Captopril Modifies the Hemodynamic and Neuroendocrine Responses to Sodium Nitroprusside in Hypertensive Patients

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SUMMARY To determine if clinically effective doses of the antihypertensive agent captopril affected the neuronal release of norepinephrine or baroreflex sensitivity, changes in plasma norepinephrine concentration and heart rate were related to the changes in mean arterial pressure seen during the intravenous infusion of stepwise incremental doses of sodium nitroprusside before and during captopril treatment in eight hypertensive men with normal or low plasma renin activity. At all times, significant linear correlations were found between 1) the decrease in mean arterial pressure and the dose of sodium nitroprusside, 2) the increase in heart rate and the decrease in mean arterial pressure, and 3) the increase in plasma norepinephrine concentration and the decrease in mean arterial pressure. When the subjects were treated with captopril (25 mg t.i.d.) for 2 to 4 weeks, supine mean arterial pressure decreased from 130 to 114 mm Hg (-12%; p < 0.05), heart rate did not change, supine and upright plasma renin activity increased, while supine plasma norepinephrine and epinephrine concentration decreased slightly. Therapy with captopril (25 mg t.i.d.) increased baroreflex sensitivity, as assessed by the slope of the regression line relating the increase in heart rate to the decrease in mean arterial pressure, and increased the responsiveness of the sympathetic nervous system, as assessed by the slope of the regression line relating the increase in plasma norepinephrine concentration to the decrease in mean arterial pressure. These increases were accompanied by a decrease in the slope of the regression line relating the decrease in mean arterial pressure to the dose of sodium nitroprusside and thus were associated with a decreased sensitivity to the vasodepressor effects of sodium nitroprusside. These observations suggest that captopril's antihypertensive mechanism of action in hypertensive subjects with normal or low plasma renin activity does not involve an impairment of the sympathetic neuronal release of norepinephrine. (Hypertension 8: 229-237, 1986)

KEY WORDS • renin-angiotensin system • sympathetic nervous system • plasma norepinephrine concentration • baroreflex sensitivity • angiotensin converting enzyme inhibition

Captopril effectively decreases blood pressure by decreasing total peripheral resistance, although the factors responsible for this vasodilation are unknown. A reasonable assumption, however, is that captopril-induced vasodilation could result from either the blockade of one or more endogenous vasoconstrictor systems or the amplification of one or more endogenous vasodilator systems. Because captopril is an orally active inhibitor of angiotensin converting enzyme, which converts angiotensin I to angiotensin II (ANG II), the first and most logical mechanism to consider is a decrease in the direct vasoconstrictor effect of ANG II. Unfortunately, the antihypertensive effect of long-term captopril therapy is independent of circulating renin. For example, the antihypertensive responses to long-term captopril therapy does not appear to be related to the pretreatment values of plasma renin activity (PRA) or plasma ANG II concentration. In addition, captopril has been reported to lower blood pressure in fluid-depleted anephric patients.

Angiotensin converting enzyme is identical with the enzyme kininase II, and blockade of this enzyme with captopril could lead to an increased bradykinin concentration in the circulation. In addition to causing direct vasodilation, bradykinin also elicits the release
of prostaglandins from many tissues, and prostaglandins such as prostacyclin are known to be potent vasodilators. Although attempts have been made to implicate bradykinin and prostaglandins in captopril’s antihypertensive mechanism of action, the results of these clinical studies are not compelling.3-7

The sympathetic nervous system is a logical alternative site of action of captopril. Angiotensin II has been shown to amplify the pressor effects of the sympathetic nervous system by acting prejunctionally to increase the release of norepinephrine (NE) from the sympathetic neuron,8 by inhibiting the neuronal uptake of NE,9 by increasing the adrenal discharge of catecholamines,10 and by sensitizing arteriolar vascular smooth muscle to the vasoconstrictor effects of NE.11 Thus, captopril could lower blood pressure by preventing these indirect pressor effects of ANG II. In animal studies conducted in vivo and in vitro, captopril has been reported to interfere with the vasoconstriction caused by noradrenergic stimulation and exogenous NE. If clinically relevant doses of captopril exerted similar pharmacologic effects in hypertensive patients, then therapy with captopril would be expected to impair the neuronal release of NE and cause predictable changes in the neuroendocrine and pharmacodynamic responses to infusions of sodium nitroprusside.

In a previous study, we found that the stepwise decrements in mean arterial pressure (MAP) caused by infusing stepwise incremental doses of sodium nitroprusside result in stepwise increments in heart rate (HR) and plasma NE concentration in untreated supine hypertensive patients.25 By relating changes in HR (ΔHR) to the changes in MAP (ΔMAP) during the infusion of each dose of sodium nitroprusside, baroreflex sensitivity was calculated. In addition, the responsiveness of the sympathetic nervous system was assessed by relating the changes in plasma norepinephrine concentration (ΔNE) to ΔMAP. Using this method, we determined that significant linear correlations existed between ΔMAP and log dose of sodium nitroprusside, ΔHR and ΔMAP, and ΔNE and ΔMAP; however, the slopes of these relationships varied widely between patients. In addition, the responsiveness of the sympathetic nervous system, as gauged by ΔNE/ΔMAP, was inversely correlated with the slope of the vasodepressor–sodium nitroprusside dose-response curve.25

In the present study, we have used this same protocol of sodium nitroprusside infusion to determine the effect of multiple-dose therapy with captopril on the relationship between ΔMAP and dose of sodium nitroprusside, ΔHR/ΔMAP, and ΔNE/ΔMAP.

Materials and Methods

Eight white men (age, 51–69 years; weight, 65–102 kg) with essential hypertension were studied. All subjects were free of objective and subjective findings of angina pectoris, myocardial infarction, congestive heart failure, hepatic disease, renal disease, or diabetes mellitus. Results of routine biochemical, hematological, radiographic, and electrocardiographic examina-

tions conducted before and during the study were within normal limits. All subjects had been followed up regularly in the general medicine clinics at the Audie Murphy Veterans Administration Hospital. Because secondary hypertension was considered unlikely on the basis of clinical and laboratory data, no further specialized diagnostic procedures were performed.

Written informed consent was obtained on forms approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio, and all antihypertensive medications were discontinued 3 weeks before the study. During this period, subjects’ supine and upright blood pressure was measured weekly in triplicate on an outpatient basis. For inclusion in the study, each subject had to have a supine diastolic blood pressure greater than 95 mm Hg but not exceeding 120 mm Hg.

Each subject was hospitalized twice, once for baseline studies and once for study during captopril therapy. Studies were conducted in the General Clinical Research Center located in the Special Diagnostics and Treatment Unit of the Audie Murphy Veterans Administration Hospital. Coffee, tea, and tobacco were not allowed during either hospitalization. When dietary salt intake was regulated to match the estimated salt intake ingested as outpatients, the range of sodium excretion was 145 to 252 mEq/24 hours. No consistent changes in body weight were noted over the duration of the study. On the second hospital day of each admission, plasma samples for the measurement of PRA were obtained from each subject through an indwelling venous catheter after 1 hour in the supine position and after 4 hours of ambulation. When the relationship of upright PRA to 24-hour sodium excretion in each subject was compared with previously published data,26 five patients (Patients 1, 2, 6, 7, and 8) were determined to have normal PRA values and three (Patients 3–5) had low PRA values. The sodium nitroprusside infusion test was performed on the third hospital day of each admission.

Beginning at 2400 on the second hospital day, the subjects received nothing by mouth except water. They remained recumbent in bed. At 0600 a pediatric scalp vein needle with a heparin lock was placed in a right forearm vein for blood sampling. A second intravenous catheter in the contralateral forearm was used to administer a constant infusion of 5% glucose (3–5 ml/min) and the sodium nitroprusside. Beginning at 0700, immediately after the administration of either a placebo (baseline admission) or the morning dose of captopril, blood pressure was measured every 5 minutes from the right arm using an Arterisonde (Roche Electronics, Nutley, NJ, USA). The HR was recorded every 5 minutes during the control period by counting the radial pulse for 1 minute. The electrocardiogram was displayed continuously on an oscillographic monitor. At 0830, an infusion of sodium nitroprusside was started. The rate of infusion was controlled by a Harvard pump (Newport Beach, CA, USA) and was increased every 10 minutes from an initial dose of 0.05 μg/kg/min to a maximal dose of 1.2 μg/kg/min. Blood
pressure and HR were recorded every 2 minutes during the sodium nitroprusside infusion. The infusion was discontinued when the diastolic blood pressure fell below 90 mm Hg, when a decrease in MAP greater than 30 mm Hg was observed, or when HR increased by more than 25 beats/min. The number of sodium nitroprusside infusion steps ranged between five and eight for individual subjects. The total volume of fluid infused ranged between 200 and 400 ml during the 80-minute study. After discontinuation of sodium nitroprusside infusion, the subjects remained in bed until 1130.

Two samples of venous blood were drawn through the scalp vein needle during the last 15 minutes of the preinfusion period, and one sample of venous blood was drawn during the eighth minute of each infusion period (i.e., 2 minutes before the next increment in the dose). The scalp vein needle was kept patent with 0.15 M saline containing heparin, 10 units/ml. Blood samples were drawn into 5-ml plastic syringes and immediately transferred to precooled tubes containing 80 μl of a solution containing ethylene glycol bis (β-aminooethyl ether)-N,N,N',N'-tetraacetic acid (60 μg/ml) and reduced glutathione (90 μg/ml). Plasma was separated at 4°C and stored at -80°C until it was analyzed for NE and epinephrine (EPI)27 and PRA.28

After completion of the baseline sodium nitroprusside infusion test, the subjects were begun on a regimen of captopril, 25 mg t.i.d., and discharged from the hospital. After receiving captopril for 2 to 4 weeks, the subjects were again admitted to the hospital for 3 days for the second sodium nitroprusside infusion test.

All group values are expressed as the mean ± SEM. Baseline MAP and HR were calculated as the mean of the 12 measurements obtained at 5-minute intervals during the 60 minutes immediately before the sodium nitroprusside infusion was begun. The MAP was calculated as the diastolic pressure plus one third of the pulse pressure. During the sodium nitroprusside infusion, HR was determined by counting the number of heartbeats recorded during a 10-second reading of the electrocardiogram. Changes in MAP and HR were taken as the difference between baseline MAP and HR and the average of the three blood pressure and HR measurements made during the last 4 minutes of each infusion period. In all subjects, analysis of variance indicated no significant differences in the values of the three measurements of blood pressure and HR made during the last 4 minutes of each infusion period.

Plasma NE and EPI concentrations were the mean of duplicate determinations for each sample. The changes in plasma NE and EPI concentrations were taken as the difference between the mean of the two baseline values and the values determined 8 minutes after each dose increment. The PRA was the mean of triplicate determinations for each sample. The change in PRA was taken as the difference between the mean of the two baseline values and the values measured 8 minutes after each dose increment.

Statistical analysis included paired Student’s t test and linear least-squares regression analysis. Significant differences were those that had less than a 5% likelihood of occurring by chance (p < 0.05).

Results

Resting Supine Hemodynamic and Neuroendocrine Measurements During Multiple-Dose Captopril Therapy

Administration of captopril (25 mg t.i.d.) for 2 to 4 weeks significantly decreased supine MAP from 130 to 114 mm Hg (−12%) but did not affect basal HR (Table 1). The magnitude of the decrease in blood pressure varied among the subjects and was not related either to supine or upright PRA or to the basal concentrations of plasma NE or EPI. Therapy with captopril caused a significant increase in both supine and upright PRA. The percentage of increase in PRA seen on assumption of upright posture was the same before and during captopril treatment. After captopril treatment, both supine plasma NE (−14%, p < NS) and EPI (−21%, p < 0.05) concentrations were decreased slightly. It is unlikely that these decreases in basal plasma catecholamine concentrations are of biological significance since larger variations in basal plasma NE and EPI concentrations have been observed in untreated subjects when blood samples were drawn on the same day or several weeks apart.29-31

Hemodynamic Response to Sodium Nitroprusside Before and During Therapy with Captopril

Sodium nitroprusside caused dose-dependent reductions in MAP before and during captopril therapy (Figure 1). Significant linear correlations were found between ΔMAP and log dose or dose of sodium nitroprusside (r > 0.60, p < 0.05) in each subject before and during captopril therapy. The range of sodium nitroprusside doses infused was similar in both situations; however, during captopril treatment the subjects’ vasodepressor response to sodium nitroprusside decreased in that the vasodepressor dose-response curve was shifted to the right (see Figure 1). The decrease in MAP caused by sodium nitroprusside doses of 0.1, 0.2, and 0.4 μg/kg/min was significantly reduced during captopril treatment. For example, at a sodium nitroprusside dose of 0.4 μg/kg/min, the average reduction in MAP was 17 ± 3 mm Hg before therapy with captopril as compared to a decrease of 11 ± 3 mm Hg during treatment with captopril. Moreover, the interpolated dose of sodium nitroprusside required to reduce MAP by 8 mm Hg was increased threefold during treatment with captopril. The increase in HR resulting from sodium nitroprusside–induced vasodepression was greater during captopril treatment (see Figure 1). Although this difference did not achieve statistical significance at the 0.1, 0.2, or 0.4 μg/kg/min doses of sodium nitroprusside, the ΔHR/ΔMAP ratio was significantly increased at these doses (Table 2).

Baroreflex sensitivity was calculated by linear regression analysis of ΔHR versus ΔMAP during a nitroprusside infusion test,23 and significant linear correlations were noted in each subject before and during
crease in the slope of the relationship AHR/AMAP with captopril. As shown in Figure 2A, five subjects (Patients 1, 2, 4, 5, and 8) exhibited an obvious increase in baseline MAP before and during captopril therapy (r = 0.60, p < 0.05). The average change in the relationship of AHR/AMAP (see Figure 2B) was unchanged in two subjects (Patients 3 and 6; Figure 2B, but the relationship of AHR/AMAP was shifted to the left (increase in y intercept), which was consistent with a "resetting" of the baroreflex.  

Patient 7 had no change in the relationship of AHR/AMAP (see Figure 2B). No relationship was found between the individual changes in baroreflex sensitivity and the respective magnitude of the vasodepressor response to captopril. Despite the variability in the patterns of change in baroreflex sensitivity, it is apparent that any given reduction in blood pressure with sodium nitroprusside resulted in a greater increase in HR during captopril therapy (see Figures 1 and 2, Table 2).

A significant positive correlation was found when the slopes of the regression lines relating ΔHR to ΔMAP increased insignificantly from 0.75 ± 0.19 to 1.13 ± 0.15 (beats/min)/mm Hg during treatment with captopril. As shown in Figure 2A, five subjects (Patients 1, 2, 4, 5, and 8) exhibited an obvious increase in the slope of the relationship ΔHR/ΔMAP with variable changes in the y intercept. The slope was unchanged in two subjects (Patients 3 and 6; Figure 2B), but the relationship of ΔHR/ΔMAP was shifted to the left (increase in y intercept), which was consistent with a "resetting" of the baroreflex.  

Patient 7 had no change in the relationship of ΔHR/ΔMAP (see Figure 2B). No relationship was found between the individual changes in baroreflex sensitivity and the respective magnitude of the vasodepressor response to captopril. Despite the variability in the patterns of change in baroreflex sensitivity, it is apparent that any given reduction in blood pressure with sodium nitroprusside resulted in a greater increase in HR during captopril therapy (see Figures 1 and 2, Table 2).

A significant positive correlation was found when each subject's baseline MAP before and during captopril treatment was related to the slope of the sodium nitroprusside dose-response curve (ΔMAP/log_{10} dose) before and during treatment with captopril (r = 0.53, p < 0.05; n = 16). Baroreflex sensitivity (ΔHR/ΔMAP) before and during captopril treatment was inversely related to baseline MAP before and during captopril therapy (r = -0.60, p < 0.05; n = 16).

**Neuroendocrine Responses to Sodium Nitroprusside Before and During Captopril Therapy**

Sodium nitroprusside–induced vasodepression produced dose-dependent increases in plasma NE concentration.

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**Table 1. Baseline Hemodynamic and Endocrine Values Before and During Therapy with Captopril (25 mg t.i.d., 2 to 4 weeks)**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Control Supine MAP (mm Hg)</th>
<th>Control Supine HR (beats/min)</th>
<th>Control Supine NE (pg/ml)</th>
<th>Control Supine EPI (pg/ml)</th>
<th>Control Supine PRA (ng ANG 1/ml/hr)</th>
<th>Captopril Supine MAP</th>
<th>Captopril Supine HR</th>
<th>Captopril Supine NE</th>
<th>Captopril Supine EPI</th>
<th>Captopril Supine PRA (ng ANG 1/ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>130</td>
<td>118</td>
<td>60</td>
<td>56</td>
<td>278</td>
<td>286</td>
<td>67</td>
<td>59</td>
<td>0.48</td>
<td>0.93</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
<td>89</td>
<td>74</td>
<td>67</td>
<td>250</td>
<td>188</td>
<td>44</td>
<td>27</td>
<td>0.49</td>
<td>0.62</td>
</tr>
<tr>
<td>3</td>
<td>119</td>
<td>108</td>
<td>68</td>
<td>72</td>
<td>180</td>
<td>120</td>
<td>38</td>
<td>19</td>
<td>0.19</td>
<td>0.10</td>
</tr>
<tr>
<td>4</td>
<td>133</td>
<td>115</td>
<td>71</td>
<td>75</td>
<td>149</td>
<td>124</td>
<td>79</td>
<td>31</td>
<td>0.13</td>
<td>1.02</td>
</tr>
<tr>
<td>5</td>
<td>130</td>
<td>118</td>
<td>52</td>
<td>52</td>
<td>245</td>
<td>125</td>
<td>48</td>
<td>23</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>6</td>
<td>120</td>
<td>106</td>
<td>76</td>
<td>79</td>
<td>356</td>
<td>336</td>
<td>95</td>
<td>87</td>
<td>0.19</td>
<td>1.46</td>
</tr>
<tr>
<td>7</td>
<td>147</td>
<td>130</td>
<td>84</td>
<td>93</td>
<td>260</td>
<td>260</td>
<td>71</td>
<td>78</td>
<td>0.46</td>
<td>0.64</td>
</tr>
<tr>
<td>8*</td>
<td>139</td>
<td>128</td>
<td>82</td>
<td>70</td>
<td>213</td>
<td>209</td>
<td>48</td>
<td>62</td>
<td>0.29</td>
<td>1.34</td>
</tr>
</tbody>
</table>

Mean ± SEM: 130 ± 4, 114 ± 5, 71 ± 4, 70 ± 5, 241 ± 22, 206 ± 29, 61 ± 7, 48 ± 9†, 0.28 ± 0.06, 0.77 ± 0.19†, 0.83 ± 0.22, 2.74 ± 0.80†

MAP = mean arterial pressure; HR = heart rate; NE = plasma norepinephrine concentration; EPI = plasma epinephrine concentration; PRA = plasma renin activity; ANG I = angiotensin I.

*Patient 8 received 50 mg of captopril (t.i.d.).

†p < 0.05, compared with control values.

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**Table 2. The Ratios of the Increases in Heart Rate and Plasma Norepinephrine Concentration to the Decreases in Mean Arterial Pressure at Specific Doses of Sodium Nitroprusside Before and During the Administration of Captopril (25 mg t.i.d.)**

<table>
<thead>
<tr>
<th>Sodium nitroprusside (µg/kg/min)</th>
<th>ΔHR/ΔMAP</th>
<th>ΔNE/ΔMAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.6 ± 0.2</td>
<td>2.6 ± 0.7*</td>
</tr>
<tr>
<td>0.2</td>
<td>1.0 ± 0.4</td>
<td>2.7 ± 0.9*</td>
</tr>
<tr>
<td>0.4</td>
<td>1.0 ± 0.3</td>
<td>1.7 ± 0.4*</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Δ = change; HR = heart rate; MAP = mean arterial pressure; NE = plasma norepinephrine concentration.

*p < 0.05, †p > 0.05, ‡p < 0.02, compared with control values.

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**Figure 1. Relationship between increases in heart rate and decreases in mean arterial pressure and the infused doses (µg/kg/min) of sodium nitroprusside before (----) and during (------) captopril therapy. Asterisk indicates significant difference between values (p < 0.05); †no significance.**

**Figure 2A.** Increase in baroreflex sensitivity (AHR/AMAP) before and during captopril therapy (r = 0.60, p < 0.05). The average change in the relationship of AHR/AMAP (see Figure 2B) was unchanged in two subjects (Patients 3 and 6; Figure 2B, but the relationship of AHR/AMAP was shifted to the left (increase in y intercept), which was consistent with a "resetting" of the baroreflex. Patient 7 had no change in the relationship of AHR/AMAP (see Figure 2B). No relationship was found between the individual changes in baroreflex sensitivity and the respective magnitude of the vasodepressor response to captopril. Despite the variability in the patterns of change in baroreflex sensitivity, it is apparent that any given reduction in blood pressure with sodium nitroprusside resulted in a greater increase in HR during captopril therapy (see Figures 1 and 2, Table 2).
tation before and during treatment with captopril; the average increase at each infusion rate of sodium nitroprusside was greater during captopril therapy (Figure 3). Because the vasodepressor response to sodium nitroprusside was decreased during treatment with captopril (see Figure 1), the ΔNE/ΔMAP ratio was increased (see Table 2). Although the increases in the ΔNE/ΔMAP ratio at the specific sodium nitroprusside doses of 0.1 and 0.4 μg/kg/min did not achieve statistical significance, the increase in the ΔNE/ΔMAP ratio was significant at the 0.2 μg/kg/min dose (see Table 2). Moreover, the average interpolated increase in plasma NE concentration in response to a decrease in MAP of 8 mm Hg rose fivefold during captopril therapy ($p < 0.05$).

The responsiveness of the sympathetic nervous system was assessed by linear regression analysis of ΔNE compared with ΔMAP, and significant linear correlations were found between ΔNE and ΔMAP in each subject before and during captopril therapy ($r > 0.60$, $p < 0.05$). The average of the slopes of the regression lines relating ΔNE to ΔMAP increased insignificantly from 6.85 ± 1.30 to 12.15 ± 3.29 (pg/ml)/mm Hg during captopril treatment. In six subjects (Patients 1, 2, 4-6, and 8), the slope of the relationship ΔNE/ΔMAP was increased with variable changes in the $y$ intercept (Figure 4A). The slope decreased and the $y$ intercept increased in Patient 7, whereas no change in slope or $y$ intercept occurred in the remaining patient (Patient 3; Figure 4B). Thus, during captopril treatment the decrease in the vasodepressor response to sodium nitroprusside (see Figure 1) was associated with an increase in the sympathetic nervous system response to a decrease in blood pressure, as assessed by ΔNE/ΔMAP (see Figures 3 and 4, Table 2).

Both before and during captopril therapy, plasma EPI concentration increased by an average of 30% at the largest dose of sodium nitroprusside, but no relationship was noted between the change in EPI concentration and ΔMAP.

The PRA increased during sodium nitroprusside infusion before and during captopril treatment, but no relationship was found between the change in PRA and either ΔMAP or ΔNE. The subjects with the lowest baseline PRA values (angiotensin I <0.3 ng/ml/hr) exhibited only a modest elevation of PRA during the baseline (no captopril) sodium nitroprusside infusion test. Despite the fact that captopril therapy increased basal supine PRA (see Table 1), the rise in PRA caused by sodium nitroprusside–induced vasodepression was only slightly greater during captopril treatment as compared to the renin response in the absence of captopril (baseline). The modest response of PRA to sodium nitroprusside–induced vasodepression is consistent with the previous observation that the baroreflexly mediated increase in PRA caused by sodium nitroprusside is proportional to the pretreatment value of PRA.$^{33}$

**Discussion**

The major finding of this study is that baroreflex sensitivity (ΔHR/ΔMAP) and sympathetic responsiveness (ΔNE/ΔMAP) determined during the infusion of stepwise incremental doses of sodium nitroprusside were increased in a group of hypertensive subjects with normal and low PRA who exhibited a decrease in...
blood pressure during treatment with captopril as a single antihypertensive agent. Moreover, these increases were associated with a decrease in the subjects' sensitivity to the vasodepressor effect of sodium nitroprusside. Our observations indicate that captopril, at clinically effective doses, did not interfere with the neuronal release of NE did occur, it must have been minor and completely overridden by the observed increase in normal or low PRA. If any impairment of the neuronal release of NE in hypertensive subjects with prusside. Our observations indicate that captopril, at sensitivity to the vasodepressor effect of sodium nitroprusside biased the results since this drug has no direct effect on NE release.34

The original suggestion that captopril interfered with the prejunctional facilitation of NE release by ANG II was based on the results of a series of studies in which captopril blunted the pressor response to electrical stimulation of the spinal cord in pithed spontaneously hypertensive rats.12-15 Because multiple-dose therapy with captopril also lessened the pressor effect of intravenously injected NE in these rats, it was concluded that captopril, by decreasing ANG II production, might interfere with both the prejunctional and postjunctional noradrenergic potentiating effects of ANG II. It should be stressed that the actual neuronal release of NE during electrical stimulation of the spinal cord, as gauged by an increase in plasma NE concentration, was not measured in these experiments.12-15 so a distinction between ANG II-mediated effects at prejunctional or postjunctional sites cannot be made.

More recent experiments conducted with pithed normotensive rats indicated that the sympathoinhibitory effect of captopril is mimicked by other inhibitors of converting enzyme and the ANG II receptor antagonist saralasin.18-19 Moreover, the ability of converting enzyme inhibitors and saralasin to blunt the blood pressure increase caused by sympathetic stimulation results from the fact that PRA is very high in pithed rats, and these drugs cause a large decrease in basal MAP by preventing the direct vasoconstrictor effects of ANG II.19-20 The decrease in basal arteriolar tone caused by these drugs appears to be the mechanism by which these drugs exert their sympathoinhibitory effects.20 This conclusion is consistent with the observation that an increase in the cross-sectional area of the resistance arterioles will decrease the pressor response to vasoconstrictor stimuli.33 Lastly, the "real" prejunctional sympathoinhibitory effect of captopril is minor and can only be demonstrated in pithed rats under carefully controlled experimental conditions.20 Based on these observations,12-20 it can be concluded that captopril primarily decreases sympathetically mediated vasoconstriction in rats by decreasing the postjunctional effects of ANG II. Therefore, it is not surprising that the increase in plasma NE concentration caused by sodium nitroprusside was not impaired in our captopril-treated subjects.

Captopril lowered blood pressure in the eight hypertensive subjects despite the fact that the average basal PRA was low to normal (see Table 1). In this context, captopril has been reported to impair the vasoconstrictor elicited by sympathetic stimulation and NE in the isolated perfused rat mesentry21,22 and kidney,23 apparently by a mechanism independent of the inhibition of ANG II formation. It is doubtful that such a direct action of captopril on vascular smooth muscle contributed to the antihypertensive effect of captopril in our subjects for two reasons. First, the concentrations of captopril used in the perfusion studies (3-100 μg/ml; see References 21-23) exceed the plasma concentrations of captopril observed after single-dose or multiple-dose therapy in humans. For example, a single 100-mg dose of captopril given orally to normotensive humans resulted in an average peak plasma concentration of 0.8 μg/ml (range, 0.5-1.3 μg/ml) at 0.5 to 1.5 hours.34 Also, when 12 normotensive humans were given 100 mg (t.i.d.) of captopril for seven doses, the average peak plasma concentration after the last dose was 0.7 ± 0.1 μg/ml.37 Second, any direct inhibitory effect of captopril on the ability of vascular smooth muscle to contract would have increased the subjects' sensitivity to the vasodepressor effect of sodium nitroprusside, yet the subjects became relatively resistant to sodium nitroprusside.

Even though several groups of investigators38-45 have assessed the effects of captopril on autonomic function in humans, comparison of the various results is difficult due to differences in experimental protocols such as duration of therapy, dosing regimen, presence or severity of hypertension, and most importantly, the method used to assess autonomic function. As a result, disparate results have been reported, and the reasons for these conflicting results are not always apparent. The findings and conclusions of previous studies can be compared with those of the present study, however, and our findings are largely consistent with the majority of these other studies.

The effect of a single oral dose of captopril on baro-
reflex function has been studied. Mancia et al. 38 found that the blood pressure increase caused by isometric handgrip and the cold pressor test was not altered by a 50-mg dose of captopril that decreased MAP from 130 to 119 mm Hg in eight hypertensive patients. In addition, they determined the effect of captopril on the change in the cardiac RR interval caused by activation of the arterial baroreceptors with the pressor agent phenylephrine and the deactivation of the arterial baroreceptors with the vasodepressor agent nitroglycerin. The slope of the increase in cardiac interval per unit increase in blood pressure with phenylephrine was not affected by captopril; however, the slope of the change in cardiac interval per unit decrease in blood pressure with nitroglycerin was much steeper after captopril. Lastly, the increase in blood pressure caused by positive neck pressure was increased after captopril, but the decrease in blood pressure caused by negative neck pressure was not affected by captopril. Thus, in agreement with our results, Mancia et al. 38 observed a potentiation of baroreflex activity when the arterial baroreceptors were deactivated with nitroglycerin or positive neck pressure. On the other hand, Imai et al. 39 found that the reflexly mediated bradycardia caused by injected NE or arginine vasopressin was enhanced in hypertensive subjects, who exhibited a lower average MAP was decreased by 14% but basal HR and plasma catecholamine concentration elicited by the decrease in blood pressure caused by negative neck pressure was increased after captopril, but the change in the cardiac RR interval caused by activation of the arterial baroreceptors with the vasodepressor agent nitroglycerin. AHR/AMAP determined when supine MAP was decreased by an intravenous infusion of stepwise incremental doses of sodium nitroprusside. In contrast to our results, captopril was found to enhance the vaso- depressor effect of sodium nitroprusside. Because a vigorous rise in PRA was seen as MAP was lowered with sodium nitroprusside, it is possible that the direct vasoconstrictor effect of ANG II made a greater contribution to the maintenance of blood pressure during the infusion of sodium nitroprusside in these young normotensive humans as compared to that in our older hypertensive subjects, who exhibited a lower average basal PRA and only a modest elevation of PRA during the infusion of sodium nitroprusside. This explanation is supported by our previous observation that the renin-angiotensin system did not appear to contribute to the maintenance of blood pressure when vasodepression was induced with sodium nitroprusside in a group of diuretic-treated hypertensive patients with low to normal PRA. 35

Niarchos et al. 41 studied the effects of multiple-dose therapy with captopril on autonomic reflexes in hypertensive patients. After a dose of 400 mg/day for 7 days, MAP was decreased by 14% but basal HR and plasma NE and EPI concentrations were unchanged. Other investigators have reported that multiple-dose therapy with captopril (300-600 mg/day) did not affect basal plasma NE and EPI concentrations 34, 40 or the increase in plasma catecholamine concentration elicited by orthostasis 42 and ergometric exercise 43 in hypertensive patients. In the latter report, the increase in MAP caused by exercise was blunted. 43 However, multiple-dose captopril therapy (150-600 mg/day) in hypertensive patients did not affect the blood pressure increase elicited by mental stress, 44 cold pressor test, 44 isometric handgrip, 44 or upright posture. 41, 42, 44 Moreover, baroreflex sensitivity, as assessed by relating the changes in cardiac interval to the changes in systolic blood pressure after the intravenous injection of phenylephrine or the inhalation of amyl nitrite, was not altered by treatment with captopril (345 mg/day). 45 Thus, in agreement with our findings, sympathetic reflexes are enhanced 38 or maintained 44, 45 during multiple-dose captopril therapy.

Warren et al. 46 presented indirect evidence that captopril decreases the contribution of the peripheral sympathetic nervous system to blood pressure maintenance in hypertensive patients. Both the absolute and relative decreases in supine blood pressure caused by the intravenous injection of phentolamine were less after a 5-day treatment with captopril (345 mg/day). In contrast, the decrease in blood pressure caused by the inhalation of amyl nitrite was of the same absolute and relative value before and during captopril treatment. Despite the claim that sympathetic drive was decreased by captopril, the urinary excretion of total catecholamines, metanephrine, and vanillylmandelic acid and plasma dopamine-β-hydroxylase activity were not affected by captopril treatment. It is possible that a sympathoinhibitory effect of captopril could have been detected in our subjects if they had been treated with doses much greater than 75 mg/day, as in the study of Warren et al. 45

The increase in baroreflex activity that we observed in our subjects during captopril treatment may represent a more general adjustment to a decrease in blood pressure per se. For example, we previously have reported that baroreflex sensitivity (ΔHR/ΔMAP) was inversely related to baseline MAP in a group of diuretic-treated hypertensive patients. 23 A similar inverse relationship between baroreflex sensitivity and baseline MAP was found in the present study when ΔHR/ΔMAP (during sodium nitroprusside infusion) was plotted against the control MAP of each subject before and during treatment with captopril. Carella et al. 46 also noted that baroreflex sensitivity varied inversely with control MAP in a group of hypertensive patients before, during, and after treatment with hydrochlorothiazide. When blood pressure was decreased with this diuretic agent, baroreflex sensitivity was increased. When treatment was discontinued, the increase in baroreflex sensitivity persisted as long as blood pressure remained decreased.

In summary, we found that treatment with captopril increased baroreflex sensitivity, as gauged by the relationship ΔHR/ΔMAP, and sympathetic responsiveness, as assessed by ΔNE/ΔMAP, during the infusion of stepwise incremental doses of sodium nitroprusside, in association with a relative resistance to the vasodepressor effects of sodium nitroprusside. These data
suggest that captopril’s antihypertensive mechanism of action in hypertensive patients with normal or low PRA does not result from an impairment of the neuronal release of NE. The increases in baroreflex sensitivity and sympathetic responsiveness may explain the absence of postural hypotension during therapy with captopril.

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References


