Converting Enzyme Inhibition and Blood Pressure Reactivity to Psychological Stressors

Joel E. Dimsdale, Paul Mills, Michael Ziegler, Karsten Leitz, and Richard Nelesen

There is considerable interest in blood pressure reactivity to psychological stressors. Because the sympathetic nervous system and the renin-angiotensin system are so responsive to stressors and are themselves the targets of many antihypertensive medications, many investigators have wondered if such medications decrease the blood pressure response to stressful stimuli. We studied 25 normotensive and 21 hypertensive men in a double-blind crossover study during which they received either placebo for 4 days or captopril (25 mg b.i.d.) for 4 days while they were hospitalized in a clinical research center. Patients were studied at resting baseline, while performing a mathematics task, and while reading out loud a disturbing newspaper article. Although captopril lowered the resting blood pressure levels, it had no effect on the amplitude of reactivity to stressors. (Hypertension 1992;20:210-213)

KEY WORDS • angiotensin converting enzyme inhibitors • captopril • stress, psychological • blood pressure • renin

There is considerable interest in the blood pressure (BP) response to exercise and psychological stressors. Whether this degree of reactivity to stimulation presages the patient's future clinical course remains debatable. However, laboratory studies and ambulatory BP studies have demonstrated that BP goes through wide excursions, and it is natural to wonder if such excursions are lessened by antihypertensive treatment. Whereas antihypertensive medications lower resting BP, do they also decrease the amplitude of the BP response to stressors?

The evidence is clear from over 60 studies that β-blockers decrease heart rate reactivity to stressors but have very little impact on the BP response to stressors (for review, see Reference 3). There are fewer studies with other antihypertensive agents (such as diuretics and reserpine), but the results seem consistent: although such medications lower resting BP, they do not decrease the amplitude of the BP response to stressors.

Given that angiotensin converting enzyme (ACE) inhibitors are currently used so widely in treating hypertension, we wondered if these agents would block stress-mediated increases in BP. Using Index Medicus and correspondence with other authors, we reviewed the literature from 1966 to 1991 on this topic. There have been relatively few human studies that have examined this question (Table 1). Most such studies were based on exercise as the stressor; these studies suggest that ACE inhibitors do not decrease the BP response to dynamic or isometric exercise. Only one study specifically examined psychological stressors, but here again, BP reactivity was not decreased by such medications. Most of these studies were nonblinded and non-sequence controlled. Additionally, the studies generally examined the response to only one stressor, and one is naturally concerned if such responses generalize to other stressors. For these reasons we examined 46 subjects using a double-blind crossover study with placebo and captopril to learn if ACE inhibition attenuates BP reactivity to different sorts of stressors.

Methods

We studied 25 normotensive control patients and 21 hypertensive patients. None of the hypertensive patients had received antihypertensive medications in the 6 months before participating in this study. All subjects were screened on two occasions with multiple (three) seated BP determinations taken on both occasions. Hypertensive patients were defined as those whose BP exceeded 140/90 mm Hg on both screening occasions. Nonnotensive subjects were those whose BP was consistently <140/90 mm Hg on the two screening occasions. Other than BP, the two groups of patients did not differ on age, relative obesity, or other criteria (Table 2).

The protocol was approved by the human subjects committee of the University of California, San Diego, and the subjects gave their written informed consent. Patients were admitted to a clinical research center for two 5-day hospitalizations. The average interval between hospitalizations was about 1 week. On one admission the patient received placebo pills twice daily. On the other admission the patient received captopril (25 mg b.i.d.) beginning on the second day of admission. Medications were administered double-blind using a sequence-controlled crossover design.
We wished to examine the impact of captopril in a setting where the renin-angiotensin system was relatively activated. Thus, we placed all subjects on an isocaloric diet providing 10 meq sodium and 100 meq potassium/day. This design allowed us to contrast reactivity in two different states: on placebo with low salt (an activated renin-angiotensin system) and on the ACE inhibitor captopril with low salt (high renin with blocked angiotensin).

All patients' reactivity was assessed on the morning of the fifth hospital day. An intracath was inserted in the patient's forearm. Blood pressure (BP) and heart rate were measured with a Dinamap 845 monitor (Critikon, Inc., Tampa, Fla.). Subjects were seated in a quiet room and given 20 minutes to acclimate to the intravenous catheter and BP monitoring apparatus. After a seated baseline measurement was determined, two stressor tasks were administered in fixed order—mental arithmetic and reading out loud a newspaper article. All patients were asked to sit quietly for 3 minutes while BP and heart rate were taken every minute and then averaged for that task. The 3-minute mental arithmetic task involved serial-7 subtraction from the number 600. The task was complicated by a ticking metronome and occasional distracting announcements about the amount of time remaining for the task. Subjects were not corrected for mistakes. The subject was then asked to read out loud for 3 minutes from a disturbing newspaper article dealing with racial violence in urban areas. After each task, the subject completed a brief visual analog form that measured anxiety and anger.

During each stressor task, BP and heart rate were measured as in the resting baseline task. Blood was collected at the end of each task into a chilled anticoagulated tube, and the plasma was stored at -80°C until the time of assay. Plasma renin activity was measured with a radioimmunoassay (INCSTAR, Stillwater, Minn.). Subjects were seated in a quiet room and given 20 minutes to acclimate to the intravenous catheter and BP monitoring apparatus. After a seated baseline measurement was determined, two stressor tasks were administered in fixed order—mental arithmetic and reading out loud a newspaper article. Seven minutes separated the two stressor tasks.

For the seated baseline measurement, subjects were asked to sit quietly for 3 minutes while BP and heart rate were taken every minute and then averaged for that task. The 3-minute mental arithmetic task involved serial-7 subtraction from the number 600. The task was complicated by a ticking metronome and occasional distracting announcements about the amount of time remaining for the task. Subjects were not corrected for mistakes. The subject was then asked to read out loud for 3 minutes from a disturbing newspaper article dealing with racial violence in urban areas. After each task, the subject completed a brief visual analog form that measured anxiety and anger.

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Table 2 provides heart rate, BP, and renin data for each task (seated baseline, mathematics, and news story) as well as an ANOVA summary table. Hypertensive subjects responded to captopril with a greater drop in BP (16/14 mm Hg versus 10/7 mm Hg in the normotensive subjects) for both systolic ($F_{1,44}=5.55$, $p=0.024$) and diastolic ($F_{1,44}=6.6$, $p=0.01$) BP. Capto-
angiotensin II fails to enhance norepinephrine receptors to enhance norepinephrine release in response to challenge. Birthday anxiety and comparable increases in anxiety (p<0.0001) and anger (p<0.05). For heart rate there was a significant task by diagnosis interaction, indicating that normotensive subjects had a greater heart rate response to the stressors compared with the hypertensive patients (F_{2.79}=3.6, p<0.05).

There was no drug effect on the magnitude of the task responses (the drug by task interactions were all non-significant, p>0.10).

**Discussion**

We were interested in examining the effects of ACE inhibitors on reactivity to psychological stressors for three reasons: ACE inhibitors are widely used antihypertensive agents, the sparse literature that exists focuses primarily on responses to exercise, and the physiological effects of ACE inhibition on sympathetic nervous system physiology are complex. Angiotensin II amplifies adrenergic vasoconstriction, and ACE inhibitors attenuate reflex sympathetic vasoconstriction in animals. Angiotensin II stimulates prejunctional receptors to enhance norepinephrine release in response to sympathetic nerve activity in animals. However in humans, angiotensin II fails to enhance norepinephrine release, and ACE inhibition fails to inhibit norepinephrine release in response to challenge.

The major observation of the present study was that captopril did not attenuate the BP or heart rate response to stressful tasks. Before we discuss these findings further, we wish to highlight some other observations and discuss some limitations of our study.

BP declined (Tables 2 and 3) from screening to hospitalization to the extent that at resting baseline, our “hypertensive” subjects were in a normotensive BP range at the time of the study. This fall in BP with hospitalization is noted commonly. If ACE inhibition diminishes reactivity to stressors, it is possible that such an effect is found in individuals with relatively more severe hypertension. However, two points suggest that this is unlikely. First, our repeatedly obtained screening BP determinations suggested that there was no doubt as to the elevated BP in our hypertensive subjects (average BP was 149/95 mm Hg). Second, our previous review of the effects of β blockers on reactivity found no lessening of reactivity in either the hypertensive or the normotensive group.

The current study used a fixed low dose of captopril. We cannot rule out the possibility that a higher dose might attenuate reactivity. However, the dose administered was sufficient to affect the renin-angiotensin system; renin levels increased and resting BP declined (Tables 2 and 3) from screening to hospitalization. The effects of ACE inhibition on sympathetic nervous system responses to short-term and longer term ACE inhibition. Since the present study did not examine ACE inhibitor effects for more than a few days, we cannot rule out diminished reactivity with long-term ACE inhibition. However, it should be noted that ACE inhibition for as long as 12 weeks had no effect on decreasing reactivity to dynamic exercise.

### Table 3. Task Responses and Analysis of Variance Summary

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Placebo</th>
<th>Captopril</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Seated</td>
<td>Math</td>
</tr>
<tr>
<td>Seated</td>
<td>Math</td>
<td>News</td>
</tr>
<tr>
<td>Mean SBP (mm Hg)</td>
<td>120 (2.4)</td>
<td>128 (3.1)</td>
</tr>
<tr>
<td>Mean DBP (mm Hg)</td>
<td>80 (2.0)</td>
<td>86 (2.2)</td>
</tr>
<tr>
<td>Mean HR (bpm)</td>
<td>78 (2.0)</td>
<td>81 (2.4)</td>
</tr>
<tr>
<td>Renin (ng/ml · hr^{-1})</td>
<td>7.2 (0.9)</td>
<td>8.2 (1.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Normotensive</th>
<th>Seated</th>
<th>Math</th>
<th>News</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SBP (mm Hg)</td>
<td>112 (1.6)</td>
<td>117 (2.2)</td>
<td>118 (1.9)</td>
</tr>
<tr>
<td>Mean DBP (mm Hg)</td>
<td>70 (1.5)</td>
<td>75 (2.2)</td>
<td>75 (2.0)</td>
</tr>
<tr>
<td>Mean HR (mm Hg)</td>
<td>70 (2.2)</td>
<td>76 (2.4)</td>
<td>76 (2.4)</td>
</tr>
<tr>
<td>Renin (ng/ml · hr^{-1})</td>
<td>8.0 (0.9)</td>
<td>9.2 (0.8)</td>
<td>8.0 (0.8)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Analysis of variance summary</th>
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<tbody>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>SBP</td>
</tr>
<tr>
<td>DBP</td>
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<tr>
<td>HR</td>
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<tr>
<td>Renin</td>
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</tbody>
</table>

Task response data are mean±SEM. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute; NS, not significant.

pril increased renin levels significantly (F_{1.27}=10.11, p=0.003).

The stressor tasks led to the expected increases in systolic and diastolic pressures, as well as in heart rate (F_{3.8}=38.6, 33.4, and 40, respectively, p<0.0001 for all three variables). Renin also increased in response to the stressors (F_{3.8}=3.53, p=0.037). Post-hoc Tukey analysis (with probability set at <0.05) indicated that the math task significantly increased renin over baseline, but there was no difference in renin levels between the news task and baseline. Both stressor tasks elicited significant and comparable increases in anxiety (p<0.0001) and anger (p<0.05). For heart rate there was a significant task by diagnosis interaction, indicating that normotensive subjects had a greater heart rate response to the stressors compared with the hypertensive patients (F_{2.79}=3.6, p<0.05).

There was no drug effect on the magnitude of the task responses (the drug by task interactions were all non-significant, p>0.10).
We observed no decreases in reactivity to the two stressor tasks we examined. It is a theoretical possibility that more stressful tasks or those posing a subtly different psychological challenge\textsuperscript{26} may be more sensitive to ACE inhibition.

We offer the above cautions mainly because of the sparseness of the literature on ACE inhibition and reactivity. However, we suspect that our observations would hold even with greater doses, duration, or different stressors. It is not that we assume the mantle of omniscience, but rather that our observations are so compatible with the numerous studies of other antihypertensive medications. There are numerous antihypertensive agents that lower resting BP. However, with the possible exception of guanethidine and \(\alpha\)-methyldopa,\textsuperscript{5} none of these types of antihypertensive therapy block the BP response to challenge, be it exercise or behavioral stress. Perhaps a human’s ability to respond to challenge is so important that it is wired in redundant fashion and thus not susceptible to blockade with most specific-acting drugs. It is, for instance, plausible that sympathetic nervous system responses are augmented in the face of ACE inhibition.

References

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