was analyzed as follows. Concentration-response curves were derived by relating the increases in mean (NE infusion) or diastolic (ANG II infusion) arterial pressure to the blood levels of NE or ANG II, respectively. Dose-response curves were calculated by relating mean (NE infusion) or diastolic (ANG II infusion) blood pressure to infused dose rates. A regression analysis was calculated using the data points lying on the steep part of the curve and pressor doses were derived as the NE or ANG II dose rates required to elevate arterial pressure.
by 20 mm Hg (ED_{BP+20}; ED = effective dose; BP = blood pressure). Based on the previous demonstration of stable plasma NE or ANG II levels at the end of a 20-minute infusion period at a given rate,^{22\textendash}25 the total plasma clearance of infused NE or ANG II was estimated by dividing the infused dose rates with the associated increases in plasma concentration of these agents.^{24} Plasma levels obtained at the end of each infusion step were used to calculate a single clearance; values used for analysis were the mean of at least three clearances obtained during consecutive infusion periods. The chronotropic isoproterenol dose was derived from the dose-response curve relating isoproterenol-induced increments of heart rate to the isoproterenol doses. The regression line was calculated using data points, and the chronotropic dose was defined as the dose causing an increase in heart rate of 25 beats/min (ED_{HR+25}; HR = heart rate).^{26}

Since natural logarithmic transformation rather than absolute values followed a gaussian distribution, the natural logarithmic transformation of plasma renin activity; doses of infused NE, ANG II, or isoproterenol; ED_{BP+20} of NE or ANG II; and ED_{HR+25} of isoproterenol was used for statistical analysis. Statistical analysis included paired Student’s t test, regression analysis, and analysis of variance and covariance.

Results

Only 17 of the 22 subjects completed the 8-week treatment with terazosin. One subject was withdrawn because of poor compliance. Four asked to withdraw because of side effects, namely, palpitations and breathlessness shortly after terazosin intake in two subjects and diarrhea (1 subject) and marked postural fall of arterial pressure (1 subject) after the 5-mg dose. The 17 subjects who completed the study did not complain of major side effects and included five women and 12 men. These subjects were treated with terazosin doses of 2 (2 patients), 5, 10, and 20 mg (5 patients each); only data obtained from these 17 subjects were included in the following analyses.

As compared with placebo treatment, 8 weeks of terazosin treatment decreased arterial pressure; the fall tended to be more pronounced in the upright than in the supine position (Table 1). Terazosin did not modify exchangeable sodium, blood volume; plasma and urinary electrolytes; creatinine clearance; supine plasma NE; supine and upright plasma renin activity, aldosterone, or epinephrine levels; or urinary excretion of NE and epinephrine. Upright plasma NE levels was slightly increased (Table 2).

The response of heart rate to isoproterenol was investigated in 10 subjects (3 women and 7 men, aged 49 ± 2 years) treated with terazosin, 11.5 ± 1.5 mg/day (range, 5–20 mg/day). As compared with placebo treatment, the response of heart rate to isoproterenol bolus injections was not modified after terazosin, as judged by the mean isoproterenol chronotropic dose (ED_{HR+25}) and the slopes of the dose-response curves (Table 3).

The response to NE infusion was studied in 13 subjects (4 women and 9 men, aged 48 ± 2 years) treated with terazosin, 11.5 ± 1.5 mg/day (range, 5–20 mg/day). As compared with placebo conditions, mean basal (preinfusion) plasma NE and NE pressor dose (ED_{BP+20}) increased significantly after terazosin (see Table 3). However, the ED_{BP+20} of NE had to be extrapolated in nine terazosin-treated subjects, in whom arterial pressure elevation during NE infusion did not reach 15 mm Hg, thereby probably causing a certain degree of overestimation.

Under placebo conditions, the increase in blood pressure (+23 ± 2 mm Hg) during NE infusion at the highest dose rate was accompanied by a significant 8% decrease in heart rate (−5 ± 1 beats/min; p < 0.001). After terazosin treatment, the modest NE-induced increase in arterial pressure (+9 ± 1 mm Hg) was accompanied by a minimal (1.4%) decrease in heart rate (−1 ± 1 beats/min); the relationship between NE-induced increments in mean blood pressure and the corresponding variations in heart rate did not differ significantly between placebo and terazosin conditions (F = 0.91).

<table>
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<tr>
<th>Variable</th>
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<td>Supine</td>
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<td>149/96±4/3*</td>
<td>151/99±3/2*</td>
<td>148/97±4/2†</td>
<td>145/96±5*/3†</td>
<td>143/93±4/7†</td>
<td>143/96±5*/2†</td>
</tr>
<tr>
<td>Upright</td>
<td>145/106±4/2</td>
<td>144/101±5/4</td>
<td>144/99±4/3*</td>
<td>143/100±4/2†</td>
<td>141/91±4/3†</td>
<td>139/95±5/4†</td>
<td>131/94±5*/3†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Supine</td>
<td>66±2</td>
<td>71±2</td>
<td>70±2</td>
<td>73±3*</td>
<td>69±2</td>
<td>71±3</td>
<td>64±2</td>
</tr>
<tr>
<td>Upright</td>
<td>79±3</td>
<td>86±3*</td>
<td>83±3</td>
<td>90±3*</td>
<td>87±3*</td>
<td>87±3*</td>
<td>82±3</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>80.6±4.8</td>
<td>80.5±4.8</td>
<td>81.0±4.7</td>
<td>81.1±4.9</td>
<td>81.3±4.8</td>
<td>81.2±4.7</td>
<td>81.0±4.7</td>
</tr>
</tbody>
</table>

Values are means ± SEM.
*p < 0.025, †p < 0.005. compared with placebo values.
TABLE 2. Body Sodium/Blood Volume State, Plasma and Urinary Electrolytes, and Pressor Factors Before and After Terazosin Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Terazosin</th>
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<tbody>
<tr>
<td>Exchangeable sodium (mmol)</td>
<td>2912 ± 104</td>
<td>2994 ± 112</td>
</tr>
<tr>
<td>Blood volume (ml)</td>
<td>4595 ± 200</td>
<td>4774 ± 189</td>
</tr>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>85 ± 2.8</td>
<td>83 ± 2.9</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>139.6 ± 0.6</td>
<td>139.2 ± 0.5</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.2 ± 0.1</td>
<td>4.1 ± 0.1</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.30 ± 0.02</td>
<td>2.24 ± 0.03</td>
</tr>
<tr>
<td>Supine renin activity (ng ANG I/ml/hr)</td>
<td>1.34 ± 0.13</td>
<td>1.42 ± 0.09</td>
</tr>
<tr>
<td>Upright renin activity (ng ANG I/ml/hr)</td>
<td>1.65 ± 0.2</td>
<td>1.92 ± 0.24</td>
</tr>
<tr>
<td>Supine aldosterone (ng/dl)</td>
<td>6.8 ± 0.8</td>
<td>5.6 ± 0.5</td>
</tr>
<tr>
<td>Upright aldosterone (ng/dl)</td>
<td>10.8 ± 1.3</td>
<td>11.1 ± 1.3</td>
</tr>
<tr>
<td>Supine norepinephrine (ng/dl)</td>
<td>43.2 ± 5.8</td>
<td>44.0 ± 4.7</td>
</tr>
<tr>
<td>Upright norepinephrine (ng/dl)</td>
<td>67.0 ± 7.0</td>
<td>91.9 ± 9.1*</td>
</tr>
<tr>
<td>Supine epinephrine (ng/dl)</td>
<td>3.1 ± 0.5</td>
<td>2.7 ± 0.4</td>
</tr>
<tr>
<td>Upright epinephrine (ng/dl)</td>
<td>3.3 ± 0.3</td>
<td>3.0 ± 0.4</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m²)</td>
<td>102 ± 5</td>
<td>98 ± 4</td>
</tr>
<tr>
<td>Urinary excretion rates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/24 hr)</td>
<td>179 ± 21</td>
<td>197 ± 17</td>
</tr>
<tr>
<td>Potassium (mmol/24 hr)</td>
<td>65 ± 5</td>
<td>67 ± 5</td>
</tr>
<tr>
<td>Norepinephrine (ng/24 hr)</td>
<td>4983 ± 578</td>
<td>5331 ± 707</td>
</tr>
<tr>
<td>Epinephrine (ng/24 hr)</td>
<td>1078 ± 125</td>
<td>1026 ± 102</td>
</tr>
</tbody>
</table>

Values are means ± SEM. ANGI = angiotensin I. *p < 0.005, †p < 0.001, compared with placebo values.

Plasma NE concentrations measured at the end of each NE infusion step correlated closely with the corresponding infusion rates and correlation was similar during placebo (r = 0.17, p < 0.001; ln y = 0.76 ln x + 1.62) and terazosin treatment (r = 0.83, p < 0.001; ln y = 0.68 ln x + 2.13) conditions. Moreover, the total plasma clearance of infused NE was also comparable (7.2 ± 0.7 vs 6.9 ± 0.5 L/min). Plasma levels of epinephrine did not change significantly during NE infusion during either placebo or terazosin treatment. The concentration-response curve of arterial pressure and plasma NE concentration was significantly displaced to the right after terazosin treatment as compared with that seen during placebo treatment (F = 21.3, p < 0.01; Figure 1).

The terazosin-induced increases in NE pressor dose tended to correlate with the terazosin-induced decrease in mean supine (r = -0.67, p < 0.01) or upright (r = -0.49, p < 0.05) arterial pressure. No significant correlation was found between the terazosin-induced increases in NE pressor dose and the terazosin dose

FIGURE 1. Relationship between norepinephrine-induced increments of arterial pressure and plasma norepinephrine level before and after terazosin treatment. Bars indicate SEM. Relationships were significantly different (p < 0.01).

(r = 0.10) or the terazosin-induced increases in preinfusion plasma NE level (r = 0.20).

The response to ANG II infusion was studied in 13 subjects (3 women and 10 men, aged 47 ± 2 years) treated with terazosin, 11.5 ± 1.5 mg/day (range,

TABLE 3. Infusion Studies Conducted Before and After Terazosin Treatment in 10 Hypertensive Subjects

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Placebo</th>
<th>Terazosin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoproterenol (bolus injections)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronotropic dose (µg)</td>
<td>2.57 ± 0.78</td>
<td>3.49 ± 1.06</td>
</tr>
<tr>
<td>Slope</td>
<td>10 ± 1</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinfusion plasma NE (ng/dl)</td>
<td>37.7 ± 3.3</td>
<td>52.2 ± 7.8*</td>
</tr>
<tr>
<td>Preinfusion plasma epinephrine (ng/dl)</td>
<td>2.6 ± 0.4</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>Pressor dose (ng/kg/min)</td>
<td>73 ± 9</td>
<td>2156 ± 496†</td>
</tr>
<tr>
<td>Slope</td>
<td>13 ± 1</td>
<td>9 ± 2</td>
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<tr>
<td>ANG II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinfusion plasma ANG II (pg/ml)</td>
<td>23 ± 4</td>
<td>35 ± 6</td>
</tr>
<tr>
<td>Preinfusion PRA (ng ANG I/ml/hr)</td>
<td>1.5 ± 0.1</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>Preinfusion plasma aldosterone (ng/dl)</td>
<td>6.1 ± 1.0</td>
<td>5.8 ± 0.8</td>
</tr>
<tr>
<td>Pressor dose (ng/kg/min)</td>
<td>10.6 ± 1.4</td>
<td>5.0 ± 0.4</td>
</tr>
<tr>
<td>Slope</td>
<td>12 ± 1</td>
<td>12 ± 1</td>
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</table>

Values are means ± SEM. The isoproterenol chronotropic dose was defined as the dose required to elevate heart rate by 25 beats/min. The NE and ANG II pressor doses were defined as the doses required to elevate mean or diastolic blood pressure, respectively, by 20 mm Hg. NE = norepinephrine; ANG = angiotensin; PRA = plasma renin activity.

*p < 0.005, †p < 0.001, compared with placebo values.
5–20 mg/day). As compared with placebo conditions, basal plasma renin activity, aldosterone and ANG II levels, and the slope of pressor response curve did not change significantly after terazosin treatment. The mean ANG II pressor dose (ED$_{50}$) decreased by approximately 50%, but the change did not reach statistical significance by paired, two-tailed t test using the natural logarithm of the dose (see Table 3). After placebo treatment, ANG II infused at the lower dose rate of 2 ng/kg/min caused a significant ($p < 0.01$) increase of plasma aldosterone to $10.7 \pm 1.4$ ng/dl; further increases to $14.5 \pm 2.0$ and $16.4 \pm 2.1$ ng/dl were caused by dose rates of 4 and 10 ng/kg/min, respectively. With terazosin treatment, the plasma levels of aldosterone measured at the end of the three ANG II infusion dose rates were comparable: $9.6 \pm 1.3$, $13.2 \pm 1.8$, and $15.9 \pm 1.9$ ng/dl.

The increase of arterial pressure induced by the 10 ng/kg/min infusion of ANG II was associated with a slight, nonsignificant decrease in heart rate during both placebo (+26 ± 3 mm Hg; −2 ± 2 beats/min; −3%) and terazosin treatment (+29 ± 1 mm Hg; −3 ± 1 beats/min; −4%). The plasma ANG II levels measured at the end of each ANG II infusion dose rate correlated closely with the corresponding infusion rates; this correlation was similar under placebo ($r = 0.76, p < 0.001$; ln $y = 0.71 \ln x + 3.6$) and terazosin ($r = 0.71, p < 0.001$; ln $y = 0.76 \ln x + 3.57$) conditions. Moreover, the total plasma clearance of infused ANG II was also comparable ($5.4 \pm 0.5$ vs $5.6 \pm 0.5$ L/min). The relationships between ANG II-induced increases of diastolic blood pressure or circulating aldosterone and the concomitant increments of plasma ANG II were not modified after terazosin treatment (Figure 2).

Percentage changes in supine or upright mean blood pressure did not differ between the subjects treated with a terazosin dose of 5 mg (−10 and −13% respectively), 10 mg (−5 and −14%), or 20 mg (−7 and −13%) but were somewhat lower in those treated with a 2-mg dose (−2% and −9%). Moreover, a comparison performed among the subgroups treated with 5, 10, and 20 mg of terazosin showed that the three subgroups did not differ in the considered study parameters under placebo conditions and that after terazosin treatment, the fall of arterial pressure and the increase of basal (preinfusion) plasma NE level or NE pressor dose (ED$_{50}$) were similar among subgroups (Table 4). The degree of rightward shift in the concentration-response curve during NE infusion was also comparable.

**Discussion**

The blood pressure lowering potential of terazosin was confirmed in the present study; blood pressure was significantly decreased in 17 subjects with essential hypertension who received a daily dose of 2 to 20 mg for 8 weeks. The fall of arterial pressure was associated with a marked inhibition of the cardiovascular pressor response to infused NE, while the concentration of circulating NE showed only a modest and variable increase. The physiological correlation relating the NE pressor responsiveness to the endogenous level of plasma NE was therefore markedly displaced to the right. This change in noradrenergic regulation was not accompanied by significant variations in the activity of other blood pressure modulating factors, such as the adrenomedullary component of the sympathetic nervous system, β-adrenergic sensitivity, renin-angiotensin-aldosterone axis, or body sodium–blood volume state. This finding suggests that the mechanism of the antihypertensive effect of terazosin is largely due to inhibition of α$_1$-mediated noradrenergic-dependent vasoconstriction.

Several mechanisms could theoretically participate in the regulation of NE pressor responsiveness during adrenergic α$_1$-blockade, including plasma clearance of infused NE, 23–24 baroreflex sensitivity, 27 and body sodium–blood volume state. 23 Stable plasma NE concentrations are reached after 5 minutes and maintained for up to 60 minutes of NE infusion at constant rates in normal and hypertensive humans. 23, 24 In the present study, plasma NE levels were measured after 20 minutes of NE infusion. In terazosin-treated subjects repeated blood samples were not obtained during NE infusion to determine the time span needed to reach stable NE levels; however, the unchanged relationship between plasma NE and NE dose rates does not support the possibility of altered NE metabolism. Baroreflex sensitivity, as judged from the responses of heart rate to the NE-induced or ANG II-induced increases in blood pressure, appeared to be unaltered. Moreover, in a previous study, carotid baroreceptor activity was not modified in seven patients with essential hypertension after α$_1$-blockade. 23 Sodium retention tends to develop during chronic sympathetic blockade, 30, 31 however, mean body weight, urinary electrolyte excretion rate (as an index of dietary intake), plasma sodium and potassium concentrations, mean blood volume (±179

![Figure 2. Relationship between angiotensin II-induced increments of arterial pressure or plasma aldosterone and plasma angiotensin II level before and after terazosin treatment. Bars indicate SEM.](http://hyper.ahajournals.org/DownloadedFrom/)
### Table 4. Clinical and Biochemical Findings Before and After Different Doses of Terazosin in 13 Hypertensive Subjects

<table>
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<th>Placebo</th>
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<tr>
<td>Supine BP (mm Hg)</td>
<td>152/104 ± 6/3</td>
<td>138/93 ± 11/6</td>
<td>149/105 ± 7/5</td>
<td>143/98 ± 11/6</td>
<td>167/103 ± 7/3</td>
<td>145/98 ± 6/3</td>
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<tr>
<td>Supine heart rate (beats/min)</td>
<td>66 ± 2</td>
<td>69 ± 4</td>
<td>73 ± 4</td>
<td>64 ± 1</td>
<td>62 ± 2</td>
<td>59 ± 2</td>
</tr>
<tr>
<td>Upright heart rate (beats/min)</td>
<td>80 ± 4</td>
<td>83 ± 4</td>
<td>88 ± 7</td>
<td>88 ± 9</td>
<td>70 ± 4</td>
<td>77 ± 3</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>84.9 ± 12.6</td>
<td>84.4 ± 12.5</td>
<td>80.3 ± 5.9</td>
<td>80.3 ± 4.3</td>
<td>86.0 ± 6.9</td>
<td>87.5 ± 7.5</td>
</tr>
<tr>
<td>Exchangeable sodium (mmol)</td>
<td>2967 ± 223</td>
<td>3221 ± 228</td>
<td>2795 ± 167</td>
<td>2986 ± 252</td>
<td>3167 ± 129</td>
<td>3320 ± 229</td>
</tr>
<tr>
<td>Blood volume (ml)</td>
<td>4535 ± 481</td>
<td>4898 ± 238</td>
<td>4174 ± 347</td>
<td>4489 ± 472</td>
<td>4997 ± 176</td>
<td>4943 ± 284</td>
</tr>
<tr>
<td>Plasma NE (ng/dl)*</td>
<td>41.4 ± 8.5 †</td>
<td>87.0 ± 16.7 †</td>
<td>27.3 ± 3.1</td>
<td>35.7 ± 4.0</td>
<td>27.4 ± 5.6 †</td>
<td>37.9 ± 7.2 †</td>
</tr>
<tr>
<td>NE pressor dose (ng/kg/min)</td>
<td>95.2 ± 17.4 †</td>
<td>2151 ± 1009 †</td>
<td>70.9 ± 19.3</td>
<td>3395 ± 1041</td>
<td>54.0 ± 6.3 †</td>
<td>1762 ± 855 †</td>
</tr>
<tr>
<td>PRA (ng ANG I/ml/hr)*</td>
<td>2.0 ± 0.2 †</td>
<td>2.0 ± 0.3 †</td>
<td>1.3 ± 0.1</td>
<td>1.5 ± 0.3</td>
<td>1.4 ± 0.2 †</td>
<td>2.2 ± 0.5 †</td>
</tr>
<tr>
<td>ANG II pressor dose (ng/kg/min)</td>
<td>12.8 ± 4.9 †</td>
<td>4.4 ± 0.80 †</td>
<td>9.5 ± 4.1</td>
<td>5.7 ± 1.0</td>
<td>9.7 ± 5.4 †</td>
<td>4.5 ± 0.5 †</td>
</tr>
<tr>
<td>Urinary sodium (mmol/24 hr)</td>
<td>205 ± 22</td>
<td>191 ± 26</td>
<td>176 ± 47</td>
<td>221 ± 46</td>
<td>203 ± 28</td>
<td>217 ± 13</td>
</tr>
</tbody>
</table>

Values are means ± SEM. BP = blood pressure; NE = norepinephrine; PRA = plasma renin activity; ANG = angiotensin.

*Preinfusion. †n = 4.

ml) and exchangeable sodium (+ 82 mmol) tended to be stable or only mildly and not significantly increased during the 8-week treatment period. Therefore, these factors could have played at most a minor role in the regulation of cardiovascular NE responsiveness during terazosin treatment.

Terazosin reduced arterial pressure and pressor responsiveness to NE in our subjects with essential hypertension. Both effects were present at a 5-mg dose, while further increases in dosage did not potentiate adrenergic antagonism, which suggests that maximal α₁-blockade was achieved at the lower dose. Plasma NE concentration tended to increase. This increase was consistent for upright plasma NE, while supine plasma NE showed a more variable response: it was unchanged when measured on the day of body sodium estimation and increased when measured before NE infusion. Since terazosin should not interfere with the regulation of NE release from the peripheral nerve endings mediated by presynaptic α₂-adrenergic receptors,

interpreation would account for the increase in plasma NE concentration under conditions of sympathetic activation such as upright posture. Terazosin is structurally related to the established α₁-antagonist prazosin. The latter compound has been shown to inhibit the pressor response of the hindlimb vasculature to nerve stimulation in different experimental preparations and decrease the vasoconstrictor response to NE in isolated blood vessels or in vascular beds of normotensive rats, dogs, and spontaneously hypertensive rats. In contrast to these observations, however, the pressor response to NE was found to be resistant to blockade by α₁-adrenergic receptor antagonists in other animal models. The reasons for these discrepancies in the literature are not obvious but could be related, at least in part, to a different distribution of α₁-adrenergic and α₂-adrenergic receptors in the studied preparations and to different preferential activity of the neurotransmitter NE on α₁-adrenergic and α₂-adrenergic receptors when it is liberated from the peripheral nerve endings or applied exogenously. In humans, prazosin was noted to blunt
the pressor response to endogenous sympathetic activation with exercise, handgrip, or cold pressor test in hypertensive patients and tended to increase plasma NE concentration after acute or chronic dosing. This compound has the disadvantage of the first-dose phenomenon. Immediate activation of the adrenergic and renin-angiotensin system causes fluid volume retention, which prevents the acute hypertensive response to any subsequent doses and also partly counteracts the hypertensive effect. Despite a similar cardiovascular profile, terazosin did not cause a first-dose phenomenon in our subjects and, during short-term administration, did not induce significant sodium-fluid volume retention. Whether and to what extent the difference between terazosin and established α1-antagonists represents a true advantage for clinical pharmacotherapy needs to be confirmed in larger clinical trials.

The mechanism whereby noradrenergic inhibition affects blood pressure control may also involve angiotensinogenic regulation. Renal renin secretion is influenced by the adrenergic system, while ANG II may activate the sympathetic system at central or peripheral sites by facilitating NE release or inhibiting NE reuptake at the nerve endings. In the present study, effective α1-adrenergic inhibition failed to modify plasma renin activity and ANG II levels; other renin modulating factors such as body sodium–volume state, renal hemodynamics, and β-adrenergic sensitivity were not changed. This finding and those from previous investigations with prazosin in normal and hypertensive subjects suggest that α1-adrenergic receptors are not directly involved in the regulation of renin release. Two ANG II–dependent cardiovascular functions, namely pressor and aldosterone sensitivity to ANG II, were not modified by terazosin. The unchanged pressor sensitivity to ANG II appears to exclude the possibility of a direct vasodilating effect of terazosin. It has been suggested that the sympathetic nervous system could exert an inhibitory influence on the responsiveness of plasma aldosterone of ANG II; however, the unchanged aldosterone–ANG II interrelationship in hypertensive subjects after terazosin treatment does not support the concept that the influence of the noradrenergic system on adrenocortical cells may be mediated by α1-adrenergic receptors.

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