Long-Term Converting Enzyme Inhibition and Sympathetic Nerve Function in Hypertensive Humans

MARIA TERESA ZANELLA, M.D., EMMANUEL L. BRAVO, M.D., FETNAT M. FOUD, M.D., AND ROBERT C. TARAZI, M.D.

SUMMARY Orthostatic hypotension is uncommon during oral converting enzyme inhibition, even when combined with salt depletion. To assess the mechanisms responsible for the cardiovascular homeostasis in this condition, we studied the blood pressure (BP), heart rate (HR), total plasma catecholamines (CA), and plasma renin activity (PRA) responses after 20 minutes of 60° head-up tilt in four groups of hypertensive patients. Group 1 included seven untreated patients; Group 2, eight patients on converting enzyme inhibitor (captopril) therapy; Group 3, six patients on diuretic therapy and Group 4, 15 patients on combined captopril and diuretic therapy. Long-term converting enzyme inhibition alone or in combination with diuretics resulted in reduction of mean arterial pressure (MAP) associated with a marked increase in PRA and fall in plasma aldosterone concentration (PAC). Pronounced increases in HR and plasma CA on tilt were observed in all groups. In Groups 1, 2, and 3, BP was maintained during tilt; in Group 4, three patients fainted between 5 and 15 minutes while the other 12 had a normal response to tilt. Plasma catecholamines increased more significantly after 15 and 20 minutes of tilt, more in Groups 3 and 4 than in Group 1, while no differences in HR response were observed among groups. Results suggest that sympathetic compensatory mechanisms are adequate in the majority of patients to maintain BP during converting enzyme inhibition even when combined with salt depletion. In a few who exhibited orthostatic hypotension, a vasovagal attack seemed to be responsible for bradycardia and fall in BP. (Hypertension 3 (suppl II): 11-216-11-221, 1981)

KEY WORDS • orthostatic hypotension • captopril-converting enzyme inhibition • sympathetic nervous system • head tilt • salt depletion • homeostatic mechanisms

THE recent availability of converting enzyme inhibitors has permitted a better evaluation of the physiological importance of the renin-angiotensin system in cardiovascular homeostasis.1-3 Sancho and coworkers4 have demonstrated severe hypotension in salt-depleted normal subjects during head-up tilt when angiotensin II blockade was achieved by intravenously administrated SQ 20,881. From this report has evolved the notion that converting enzyme inhibition in salt- and water-depleted patients will seriously compromise their cardiovascular homeostatic mechanisms. This could be a serious drawback to the clinical use of these inhibitors because of the frequent need for added sodium restriction or diuretics.4

Our experience, however, has shown that orthostatic hypotension was an uncommon feature even with combined therapy. We report here studies designed to evaluate the humoral and cardiovascular response to upright tilt in hypertensive patients on long-term captopril therapy in order to define the mechanisms responsible for cardiovascular homeostasis during orthostatic stress in both salt-replete and -deplete states.

Methods

Patients

Twenty-seven hypertensive patients (13 men and 14 women) ranging in age from 25 to 69 years were studied. The study protocol was approved by the Research Projects and Institutional Review Committee of the Cleveland Clinic Foundation, and all patients freely consented to participate in the study. Patients were divided into four groups according to administered treatment. Some of them were included in more than one group, as they were studied at different times on different modes of therapy.

In Group 1, seven patients without treatment for at least 2 weeks were studied. Five of them had essential hypertension and two had primary hyperaldos-
steronism due to aldosterone-producing adenomas. Group 2 included eight patients, five with essential hypertension and three with renal artery disease on captopril therapy (200-600 mg/day) for a period ranging from 2 to 33 months. In Group 3, six essential hypertensive patients were studied while on diuretic therapy alone (hydrochlorothiazide 25-100 mg/day) for at least 7 days. Group 4 included 15 patients, 12 with essential hypertension and three with renovascular hypertension, on captopril (150-600 mg/day) for 4 to 31 months and diuretic therapy (hydrochlorothiazide 25-100 mg/day) for at least 7 days.

Studies were always performed between 8:00-12:00 noon. Patients were kept fasting overnight and rested supine in a quiet room for at least 30 minutes before the study. After this period, mean arterial pressure (MAP) (by sphygmomanometer) and heart rate (HR) were recorded and plasma renin activity (PRA) and plasma catecholamine (CA) determined three times by collecting blood samples 5 minutes apart through an i.v. needle inserted 20 minutes previously. Patients were then tilted upright to 60° and remained in this position for 20 minutes. BP and HR were determined at 5, 10, 15, and 20 minutes during tilt. Blood samples were obtained simultaneously for PRA and plasma CA measurements. Plasma aldosterone (PAC) concentration, plasma volume (PV), and PRA were also determined before and during treatment.

Laboratory Analysis

After collection, all blood samples were chilled and centrifuged immediately; the plasma was separated and frozen until processing. Total plasma CA (norepinephrine and epinephrine) were measured by a radioenzymatic assay described by Peuler and Johnson. The method is sensitive to 5.0 pg/100 μl plasma (SD). The methods used to determine PAC, PRA, and supine values in 44 healthy adults averaged 260 ± 120 ng/dl and for PAC range from 3-10 ng/dl and for PRA from 0.6 to 2.6 ng/ml/hr; PV values are expressed in ml/cm of height.

All results are expressed as the mean ± sem. Statistical significance was tested by analysis of variance, Student’s t and Wilcoxon tests for unpaired and paired data. The significance of correlation coefficients was tested using Spearman’s test.

Results

The clinical and humoral data of the four groups and the effects of treatment with diuretics, captopril alone, or captopril plus diuretics are summarized in table 1.

Captopril-Treated Patients (Group 2)

Captopril therapy in a mean daily dose of 460 ± 60 mg resulted in a 15.7% ± 2.86% reduction of MAP in seven of the eight patients studied, without significant changes in HR. The PV decreased by 11.4% ± 2.9% in four patients and remained essentially the same in the other four. Thus, no correlation was found between changes in MAP and changes in PV during treatment. The PAC rose by 258.2% ± 141.8% while PAC decreased in all patients but one by 50.7% ± 9.5%.

Diuretic-Treated Patients (Group 3)

Diuretic therapy reduced BP to normal levels in four of six patients, but left it practically unchanged in the other two. No changes in HR were observed with treatment. The PV decreased in all patients by 12.9% ± 3.4%. PRA and PAC rose markedly by 852.4% ± 546.5% and 150% ± 44.8%, respectively.

Captopril Plus Diuretic-Treated Patients (Group 4)

Captopril (mean daily dose of 430 ± 60 mg) in combination with a diuretic resulted in a 22.1% ± 3.4% reduction of MAP from pretreatment levels, in 13 of 15 patients, while HR remained unchanged. PV also decreased by 14.1% ± 2% in 13 of 15

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**Table 1. Effects of Long Term Therapy with Captopril and/or Diuretics in Hypertensive Patients**

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Group 1 (n = 7)</th>
<th>Group 2 (n = 8)</th>
<th>Group 3 (n = 6)</th>
<th>Group 4 (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
<td>±3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>±6</td>
<td>±4</td>
<td>±5</td>
<td>±2</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>1.7±</td>
<td>1.0±</td>
<td>2.1±</td>
<td>4.4</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>±8</td>
<td>±5.9</td>
<td>±12</td>
<td>±2.5</td>
</tr>
<tr>
<td>Plasma volume (ml/cm Ht)</td>
<td>17.5±</td>
<td>16.4±</td>
<td>17.4±</td>
<td>18.7±</td>
</tr>
</tbody>
</table>

All values are means ± SEM; C = control; Cap = captopril; D = diuretics.

* p < 0.05.

† p < 0.01.
A significant correlation between changes in MAP and changes in PV was found in this group ($r = 0.825$, $p < 0.001$). PRA rose markedly (8-fold), this increase was significantly greater than that observed in patients on captopril therapy alone ($p < 0.05$). On the other hand, PAC, which was decreased by 42.8% ± 6.6% in this group, was not significantly different from that found in patients on captopril therapy alone.

Effects of Head-Up Tilt in the Absence of Diuretics

There were no significant differences between the mean basal levels of MAP, HR, total plasma CA, and PV in untreated patients (Group 1) and those taking captopril (Group 2). Mean basal PRA was higher (10.4 ± 5.9 vs 1.7 ± 0.8 ng/ml/hr; $p < 0.05$) and mean basal PAC was lower (9.3 ± 1.5 vs 22.9 ± 3.4 ng/ml/hr, $p < 0.005$) in Group 2 than in Group 1.
During tilt (fig. 1), MAP was maintained in both groups while HR and CA rose markedly. Those responses were not significantly different between the two groups, although the mean levels of CA observed in Group 2 tended to be higher than in Group 1. Significant correlations were found between changes in HR and simultaneous changes in CA during tilt in both groups ($r = 0.71$ for Group 1 and $r = 0.54$ for Group 2; $p < 0.01$ for both) (fig. 2). The slope of the regression line in the captopril-treated group was less pronounced than in the nontreated group, but the difference did not attain statistical significance ($0.030$ vs $0.077$; $p > 0.05$). PRA showed a tendency to increase with tilt in both groups, but the change did not attain statistical significance.

Effects of Tilt During Diuretic Therapy Alone or With Captopril

Groups 3 and 4 showed no significant difference in resting MAP and HR; mean basal PRA was higher ($32.2 \pm 6.6$ vs $6.1 \pm 1.6$ ng/ml/hr; $p < 0.01$) and mean basal PAC was lower ($10.8 \pm 0.95$ vs $44 \pm 13.8$ ng/ml/hr; $p < 0.01$) in Group 4 than in Group 3. No significant differences in mean PV and basal CA were observed.

During tilt, MAP was maintained in all patients on diuretic therapy alone (fig. 3). Three of the patients on combined captopril and diuretic therapy fainted at between 5 and 15 minutes of tilt. The rapid fall in BP in those patients was associated with a sudden drop in HR despite marked increase in CA (fig. 4). In the remaining 12 patients, MAP was essentially unchanged during tilt (fig. 1). Pronounced increases in HR and CA were observed, and those responses were quantitatively and qualitatively similar to those observed in Group 3.

In the diuretic-treated group (Group 3), changes in CA during tilt did not correlate with simultaneous changes in HR, while a weak but significant correlation ($r = 0.36$; $p < 0.05$) was found in the group on combined captopril and diuretic therapy (fig. 2). The slope of the regression line of this group was not different from that observed in Group 2 but was found to be significantly smaller than that obtained in Group 1 ($0.0128$ vs $0.0772$; $p < 0.05$). It must be pointed out that the levels of CA observed at 0, 15, and 20 minutes of tilt in Groups 3 and 4 were significantly higher than those observed in untreated patients, while HR reached similar values.

PRA increased significantly at 10 and 15 minutes of tilt, in Groups 3 and 4 respectively, and the percent increments at 20 minutes were greater in Group 4 than in Group 3 ($88\%$ vs $43\%$; $p < 0.05$).
FIGURE 4. Individual values of mean arterial pressure (MAP), heart rate (HR), plasma renin activity (PRA), and plasma catecholamines (CA) in the three patients who fainted in response to tilt.

Discussion

The results of the present studies confirm the previously reported antihypertensive effects of captopril.10-14 Continued therapy with this drug alone or in combination with diuretics resulted in a sustained reduction of BP in the majority of the patients studied. No clinical evidence of orthostatic hypotension was observed in daily life although vasovagal faint occurred in three of 15 patients during passive tilt.

Although the circulating levels of angiotensin II were not measured, evidence of angiotensin-converting enzyme inhibition was provided by the significant increase in PRA in all treated patients resulting probably from release of PRA suppression by angiotensin II.8 The pronounced fall in PAC during therapy can also be considered as another evidence of converting enzyme inhibition.

During tilt, BP was adequately maintained during captopril therapy in all salt-replete patients, and the HR and CA responses did not differ significantly between captopril-treated and nontreated groups. These observations indicate that sympathetic compensatory mechanisms during angiotensin converting enzyme inhibition were both operative and sufficient to avoid orthostatic hypotension. More important for our purpose, MAP also was maintained during tilt in all patients on diuretic therapy and in the majority of patients on combined captopril and diuretic therapy.

Heart rate and CA responses were practically the same in these salt-depleted groups. These observations suggest, again, that the sympathetic nervous system was able to support the BP during orthostatic stress even in the salt-depleted state whether in the presence or absence of converting enzyme inhibition. Conway et al.15 suggested that converting enzyme inhibition reduced chronotropic responses in anesthetized dogs. However, our results in man indicate that captopril therapy does not alter the responses to postural stimuli. This conclusion is supported by an earlier study,6 which showed that severe sodium restriction in captopril-treated hypertensive patients did not prevent the expected rise in systemic vascular resistance in response to upright tilt. In the patients who fainted during tilt, a sudden fall in both MAP and HR associated with simultaneous increases in plasma CA indicated a vasovagal syndrome, a response quite different from an inadequate sympathetic response to orthostasis.16 The reasons for those episodes are not clear.

We have observed significant correlations between changes in HR and changes in CA in the salt-replete groups during tilt. In salt-depleted groups, however, similar changes in HR corresponded to greater increments in CA, at 15 and 20 minutes. There was a weak correlation between these variables in the group on combined captopril and diuretic therapy, and the
slope of the regression line was smaller than that observed in the nontreated group. On the other hand, no significant correlation was found in the group on diuretic therapy. These observations could suggest a diminution of chronotropic responses to endogenous catecholamines during diuretic therapy. To relate this phenomenon to enhancement of parasympathetic tone is still speculative. This possibility, however, would provide an explanation for some hypotensive episodes observed during angiotensin converting-enzyme inhibition and salt depletion. Increased parasympathetic activity was shown to occur with angiotensin II antagonists both in humans and in sodium-depleted dogs. However, the relevance of acute studies to chronic therapy needs to be established.

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