Cardiovascular and Metabolic Profile During Intervention with Urapidil in Humans

ANDREAS GERBER, PETER WEIDMANN, CLAUDIO MARONE, DOMINIK UEHLINGER, AND WALTER RIESEN

SUMMARY Increased sympathetic activity or vascular reactivity to norepinephrine or both may play a complementary role in the pathogenesis of essential hypertension. Therefore, blood pressure regulation and metabolic correlates of cardiovascular risk were evaluated in 19 normal subjects and in 13 subjects with essential hypertension receiving placebo and after 4 weeks of intervention with urapidil, an agent that was found experimentally to exert a combined central sympathetic and peripheral α-adrenergic receptor inhibition. In hypertensive patients, urapidil normalized the initially low norepinephrine pressor dose (+106%), mildly increased basal plasma norepinephrine levels (+36%), and markedly shifted the plasma norepinephrine concentration–blood pressure response curve (p < 0.01). Blood pressure was decreased (p < 0.001). In normal subjects, urapidil produced only mild increases in norepinephrine plasma levels (+22%) and norepinephrine pressor dose (+38%) and no change in blood pressure. Body weight, exchangeable sodium, and blood volume were unaltered or increased slightly. Heart rate; plasma epinephrine, renin, angiotensin II, basal aldosterone, and electrolyte levels; plasma clearances of norepinephrine and angiotensin II; pressor effects of angiotensin II; chronotropic responses to isoproteenol or a norepinephrine-induced rise in blood pressure; and urinary prostaglandin E2 excretion, as well as serum lipoprotein fractions and glucose, insulin, and uric acid levels, were not significantly modified by urapidil. Aldosterone responsiveness to angiotensin II was increased by urapidil in normal (p < 0.05) but not in hypertensive subjects. These findings suggest that urapidil may decrease blood pressure in essential hypertension predominantly through peripheral α-adrenergic receptor inhibition by lowering an abnormally high vascular norepinephrine reactivity without causing an equivalent increase in adrenergic activity. No alteration in metabolic correlates of cardiovascular risk occurred. A physiological sympathetic inhibition of angiotensin II-stimulated aldosterone release may be mediated by an α-adrenergic receptor related mechanism that seems to be impaired in essential hypertension. (Hypertension 7: 963–971, 1985)

KEY WORDS • sympathetic nervous system • α-adrenergic receptor inhibition • blood pressure regulation • norepinephrine • angiotensin II • cardiovascular responsiveness • aldosterone regulation • metabolic correlates of cardiovascular risk

An increased sympathetic activity or vascular hyperreactivity to norepinephrine (NE) or both may play an important complementary role in the pathogenesis of essential hypertension (EH). Considering this constellation, pharmacological agents that improve the disturbed relationship between sympathetic activity and vascular NE reactivity should be of particular therapeutic interest in EH. The phenylpiperazine derivate urapidil is a new agent that has been found in vitro and in animal experiments to exert a central, but not clonidinelike, sympatholytic effect combined with peripheral postsynaptic vascular α-adrenergic receptor blockade. It is evident that such a dual action could simultaneously counteract the two major catecholamine-related disturbances incriminated in the pathogenesis of EH. Therefore, the present study was undertaken to assess the effects of intervention with urapidil on a spectrum of blood pressure (BP) regulating factors in humans. Interactions with plasma catecholamine and angiotensin II (ANG II) levels, cardiovascular responsiveness to NE, ANG II, and cardiac β-adrenergic receptor stimulation, the body sodium–blood volume state, and urinary prostaglandins were investigated in patients with mild to moderate EH and in normal subjects. Because of the importance of...
the metabolic side effect profile of any new antihypertensive agent, levels of serum lipoproteins, glucose, insulin, and uric acid also were evaluated.

Subjects and Methods

We studied 19 normal subjects (6 women and 13 men, aged 21–51 yr) and 13 with mild to moderate EH (5 women and 8 men, aged 31–64 yr). The normal subjects were healthy volunteers with a BP consistently below 140/90 mm Hg. In the hypertensive patients, untreated BP ranged between 140/90 and 185/120 mm Hg. Secondary forms of hypertension were excluded by the usual tests. No patient had malignant phase hypertension (retinopathy Keith-Wagener stage III–IV), edema, heart failure, stroke, or a plasma creatinine level greater than 1.2 mg/dl (>109 μmol/L). Any antihypertensive and other drugs were discontinued 4 weeks before study. The subjects were instructed to maintain their usual diet, but to avoid very salty foods. Physical activity was unchanged during the study. Alcohol abusers were excluded, and no woman was taking hormonal contraceptives. Side effects were evaluated at the end of the placebo and treatment phases by a self-administered standard questionnaire. All subjects gave their informed consent.

In a single-blind approach, a matched placebo, one capsule every morning and evening, was given for 4 weeks (placebo phase). The placebo was then replaced by active urapidil, a slow-release capsule (30 mg; Byk Gulden, Konstanz, West Germany) twice daily for 4 weeks. No other antihypertensive drug was added during the active phase.

At the end of the placebo and urapidil treatment phases, the following measurements were made. After the collection of a 24-hour urine sample (for determination of sodium, potassium, creatinine, NE, epinephrine, and prostaglandin E2 and F2a excretion rates), body weight, BP, heart rate, plasma and blood volume, exchangeable body sodium, hemocrit, plasma sodium, potassium, chloride, calcium, creatinine, glucose, insulin, remin activity (PRA), aldosterone, NE, and epinephrine levels, and serum total cholesterol, triglycerides, and lipoprotein fractions were obtained. The serum total lipids and lipoprotein fractions were determined twice within 3 to 5 days, and the mean of the two values was used for analysis. These blood analyses were made between 0800 and 1000 hours (placebo phase). The BP was measured with standard cuff and sphygmomanometer; the mean of three readings was used for analysis. During the infusion studies, BP was monitored with an automatic recorder (Model SR 2, Physiometrics International, Malibu, CA, USA); the mean of 9 to 11 measurements was used for analysis. Mean arterial pressure was calculated as the sum of the diastolic and one-third of the pulse pressure. During the isoproterenol sensitivity test, heart rate was monitored by electrocardiography; after the subject had been supine for 30 minutes, resting heart rate was calculated as the mean resting rate from the R-R intervals over 1 minute. The heart rate after isoproterenol was obtained from the shortest R-R interval after injection.

Cardiovascular responsiveness was analyzed in the following manner. Increases in mean BP (NE infusion) or diastolic BP (ANG II infusion) were related to plasma NE or ANG II levels, respectively, obtained before and during infusions. Pressor doses of NE or ANG II necessary to increase mean (NE infusion) or diastolic (ANG II infusion) BP by 20 mm Hg were calculated from dose-response curves. To estimate baroreceptor function, the negative chronotropic effect of a 20 mm Hg increase in mean BP during NE infusion was assessed from BP–heart rate response curves.
mined from dose–heart rate response curves; it was
defined as the dose increasing supine heart rate by 25
beats/min.

The total plasma clearances of NE and ANG II were
calculated by the formula: Clearance (L/min) = NE
or ANG II (dose/min)/(corresponding plasma NE or
ANG II — basal plasma NE or ANG II). Each clearance
value consisted of the mean of two to three single
clearances obtained with the different infusion rates.

Plasma and urinary sodium and potassium were
measured by flame photometer; chloride, calcium,
creatinine, and uric acid by autoanalyzer; calcium
by fluorimetric titration with ethyleneglycol bis(β-
aminoethyl ether)-N,N-tetraacetic acid; plasma glu-
cose by the hexokinase method; insulin by double anti-
body radioimmunoassay; plasma and blood volumes
and exchangeable sodium by isotope dilution meth-
ods; PRA, plasma ANG II, aldosterone, and ur-
inary prostaglandin E and F2α by radioimmunoassay;
plasma and urinary NE and epinephrine by a radio-
enzymatic method; total serum cholesterol and
triglycerides by Technicon AAII autoanalyzer (Tar-
ytown, NY, USA); lipoprotein fractions by an ultra-
centrifugation technique according to the Lipid Re-
search Clinic Program; apoproteins A1 and A2 by
radioimmunoassay; and apoprotein B by radial immuno-
diffusion, as reported previously from our laborato-
ries. Since natural logarithmic transformation rather than
absolute values followed a gaussian distribution, for
statistical analysis we used the natural logarithmic
transformation of PRA, ANG II, and aldosterone,
plasma epinephrine, and exchangeable potassium, and
sodium levels; doses of infused NE, ANG II, or
isoproterenol; pressor doses of NE or ANG II; chrono-
tropic doses of isoproterenol; and prostaglandin excre-
tion rates. Statistical analysis included paired and un-
paired (2-tailed) Student’s t test, regression analysis,
and analysis of covariance. Data are expressed as
means ± SEM.

Results
Blood Pressure, Heart Rate, and Some Clinical,
Biochemical, and Pressor Factors

Under placebo conditions, the measured parameters
did not differ significantly between the normal and
hypertensive groups, except for a higher mean age
(p < 0.05) and BP and a lower upright PRA
(p < 0.05) in the hypertensive group (Table 1). During treatment
with urapidil, supine and upright BP were significantly
increased in the hypertensive group (+36% and +22%;
Table 1). The pressor dose of NE was increased
markedly in the hypertensive subjects (+106%;
(p < 0.005), but only slightly in the normal subjects
(+38%; p < 0.005). The NE pressor dose during
urapidil therapy no longer differed significantly be-
tween the two groups. Urapidil significantly displaced
the relationship between NE-induced changes in mean
BP and concomitant plasma NE concentrations to the
right in the hypertensive patients (f = 12.44, p <
0.01) and somewhat less in the normal subjects
(f = 11.19, p < 0.01; Figure 1). Similar shifts (f < 0.01)
were found for the relationship between NE infusion
rate and changes in mean BP (Figure 1), while the
slope of the curves was unchanged. The decrease in
heart rate in response to an increase in mean BP of 20
mm Hg averaged —6 ± 2 beats/min in hypertensive
subjects and —4 ± 2 beats/min in normal subjects.

Plasma NE concentrations measured at the end of each
NE infusion step correlated closely with the cor-
responding infusion rates (during placebo: r = +0.86
in hypertensive and +0.91 in normotensive subjects;
(p < 0.001). These relationships were similar in the two
groups and unchanged during urapidil treatment. The
total plasma clearance of infused NE also was not
consistently altered by urapidil (Table 2).

Urapidil-induced changes in supine mean or systolic
BP correlated significantly with concomitant changes in
NE pressor dose in both groups analyzed jointly
(r = —0.35 and —0.39 respectively, p < 0.05), but
not in the normal or hypertensive subjects considered
separately.

Angiotensin II Infusion

Under placebo conditions, basal (pre-ANG II infu-
sion) NE levels, the slope of the NE infusion rate–pressor response curve (15 ± 1 in hypertensive,
16 ± 1 in normal subjects), and the plasma clearance
of NE did not differ significantly between the two
groups (Table 2). However, the NE pressor dose was
lower in the hypertensive group (p < 0.05). The
decrease in heart rate in response to an increase in mean
BP of 20 mm Hg averaged —10 ± 2 beats/min in the
hypertensive subjects and —5 ± 1 beats/min in the
normal subjects.

Following urapidil treatment, basal (pre-NE infu-
sion) plasma NE was slightly increased in the hyper-
tensive and normal groups (+36% and +22%; p <
0.05; Table 2). The pressor dose of NE was increased
markedly in the hypertensive subjects (+106%;
(p < 0.005), but only slightly in the normal subjects
(+38%; p < 0.005). The NE pressor dose during
urapidil therapy no longer differed significantly be-
tween the two groups. Urapidil significantly displaced
the relationship between NE-induced changes in mean
BP and concomitant plasma NE concentrations to the
right in the hypertensive patients (f = 12.44, p <
0.01) and somewhat less in the normal subjects
(f = 11.19, p < 0.01; Figure 1). Similar shifts (f < 0.01)
were found for the relationship between NE infusion
rate and changes in mean BP (Figure 1), while the
slope of the curves was unchanged. The decrease in
heart rate in response to an increase in mean BP of 20
mm Hg averaged —6 ± 2 beats/min in hypertensive
subjects and —4 ± 2 beats/min in normal subjects.

Plasma NE concentrations measured at the end of each
NE infusion step correlated closely with the cor-
responding infusion rates (during placebo: r = +0.86
in hypertensive and +0.91 in normotensive subjects;
(p < 0.001). These relationships were similar in the two
groups and unchanged during urapidil treatment. The
total plasma clearance of infused NE also was not
consistently altered by urapidil (Table 2).

Urapidil-induced changes in supine mean or systolic
BP correlated significantly with concomitant changes in
NE pressor dose in both groups analyzed jointly
(r = —0.35 and —0.39 respectively, p < 0.05), but
not in the normal or hypertensive subjects considered
separately.

Angiotensin II Infusion

Under placebo conditions, basal (pre-ANG II infu-
sion) PRA, plasma ANG II and aldosterone levels, the
ANG II pressor dose, the slope of the ANG II infusion
rate–pressor response curve (10 ± 1 in hypertensive
and 11 ± 1 in normal subjects), the total plasma clear-
ance of ANG II (Table 2), and the relationship between
ANG II-induced changes in diastolic BP and concomi-
tant plasma ANG II levels (Figure 2) did not differ
Table 1. Blood Pressure and Pressor Correlates on Placebo and During Urapidil Treatment in Subjects with Essential Hypertension and Normotensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 13)</th>
<th>Urapidil</th>
<th>Placebo (n = 19)</th>
<th>Urapidil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48 ± 3*</td>
<td></td>
<td>32 ± 2</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Supine</td>
<td>156/100 ± 5/2†</td>
<td>143/92 ± 5/3‡</td>
<td>112/73 ± 2/2</td>
<td>111/72 ± 2/1</td>
</tr>
<tr>
<td>Upright</td>
<td>156/105 ± 5/2†</td>
<td>145/100 ± 4/3§</td>
<td>113/82 ± 3/2</td>
<td>111/82 ± 3/2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>65 ± 3</td>
<td>63 ± 2</td>
<td>63 ± 2</td>
<td>63 ± 2</td>
</tr>
<tr>
<td>Upright</td>
<td>80 ± 3</td>
<td>82 ± 4</td>
<td>79 ± 3</td>
<td>81 ± 2</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>76.7 ± 3.0</td>
<td>77.2 ± 2.8</td>
<td>71.7 ± 2.5</td>
<td>71.8 ± 2.4</td>
</tr>
<tr>
<td>Plasma concentrations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.97 ± 0.03</td>
<td>0.98 ± 0.03</td>
<td>1.02 ± 0.03</td>
<td>1.03 ± 0.03</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>139 ± 1.0</td>
<td>142 ± 0.5</td>
<td>139 ± 0.5</td>
<td>139 ± 1.0</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.1 ± 0.05</td>
<td>4.1 ± 0.1</td>
<td>4.1 ± 0.05</td>
<td>3.9 ± 0.05</td>
</tr>
<tr>
<td>Renin activity (ng/mL/hr)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Supine</td>
<td>1.6 ± 0.3</td>
<td>1.7 ± 0.2</td>
<td>1.6 ± 0.3</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>Upright</td>
<td>2.8 ± 0.4 ‖</td>
<td>2.9 ± 0.3</td>
<td>3.9 ± 0.4</td>
<td>3.8 ± 0.5</td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>6.9 ± 0.9</td>
<td>6.3 ± 1.1</td>
<td>9.8 ± 1.2</td>
<td>9.0 ± 0.9</td>
</tr>
<tr>
<td>Upright</td>
<td>20.7 ± 2.5</td>
<td>16.7 ± 2.2</td>
<td>25.5 ± 3.0</td>
<td>22.4 ± 3.0</td>
</tr>
<tr>
<td>Norepinephrine (ng/dl)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Supine</td>
<td>27.7 ± 6.1</td>
<td>31.8 ± 6.1‡</td>
<td>27.6 ± 3.2</td>
<td>29.9 ± 3.5</td>
</tr>
<tr>
<td>Upright</td>
<td>60.1 ± 8.0</td>
<td>64.6 ± 7.5</td>
<td>58.9 ± 5.4</td>
<td>64.0 ± 5.9</td>
</tr>
<tr>
<td>Epinephrine (ng/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>4.0 ± 1.2</td>
<td>3.4 ± 0.8</td>
<td>2.7 ± 0.6</td>
<td>3.1 ± 0.6</td>
</tr>
<tr>
<td>Upright</td>
<td>5.4 ± 1.3</td>
<td>5.8 ± 1.3</td>
<td>4.9 ± 1.4</td>
<td>6.9 ± 1.3‡</td>
</tr>
<tr>
<td>Hematocrit (%)**</td>
<td>43 ± 1</td>
<td>42 ± 1.5</td>
<td>43 ± 0.5</td>
<td>42 ± 0.5‡</td>
</tr>
<tr>
<td>Blood volume (%)**</td>
<td>98 ± 2</td>
<td>100 ± 2</td>
<td>101 ± 2</td>
<td>107 ± 2§</td>
</tr>
<tr>
<td>Exchangeable sodium (%)**</td>
<td>101 ± 3</td>
<td>108 ± 3‡</td>
<td>105 ± 2</td>
<td>103 ± 2</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m²)</td>
<td>94 ± 4</td>
<td>92 ± 6</td>
<td>94 ± 4</td>
<td>95 ± 4</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/g creatinine)</td>
<td>130 ± 15</td>
<td>125 ± 16</td>
<td>106 ± 14</td>
<td>116 ± 13</td>
</tr>
<tr>
<td>Potassium (mmol/g creatinine)</td>
<td>58 ± 7</td>
<td>48 ± 4</td>
<td>50 ± 4</td>
<td>52 ± 4</td>
</tr>
<tr>
<td>Prostaglandin (ng/24 hr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2</td>
<td>203 ± 61</td>
<td>294 ± 134</td>
<td>202 ± 75</td>
<td>1163 ± 416§</td>
</tr>
<tr>
<td>F2a</td>
<td>707 ± 172</td>
<td>690 ± 144</td>
<td>674 ± 107</td>
<td>700 ± 99</td>
</tr>
<tr>
<td>Norepinephrine (µg/g creatinine)</td>
<td>35.0 ± 3.8</td>
<td>38.0 ± 5.0</td>
<td>36.3 ± 4.4</td>
<td>36.8 ± 4.3</td>
</tr>
<tr>
<td>Epinephrine (µg/g creatinine)</td>
<td>8.5 ± 1.0</td>
<td>7.3 ± 0.7</td>
<td>12.0 ± 2.4</td>
<td>11.4 ± 3.6</td>
</tr>
</tbody>
</table>

Values are means ± SEM.  
*p < 0.01, †p < 0.001, ‖ p < 0.05 compared with normotensive subjects; §p < 0.001, ¶p < 0.01, ‼p < 0.05 compared with placebo; **percent of mean normal values as related to body surface area and considering the gender in 110 normal subjects.  

Significantly between the hypertensive and normal groups. Moreover, these parameters were not consistently changed during urapidil treatment. Plasma ANG II levels measured at the end of each ANG II infusion step correlated closely with the corresponding infusion rates; these correlations did not differ between hypertensive and normal subjects receiving placebo or urapidil (r = 0.82–0.95, p < 0.001).  
Plasma aldosterone before and after urapidil correlated (r = 0.40–0.74, p < 0.001) with corresponding plasma ANG II concentrations during ANG II infusion (Figure 3). During treatment with placebo, this rela-
TABLE 2. Effects of Intervention with Urapidil on Cardiovascular Responsiveness to Norepinephrine (NE), Angiotensin II (ANG II), and a Chronotropic Dose of Isoproterenol in Subjects with Essential Hypertension and Normotensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive</th>
<th>Normotensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 13)</td>
<td>(n = 19)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Urapidil</td>
</tr>
<tr>
<td>Preinfusion plasma NE (ng/dl)</td>
<td>25.4±5.0</td>
<td>34.5±7.4*</td>
</tr>
<tr>
<td>Pressor dose (ng/kg/min)</td>
<td>81±17§</td>
<td>167±30§</td>
</tr>
<tr>
<td>Plasma NE clearance (L/min/1.73 m²)</td>
<td>5.0±0.6</td>
<td>5.3±0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angiotensin II</td>
<td></td>
</tr>
<tr>
<td>Preinfusion PRA (ng/ml/hr)</td>
<td>1.9±0.3</td>
<td>2.1±0.2</td>
</tr>
<tr>
<td>Plasma ANG II (pg/ml)</td>
<td>13.9±1.9</td>
<td>16.8±2.4</td>
</tr>
<tr>
<td>Pressor dose (ng/kg/min)</td>
<td>7.7±1.5</td>
<td>10.0±2.4</td>
</tr>
<tr>
<td>Plasma ANG II clearance (L/min/1.73 m²)</td>
<td>5.3±1.4</td>
<td>4.3±0.6</td>
</tr>
<tr>
<td></td>
<td>2.3±0.6</td>
<td>1.9±0.4</td>
</tr>
</tbody>
</table>

Values are means ± SEM.
PRA = plasma renin activity.
*p < 0.05, §p < 0.005 compared with placebo; tP < 0.05 compared with normal subjects; t dose increasing mean (NE) or diastolic (ANG II) blood pressure by 20 mm Hg; || dose increasing supine heart rate by 25 beats/min.

Figure 1. Relation between norepinephrine infusion rate or concomitant plasma norepinephrine concentrations and accompanying changes in mean blood pressure in normal and hypertensive subjects receiving placebo and following intervention with urapidil. Values are means ± SEM. The p values indicate significant shifts of curves during urapidil treatment as compared with placebo.

Figure 2. Relation between angiotensin II infusion rate or concomitant plasma angiotensin II concentrations and accompanying changes in diastolic blood pressure in normal and hypertensive subjects receiving placebo and following intervention with urapidil. Values are means ± SEM.
Figure 3. Relation between plasma angiotensin II and aldosterone levels before and during angiotensin II infusion in normal and hypertensive subjects receiving placebo and following intervention with urapidil. Values are means ± SEM. The \( p \) value indicates a significant shift of the curve during urapidil treatment as compared with placebo.

The relationship did not differ significantly between the normal and hypertensive groups. However, urapidil significantly displaced the correlation to the left in normal subjects (\( f = 6.27, p < 0.05 \)), but not in the hypertensive group.

**Isoproterenol Testing**

During treatment with placebo, the response of heart rate to isoproterenol did not differ significantly between the hypertensive and normal groups, as judged by the mean chronotropic dose (heart rate, +25 beats/min) and the slope of the dose-response curves (Table 2). Isoproterenol sensitivity was also unchanged following urapidil treatment.

**Metabolic Parameters**

During treatment with placebo, the hypertensive patients had significantly higher mean serum apoprotein B levels and also tended to have slightly higher serum total and low density lipoprotein cholesterol and lower high density lipoprotein cholesterol values than the normal subjects (Table 3). Serum total lipids, lipoprotein composition, and plasma glucose, insulin, and uric acid levels were not significantly modified during urapidil treatment.

**Side Effects**

Based on the self-administered questionnaire, subjective symptoms during placebo treatment were subtracted from those reported during urapidil treatment. Most side effects appearing during urapidil treatment were reported by normal subjects and were mild, never necessitating drug discontinuation. These symptoms included palpitation in five normal subjects and one hypertensive subject, fatigue (6/0), lightheadedness (5/0), stuffy nose (2/0), cold fingers or feet (2/0), palpitation in five normal subjects and one hypertensive subject, fatigue (6/0), lightheadedness (5/0), stuffy nose (2/0), cold fingers or feet (2/0), palpitation in five normal subjects and one hypertensive subject, fatigue (6/0), lightheadedness (5/0), stuffy nose (2/0), cold fingers or feet (2/0), palpitation in five normal subjects and one hypertensive subject, fatigue (6/0), lightheadedness (5/0), stuffy nose (2/0), cold fingers or feet (2/0), palpitation in five normal subjects and one hypertensive subject, fatigue (6/0), lightheadedness (5/0), stuffy nose (2/0), cold fingers or feet (2/0).

**Table 3. Effect of Intervention with Urapidil on Some Metabolic Parameters in Subjects with Essential Hypertension and Normotensive Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive (( n = 13 ))</th>
<th>Normotensive (( n = 19 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Urapidil</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>209 ± 11</td>
<td>213 ± 12</td>
</tr>
<tr>
<td>LDL</td>
<td>138 ± 7</td>
<td>140 ± 9</td>
</tr>
<tr>
<td>VLDL</td>
<td>18 ± 3</td>
<td>15 ± 3*</td>
</tr>
<tr>
<td>HDL</td>
<td>46 ± 2</td>
<td>46 ± 2</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>100 ± 10</td>
<td>104 ± 11</td>
</tr>
<tr>
<td>LDL</td>
<td>24 ± 4</td>
<td>26 ± 5</td>
</tr>
<tr>
<td>VLDL</td>
<td>54 ± 6</td>
<td>52 ± 7</td>
</tr>
<tr>
<td>HDL</td>
<td>25 ± 2</td>
<td>25 ± 2</td>
</tr>
<tr>
<td>Serum apoproteins (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>96 ± 7†</td>
<td>93 ± 7</td>
</tr>
<tr>
<td>A1</td>
<td>122 ± 5</td>
<td>122 ± 4</td>
</tr>
<tr>
<td>A2</td>
<td>44 ± 1</td>
<td>46 ± 2</td>
</tr>
<tr>
<td>Plasma glucose (mg/dl)</td>
<td>96 ± 3</td>
<td>97 ± 2</td>
</tr>
<tr>
<td>Plasma insulin (( \mu U/L ))</td>
<td>19.6 ± 2.6</td>
<td>18.5 ± 2.0</td>
</tr>
<tr>
<td>Plasma uric acid (mg/dl)</td>
<td>4.9 ± 0.2</td>
<td>5.0 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

* \( p < 0.005 \) compared with placebo; \( p < 0.02 \) compared with normal subjects.

LDL = low density lipoprotein; VLDL = very low density lipoprotein; HDL = high density lipoprotein.
headache (1/1), chest discomfort (1/1), constipation (1/1), increased dreaming (1/0), dry mouth (0/1), and nausea (1/0).

Discussion
Urapidil has previously been shown in the experimental animal to modulate the function of the sympathetic nervous system by inhibition of peripheral postsynaptic \( \alpha \)-adrenergic receptors and, to a much lesser extent, \( \alpha_2 \)-adrenergic receptors, as well as a distinct central sympatholytic effect.\(^9\) \(^{-11}\) Thus, urapidil differs from prazosin by a weaker \( \alpha_2 \)-adrenergic receptor affinity and its additional \( \alpha_2 \)-adrenergic effect, and from clonidine by a central action that was not inhibited by yohimbine and thus seems to be independent of central \( \alpha_2 \)-adrenergic receptors.\(^9\) \(^{-11}\) At the cardiovascular level, urapidil given to hypertensive animals or humans lowered both BP and total peripheral vascular resistance.\(^9\) \(^{-11}\) Since 60 mg/day was noted to be an effective antihypertensive dose,\(^9\) this dosage was also chosen for the present study.

The sympathetic regulatory axis in our patients with mild to moderate essential hypertension under placebo conditions was characterized by an exaggerated vascular reactivity to NE in the presence of largely normal cardiac \( \beta \)-adrenergic receptor responsiveness, basal plasma NE and epinephrine concentrations, plasma NE clearance, and urinary NE and epinephrine excretion rates, as noted previously.\(^2\) \(^{-5}\) \(^{-6}\) \(^{-12}\) \(^{-14}\) \(^{-17}\) \(^{-18}\) The hypertensive group was also on average slightly older than the normal group, but the NE pressor responsiveness has been found to be unrelated to age in such subjects.\(^32\) Intervention with urapidil in the normal and hypertensive subjects had no influence on plasma epinephrine, urinary epinephrine and NE, plasma NE clearance values, and cardiac \( \beta \)-adrenergic receptor responsiveness. Moreover, in the normal group, urapidil treatment was accompanied by mild increases in basal circulating NE (+22%) and the NE pressor dose (+38%), while BP was unchanged. In contrast, urapidil caused a greater rise in NE pressor dose (+106%) and shift in the plasma NE-pressor response curve (obtained during NE infusion) in the hypertensive group, despite a mild increase in plasma NE (+36%) similar to that in normal subjects. In fact, NE pressor responsiveness in the hypertensive patients was restored toward normal values, while supine BP was decreased on average from 156/100 to 143/92 mm Hg \((p < 0.001)\). Urapidil's effects on mean BP in all subjects analyzed jointly correlated significantly with concomitant variations in NE pressor dose \((r = -0.35, p < 0.05)\) but not with other measured parameters. These findings suggest that urapidil may decrease BP in EH by lowering an abnormally high cardiovascular NE reactivity without causing an equivalent increase in peripheral sympathetic outflow.

Mild variations in plasma NE, in the presence of an unaltered plasma NE clearance, during urapidil treatment in both the normal and hypertensive groups could reflect a slightly altered sympathetic nerve activity or diminished reuptake of NE into nerve endings. Considering the experimental evidence for a central nervous sympatholytic effect of urapidil,\(^9\) \(^{-11}\) a decreased peripheral NE outflow would be expected. On the other hand, the slight inhibitory influence of urapidil on peripheral \( \alpha_2 \)-adrenergic receptors may possibly affect not only postsynaptic, but also presynaptic sites.\(^8\) Such presynaptic inhibition of \( \alpha \)-adrenergic receptors, although certainly minor in comparison with the influence of the nonselective phenolamine,\(^9\) could nevertheless increase peripheral NE discharge and therefore perhaps mask a central sympatholytic component. An action on the brain is supported by characteristic central nervous side effects observed in some of our subjects and reported by others.\(^9\) There are presently no methods available to measure NE concentrations in the synaptic cleft, but it is generally accepted that heart rate is a sensitive biological index of changes in adrenergic activity. Therefore, the unaltered heart rates during urapidil treatment in this and previous short-term or long-term studies in humans\(^9\) \(^{-11}\) complement the stable urinary NE and epinephrine excretion rates as arguments against a relevant increase in adrenergic tone.

The reduction in vascular NE reactivity during urapidil treatment seems to be largely a direct consequence of postsynaptic \( \alpha \)-adrenergic receptor inhibition. The mild blunting of NE pressor responsiveness even in the normal subjects could not be explained as an unspecific effect of a decrease in basal (preinfusion) BP. Exaggerated responses of BP to NE in untreated EH,\(^24\)\(^{-27}\) and their improvement by urapidil, also were not due to changes in baroreflex function. In fact, the tendency for a slight decrement in the heart rate response to the NE-induced rise in BP during urapidil, particularly in the hypertensive group, could reflect a slightly blunted baroreflex, which would have antagonized rather than promoted a lowered pressor reactivity. A similar conclusion applies to the observed mild sodium retention evidenced by an increase in body weight and exchangeable sodium during urapidil treatment in the hypertensive group. This tendency is probably at most minimal in the majority of patients on long-term treatment.\(^9\) Nevertheless, a somewhat positive sodium–fluid volume balance has sometimes also occurred when BP was decreased with certain other \( \alpha \)-adrenergic receptor blockers or sympatholytics.\(^33\)\(^{-34}\) Such agents may also promote venous pooling\(^32\)\(^{-33}\) which could well explain the constellation of increased blood volume, decreased hematocrit, and unchanged body weight in our urapidil-treated normal subjects.

Urinary prostaglandin \( E_2 \) excretion was increased significantly \((p < 0.01)\) in the normal subjects, but only slightly and not significantly in the hypertensive group in which NE responsiveness was increased most markedly. Nevertheless, the possibility of a contributory role of renal vasodilatory prostaglandin \( E_2 \) to urapidil's cardiovascular effects deserves further consideration. It is evident that urapidil has multiple sites of action, and its pharmacological profile is difficult to ascribe to any single, discrete effect of the drug. Some additional factors that can interact with sympathetic
cardiovascular regulation or BP control or both, were not significantly modified during intervention with urapidil; these include the activity of the renin-angiotensin system, plasma clearance and pressor effects of ANG II, basal plasma aldosterone concentrations, plasma calcium levels, and plasma and urinary potassium values.

The relation between plasma aldosterone and circulating ANG II before and during ANG II infusion was modified by urapidil only in the normal subjects. Therefore, in the normal group only, a significant (p < 0.05) shift to the left of the plasma ANG II-aldosterone curve occurred during urapidil treatment. An influence of the difference in age between the two groups cannot be excluded; however, a similar finding following postganglionic adrenergic neuron blockade, which lowered circulating NE by 45%, led to our recent proposal that the sympathetic nervous system exerts an inhibitory influence on aldosterone responsiveness to ANG II in normal humans and that this physiological interaction is impaired in EH. The present observations with urapidil not only may corroborate this concept in entirely different study groups, but also are consistent with the possibility that the sympathetic modulation of ANG II-stimulated aldosterone release may be mediated by an α-adrenergic receptor related mechanism that seems to be defective in EH.

The assessment of the pharmacological profile of any new antihypertensive agent should include information on metabolic correlates of cardiovascular risk. Urapidil treatment caused no alterations in serum total lipids, the various lipoprotein cholesterol or triglyceride fractions, apoproteins A1, A2, or B, or glucose, insulin, potassium, or uric acid levels in our normal and hypertensive subjects. Other sympatholytic agents of various types, including reserpine, the central α-stimulator clonidine, the postganglionic neuron blocker debrisoquin, the combined α- and β-adrenergic receptor blocking agent labetalol, and the postsynaptic α,-adrenergic blocking agent prazosin also had no adverse influence or tended even to slightly lower the potentially atherogenic low and very low density lipoprotein cholesterol or serum triglyceride levels. Metabolic “neutrality” is a desirable characteristic of agents and their dosages used in the treatment of hypertension.

A disturbance of α-adrenergic receptor mediated signals may well be involved in the pathogenesis of EH. The demonstration of vascular hyperreactivity to NE but not ANG II in normotensive offspring of hypertensive families as well as enhanced α-adrenergic receptor mediated vasoconstriction in EH are consistent with this notion. Moreover, the relative importance of possible underlying abnormalities, such as an increased in sympathetic drive, or a postreceptor defect involving cations or other factors, remains to be elucidated. Considering the available pharmacological data in the light of the findings of the present study, urapidil’s antihypertensive action in humans could involve an improvement of any of the two latter mechanisms. Nevertheless, this agent may do more than just correct an abnormality in EH, since cardiovascular NE responsiveness also was reduced slightly in our normal subjects.

Interestingly, short-term therapy with the calcium channel blocker nifedipine similarly lowered NE pressor reactivity in both normal and hypertensive subjects. Moreover, the thiazide-like diuretic chlorthalidone and the newer compound indapamide also may exert their antihypertensive effect in part by lowering an exaggerated vascular NE reactivity without causing an equivalent increase in adrenergic activity, although no modification of NE responsiveness in normal subjects occurred with these agents. Therefore, it seems that different therapeutic principles can lead to an improved relation between sympathetic activity and noradrenergic cardiovascular reactivity as an important common principle in the treatment of EH.

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References


40. Blaustein MP. Sodium transport and hypertension. Hypertension 1984;5:445-453

