

## EFFECT OF BRADYKININ-RECEPTOR BLOCKADE ON THE RESPONSE TO ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

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### ABSTRACT

**Background** Angiotensin-converting-enzyme (ACE) inhibitors not only decrease the production of angiotensin II but also decrease the degradation of bradykinin. In this study, a specific bradykinin-receptor antagonist, icatibant acetate (HOE 140), was used to determine the contribution of bradykinin to the short-term effects of ACE inhibition on blood pressure and plasma renin activity in both normotensive and hypertensive subjects.

**Methods** We compared the hemodynamic, renal, and endocrine effects of captopril alone (25 mg), captopril plus icatibant (100  $\mu$ g per kilogram of body weight), the angiotensin II subtype 1-receptor antagonist losartan (75 mg), and placebo in 20 subjects with normal blood pressure and 7 subjects with hypertension. The subjects were studied while they were salt depleted (i.e., in balance on a diet in which they were allowed 10 mmol of sodium per day). The drugs were administered on four separate study days in a single-blind, randomized fashion.

**Results** The coadministration of icatibant significantly attenuated the hypotensive effect of captopril (maximal decrease in mean [ $\pm$ SE] arterial pressure for all subjects combined,  $10.5 \pm 1.0$  mm Hg, as compared with  $14.0 \pm 1.0$  mm Hg for captopril alone;  $P=0.001$ ), in such a way that the decrease in blood pressure after the administration of captopril plus icatibant was similar to that after the administration of losartan (maximal decrease in mean arterial pressure,  $11.0 \pm 1.7$  mm Hg). Icatibant did not alter the renal hemodynamic response to captopril, but it significantly altered the change in plasma renin activity in response to ACE inhibition ( $-0.4 \pm 0.4$  ng of angiotensin I per milliliter per hour, as compared with  $2.0 \pm 0.7$  ng per milliliter per hour for captopril alone;  $P=0.007$ ). The magnitude of these effects was similar in both the normotensive and the hypertensive subjects, as well as in both the black subjects and the white subjects.

**Conclusions** These data confirm that bradykinin contributes to the short-term effects of ACE inhibition on blood pressure in normotensive and hypertensive persons and suggest that bradykinin also contributes to the short-term effects of ACE inhibition on the renin-angiotensin system. (N Engl J Med 1998;339:1285-92.)

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**A**NGIOTENSIN-CONVERTING enzyme (ACE) catalyzes the formation of angiotensin II from angiotensin I and the breakdown of bradykinin into inactive products.<sup>1</sup> ACE inhibitors are widely used in the treatment of hypertension, congestive heart failure, and diabetic nephropathy, and they decrease blood pressure without increasing the heart rate.<sup>2</sup> Given over the short term, they decrease angiotensin II and aldosterone concentrations and increase plasma renin activity.<sup>2</sup> Under most conditions, ACE inhibitors cause natriuresis and increase renal plasma flow without altering the glomerular filtration rate.<sup>3-5</sup>

The contribution of bradykinin to the actions of ACE inhibitors has been the subject of debate. With long-term administration, ACE inhibitors lower blood pressure, even in patients with low-renin hypertension,<sup>2</sup> suggesting an effect that is independent of a decrease in angiotensin II. Bradykinin is a potent vasodilator, acting through the release of prostacyclin, nitric oxide, and endothelial-derived hyperpolarizing factor.<sup>6</sup> Accurate measurement of bradykinin concentrations is technically difficult, and bradykinin concentrations have been reported to be increased<sup>7</sup> or unchanged<sup>8</sup> after ACE inhibition. ACE inhibition potentiates the hemodynamic effects of exogenous bradykinin,<sup>9</sup> but this observation does not address whether endogenous bradykinin plays a part in the actions of ACE inhibitors. Determining the contribution of bradykinin to the effects of ACE inhibitors is relevant, given the widespread use of these agents and the introduction of specific angiotensin II subtype 1-receptor antagonists.

The availability of a specific bradykinin-receptor antagonist, icatibant acetate (HOE 140),<sup>10</sup> has allowed investigators to determine the contribution of bradykinin to the effects of ACE inhibitors in animals. Administration of icatibant attenuates the hypotensive response to ACE inhibition in rats<sup>11,12</sup> and dogs.<sup>13</sup> Using icatibant, Hornig et al. recently demonstrated that bradykinin contributes to ACE-inhibitor-induced vasodilatation in the human forearm.<sup>14</sup> Our purpose in the present study was to measure

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the contribution of bradykinin to the hemodynamic, endocrine, and renal responses to short-term ACE inhibition by comparing the effects of the ACE inhibitor captopril, captopril plus icatibant, the angiotensin-receptor antagonist losartan, and placebo in healthy normotensive and hypertensive subjects who were salt depleted.

## METHODS

The subjects provided a complete history and underwent physical and laboratory examinations. Those with diseases other than hypertension were excluded from the study, as were pregnant women. Subjects were considered to have hypertension if they had a documented untreated diastolic blood pressure of 90 mm Hg or more on at least three occasions or had had hypertension for at least six months. Written informed consent was obtained from all the subjects, and the protocol was approved by the institutional review board of Vanderbilt University Medical Center.

Each subject was provided a daily diet containing 10 mmol of sodium, 100 mmol of potassium, and 2500 ml of water for a total of 12 days. The subjects were studied under conditions of salt depletion because angiotensin and kinin are maximally stimulated by sodium depletion.<sup>15</sup> On days 6, 8, 10, and 12 of the diet, the subjects reported to the Vanderbilt Clinical Research Center at 7 a.m. after an overnight fast. A catheter was inserted into each antecubital vein, one for the infusion of drug and the other for drawing blood. On day 6 of the diet, blood was drawn for the determination of plasma renin activity after the subject had been standing for at least one half-hour. (Subjects with normal-to-high levels of renin activity were defined as those who had plasma renin activity of at least 2.4 ng of angiotensin I per milliliter per hour while in an upright position.<sup>16</sup>) The subjects remained in the supine position and fasted during the remainder of the study and on days 8, 10, and 12. After collection of a control blood sample, loading doses of aminohippurate (8 mg per kilogram of body weight, Merck Sharp and Dohme, West Point, Pa.) and inulin (50 mg per kilogram, Iso-Tex Diagnostics, Friendswood, Tex.) were given. Constant infusions were then initiated at a rate of 12 mg per minute for aminohippurate and 30 mg per minute for inulin.<sup>16</sup> Plasma samples were obtained 90 minutes after the start of the infusion of aminohippurate and inulin and 1, 3, and 4 hours after the administration of the study drugs. Renal vascular resistance was calculated as the ratio of mean arterial pressure to renal plasma flow.

Study drugs were administered in a single-blind fashion on each of the four study days as follows: 25 mg of oral captopril (Capoten, Bristol-Myers Squibb, Princeton, N.J.) plus intravenous vehicle (normal saline), 25 mg of oral captopril plus 100  $\mu$ g per kilogram of intravenous icatibant (a gift from Hoechst, Frankfurt, Germany), 75 mg of oral losartan (Cozaar, Merck Sharp and Dohme) plus intravenous vehicle, and oral placebo plus intravenous vehicle. The order in which the subjects received the treatments was randomly assigned. Oral medications were given at time 0 in opaque, identical-appearing capsules. The 25-mg dose of captopril was chosen because maximal renal vasodilation occurs at this dose,<sup>3</sup> with the peak response occurring within one hour after administration.<sup>17</sup> A dose of approximately 75 mg of losartan has been shown to block most fully the pressor response to angiotensin II in normal subjects,<sup>18</sup> with the peak response occurring three to four hours after administration.<sup>19</sup> Icatibant (100  $\mu$ g per milliliter) or vehicle was infused for the first hour. The total dose of icatibant (100  $\mu$ g per kilogram) has been previously shown to inhibit the vasodilator response to bradykinin in the forearm without affecting blood pressure or heart rate in normal controls.<sup>20</sup> Pilot studies in three normotensive and two hypertensive subjects confirmed bradykinin antagonism over the period of the study and the lack of effect of icatibant alone on blood pressure or heart rate.

Blood was collected for the determination of plasma renin activity and aldosterone concentrations at time 0 and four hours after the administration of the oral drugs. Urine was collected at

time 0 and two and four hours after oral-drug administration for measurement of urine electrolytes and the stable hydrolysis product of prostacyclin, 2,3-dinor-6-keto-prostaglandin-F<sub>1 $\alpha$</sub> .

## Laboratory Analysis

Blood samples were collected, placed on ice, and spun immediately, and the supernatant was frozen at  $-70^{\circ}\text{C}$  until the samples were assayed. Urinary sodium concentrations were measured by flame photometry. The concentrations of aminohippurate and inulin were measured by an AutoAnalyzer.<sup>16</sup> Plasma renin activity was measured by radioimmunoassay for angiotensin I at  $37^{\circ}\text{C}$  and pH 7.4.<sup>21</sup> Aldosterone concentrations were measured by radioimmunoassay (Coatcount Products, Los Angeles). 2,3-Dinor-6-keto-prostaglandin-F<sub>1 $\alpha$</sub>  was measured by gas chromatography–negative-ion chemical-ionization mass spectrometry.<sup>22</sup>

## Statistical Analysis

Data are expressed as means  $\pm$ SE. Missing values (see below) were excluded from the calculations of the means. Comparisons among drug treatments were made by analysis of variance with repeated measures in which the within-subject variables were drug and time. The between-subject variables were race, disease status (hypertension as compared with normotension), and renin status (low as compared with normal-to-high activity). Comparisons between drug treatments at a specific time were made with the use of a paired t-test or, if appropriate, the Wilcoxon signed-rank test. Comparisons between groups were made with the use of an unpaired t-test or the Mann–Whitney U test. All P values are two-sided.

## RESULTS

Twenty subjects with normal blood pressure (10 blacks and 10 whites; 12 men and 8 women) and 7 subjects with hypertension (3 blacks and 4 whites; 3 men and 4 women) completed the study. Two normotensive subjects withdrew after one study day, and one was excluded because of noncompliance with the dietary requirements. Due to technical difficulties, blood samples for aminohippurate and inulin measurements were not obtained from one normotensive black subject during treatment with losartan and from two other subjects at one time during placebo treatment; blood samples were not obtained from one hypertensive white subject for the determination of renin activity and aldosterone concentrations during treatment with losartan.

The mean untreated blood pressure of the hypertensive subjects while seated and before sodium depletion was  $147 \pm 2.9/95.1 \pm 2.6$  mm Hg. As compared with the normotensive subjects, the hypertensive subjects were significantly older ( $42.6 \pm 4.7$  vs.  $29.9 \pm 1.8$  years,  $P=0.005$ ) and heavier (body-mass index [the weight in kilograms divided by the square of the height in meters],  $32.4 \pm 1.7$  vs.  $25.2 \pm 1.0$ ;  $P=0.002$ ). Seven of the 20 normotensive subjects (4 of the 10 whites and 3 of the 10 blacks) and 5 of the 7 hypertensive subjects (3 of the 4 whites and 2 of the 3 blacks) had low renin activity when in an upright position.

The base-line characteristics of the subjects are shown in Table 1. The mean arterial pressure was significantly higher in the hypertensive subjects than in the normotensive subjects ( $P<0.001$  for all study days). Renal vascular resistance was significantly high-

TABLE 1. BASE-LINE DATA AND URINARY SODIUM EXCRETION AFTER EACH TREATMENT.\*

VARIABLE	PLACEBO	CAPTAPRIL	CAPTAPRIL + ICATIBANT	LOSARTAN
Mean arterial pressure (mm Hg)				
All subjects	85.1±1.8	86.6±2.0	85.4±1.8	84.4±2.0
Normotensive subjects	81.5±1.6	83.1±1.8	82.1±1.7	80.7±1.8
Hypertensive subjects	95.5±2.4†	96.8±4.2†	94.9±2.6†	94.5±3.3†
Heart rate (beats/min)				
All subjects	61.8±1.9	62.1±1.8	61.4±1.8	62.4±1.7
Normotensive subjects	60.1±2.1	61.2±2.2	59.9±2.1	61.1±2.0
Hypertensive subjects	66.6±3.6	64.5±3.3	65.6±2.7	66.3±2.8
Plasma renin activity while supine (ng of angiotensin I/ml/hr)				
All subjects	1.7±0.3	1.4±0.2	2.0±0.6	1.4±0.3
Normotensive subjects	1.5±0.3	1.6±0.2	2.0±0.7	1.5±0.3
Hypertensive subjects	2.0±0.8	0.9±0.3	1.9±1.4	1.2±0.7
Aldosterone while supine (ng/dl)				
All subjects	22.1±2.8	17.5±1.3	19.7±2.0	17.7±1.6
Normotensive subjects	22.2±3.5	18.3±1.5	19.1±2.4	16.4±1.9
Hypertensive subjects	21.7±4.2	15.0±2.1	21.3±4.1	22.0±2.3
24-Hr urinary sodium excretion (mmol)				
All subjects	13.3±2.8	13.5±2.1	15.8±3.1	17.1±4.6
Normotensive subjects	12.3±3.4	13.1±2.5	15.1±2.8	17.1±5.9
Hypertensive subjects	16.4±5.2	16.3±3.9	17.7±9.2	17.2±6.3
Renal vascular resistance (mm Hg/ml/min/1.73 m <sup>2</sup> )				
All subjects	0.159±0.007	0.160±0.008	0.153±0.008	0.162±0.009
Normotensive subjects	0.148±0.007	0.151±0.008	0.143±0.008	0.156±0.011
Hypertensive subjects	0.189±0.016‡	0.187±0.021‡	0.183±0.018‡	0.179±0.011
Glomerular filtration rate (ml/min/1.73 m <sup>2</sup> )				
All subjects	101.7±3.0	107.9±3.3	103.0±3.0	102.8±2.9
Normotensive subjects	102.1±3.6	105.0±3.4	103.4±3.9	102.3±3.4
Hypertensive subjects	100.4±5.4	116.0±7.7	101.9±3.9	104.3±6.2
Urinary sodium excretion 0–4 hr after drug (mmol)				
All subjects	11.9±1.7	14.1±1.9§¶	14.6±1.6§¶	19.3±2.0
Normotensive subjects	11.9±2.1	12.6±2.2¶	14.8±2.2§**	19.3±2.6
Hypertensive subjects	11.9±3.0	18.1±3.5	14.0±1.4	19.3±2.5

\*Values are means ±SE.

†P<0.005 for the comparison with normotensive subjects.

‡P<0.05 for the comparison with normotensive subjects.

§P<0.05 for the comparison with placebo.

¶P<0.005 for the comparison with losartan.

||P<0.005 for the comparison with placebo.

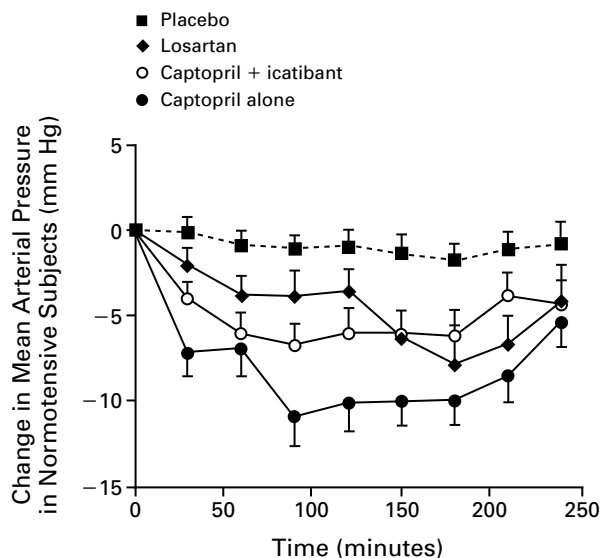
\*\*P<0.05 for the comparison with losartan.

er in the hypertensive subjects than in the normotensive subjects ( $0.185 \pm 0.014$  vs.  $0.149 \pm 0.008$  mm Hg per milliliter per minute per  $1.73 \text{ m}^2$  of body-surface area,  $P=0.029$ ); it was also higher in the black subjects than in the white subjects ( $0.177 \pm 0.01$  vs.  $0.141 \pm 0.009$  mm Hg per milliliter per minute per  $1.73 \text{ m}^2$ ,  $P=0.012$ ). There were no significant differences among study days in base-line mean arterial pressure, heart rate, 24-hour urinary sodium excretion, plasma renin activity, aldosterone concentration, renal plasma flow, renal vascular resistance, and glomerular filtration rate. There was no evidence of a carryover effect of any treatment on these measurements.

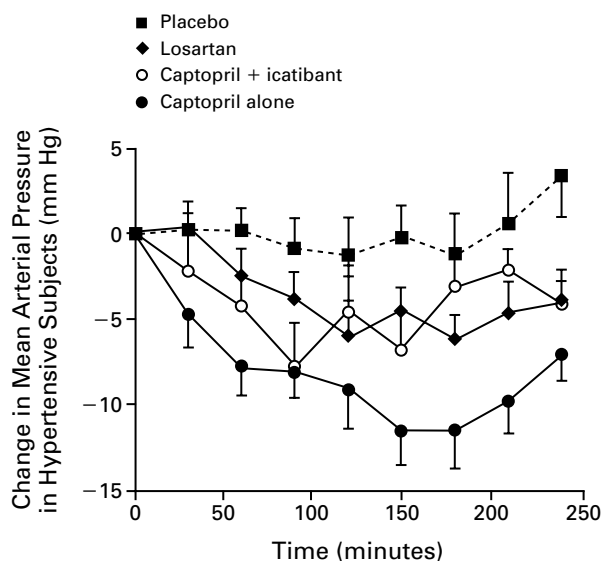
#### Hemodynamic Effects

Figures 1 and 2 show the change in the mean arterial pressure over time in response to each treatment

in the normotensive subjects and the hypertensive subjects. The mean arterial pressure for all subjects combined decreased significantly from base-line values after the administration of captopril, captopril plus icatibant, and losartan, but not after the administration of placebo. The decreases in the mean arterial pressure in response to captopril ( $F=42.2$ ,  $P<0.001$  for the comparison with placebo), captopril plus icatibant ( $F=16.7$ ,  $P=0.001$ ), and losartan ( $F=5.6$ ,  $P=0.03$ ) were significantly greater than the decrease in response to placebo. The decrease in the mean arterial pressure in response to short-term captopril administration was significantly greater than that in response to losartan ( $F=7.2$ ,  $P=0.01$ ). Icatibant significantly attenuated the decrease in the mean arterial pressure in response to captopril ( $F=14.9$ ,  $P=0.001$ ). This effect was seen both in the normotensive subjects ( $F=10.0$ ,  $P=0.005$ ) (Fig. 1) and in the hypertensive



**Figure 1.** Mean ( $\pm$ SE) Changes in Mean Arterial Pressure after the Administration of Oral Drugs in 20 Normotensive Subjects. Icatibant or vehicle was administered intravenously from 0 to 60 minutes after the oral drugs. The decreases in mean arterial pressure after the administration of captopril ( $F=33.3$ ,  $P<0.001$ ), captopril plus icatibant ( $F=17.3$ ,  $P=0.001$ ), and losartan ( $F=8.5$ ,  $P=0.01$ ) were significantly greater than that after placebo. The decrease in mean arterial pressure after captopril alone was significantly greater than that after captopril plus icatibant ( $F=10.0$ ,  $P=0.005$ ) and losartan ( $F=5.7$ ,  $P=0.03$ ).



**Figure 2.** Mean ( $\pm$ SE) Changes in Mean Arterial Pressure after the Administration of Oral Drugs in Seven Hypertensive Subjects. Icatibant or vehicle was administered intravenously from 0 to 60 minutes after the oral drugs. The decrease in mean arterial pressure after the administration of captopril was significantly greater than those after placebo ( $F=13.5$ ,  $P=0.01$ ), captopril plus icatibant ( $F=8.3$ ,  $P=0.03$ ), and losartan ( $F=9.0$ ,  $P=0.024$ ).

subjects ( $F=8.3$ ,  $P=0.03$ ) (Fig. 2). Thus, for all subjects combined the maximal decrease in the mean arterial pressure after the administration of captopril plus icatibant ( $10.5\pm 1.0$  mm Hg) was significantly less than that after captopril alone ( $14.0\pm 1.0$  mm Hg,  $P=0.001$ ) and similar to that after losartan ( $11.0\pm 1.7$  mm Hg).

There was no significant effect of race, renin status, or disease status on the change in mean arterial pressure in response to any treatment. The degree to which icatibant attenuated the response of blood pressure to captopril tended to be greater in the subjects with normal-to-high plasma renin activity than in those with low plasma renin activity, but this difference was not significant (decrease in response,  $66\pm 17$  percent vs.  $36\pm 16$  percent;  $P=0.19$ ).

The heart rate decreased significantly in response to captopril ( $F=2.6$ ,  $P=0.046$ ); in response to losartan it decreased significantly in the normotensive subjects but not in the hypertensive subjects ( $F=5.0$ ,  $P=0.04$ ). However, there were no significant differences among treatments in the heart-rate response. There was no significant effect of race, renin status, or disease status on the heart-rate response to any drug.

#### Renal Effects

Table 1 shows urinary sodium excretion four hours after the oral administration of the study drugs. Urinary sodium excretion was significantly higher after the administration of losartan ( $P<0.001$  for the comparison with placebo), captopril ( $P=0.04$ ), and captopril plus icatibant ( $P=0.02$ ). Urinary sodium excretion after the administration of losartan was also significantly higher than that after either captopril ( $P=0.004$ ) or captopril plus icatibant ( $P=0.003$ ). Although there was no significant effect of race on urinary sodium excretion after the administration of any of the study drugs, it tended to be lower in the black subjects than in the white subjects after captopril and captopril plus icatibant (captopril,  $12.1\pm 2.1$  mmol and  $15.8\pm 3.0$  mmol; captopril plus icatibant,  $14.0\pm 2.5$  mmol and  $15.2\pm 2.2$  mmol; placebo,  $11.4\pm 2.4$  mmol and  $12.4\pm 2.5$  mmol). Thus, urinary sodium excretion after the administration of captopril and captopril plus icatibant was not significantly increased as compared with that after the administration of placebo in the black subjects.

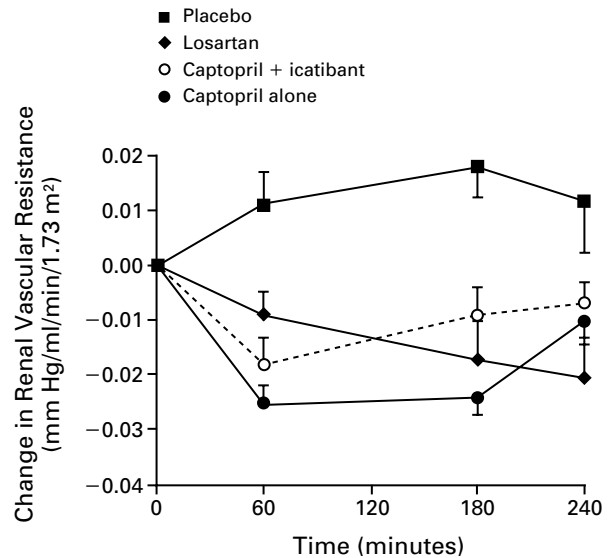
Urinary sodium excretion was significantly greater after the administration of losartan ( $19.3\pm 3.4$  mmol in the black subjects and  $19.3\pm 2.3$  mmol in the white subjects) than after placebo in both blacks and whites. There was no significant effect of renin status or disease status on urinary sodium excretion in response to any drug. There were no significant differences among treatments in urine volume or creatinine excretion. The urinary excretion of 2,3-dinor-6-keto-prostaglandin- $F_{1\alpha}$  did not increase after the administration of either captopril or losartan (data not shown).

Renal plasma flow increased in response to captopril, captopril plus icatibant, and losartan but not placebo (data not shown). Because the mean-arterial-pressure response (and therefore the renal perfusion pressure) was different during the various treatments, renal vascular resistance was used to compare treatments (Fig. 3). The decreases in renal vascular resistance after the administration of captopril ( $F=19.0$ ,  $P<0.001$  for the comparison with placebo), captopril plus icatibant ( $F=9.1$ ,  $P=0.007$ ), and losartan ( $F=6.2$ ,  $P=0.024$ ) were significantly greater than that after placebo. The addition of icatibant to captopril did not significantly attenuate the decrease in renal vascular resistance observed with captopril alone ( $F=2.1$ ,  $P=0.16$ ; difference in mean change in renal vascular resistance between captopril and captopril plus icatibant,  $0.0087$  mm Hg per milliliter per minute per  $1.73$  m<sup>2</sup> [95 percent confidence interval,  $-0.0014$  to  $0.0187$ ]). Despite the observed effects of race and disease status on base-line renal vascular resistance, there was no effect of race, disease status, or renin status on the change in renal vascular resistance after the administration of any drug ( $P>0.3$  for each variable for all drugs). There were no significant differences among treatments in the glomerular filtration rate (data not shown), and there was no effect of race, disease status, or renin status on the glomerular filtration rate in response to any drug.

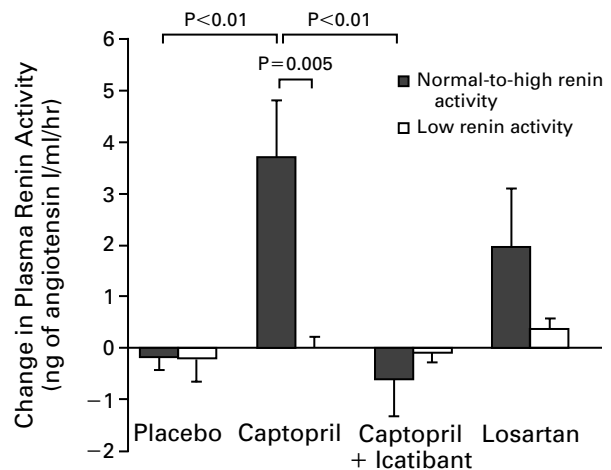
**Renin-Angiotensin System**

Plasma renin activity increased in response to both captopril (mean change,  $2.0 \pm 0.7$  ng of angiotensin I per milliliter per hour, as compared with  $-0.2 \pm 0.2$  ng of angiotensin I per milliliter per hour with placebo;  $P=0.007$ ) and losartan ( $1.2 \pm 0.6$  ng of angiotensin I per milliliter per hour,  $P=0.04$  for the comparison with placebo), but not in response to captopril plus icatibant ( $-0.4 \pm 0.4$  ng of angiotensin I per milliliter per hour,  $P=0.7$ ). Concurrent administration of icatibant eliminated the increase in plasma renin activity that occurred after the administration of captopril alone ( $P=0.007$ ). Although there was no effect of either race or disease status, base-line renin status had a dramatic effect on the response of plasma renin to the study drugs. Plasma renin activity increased in response to captopril in the subjects with normal-to-high levels of renin activity but not in those with low renin activity ( $3.7 \pm 1.1$  vs.  $-0.01 \pm 0.2$  ng of angiotensin I per milliliter per hour,  $P=0.005$ ) (Fig. 4). The plasma renin response to losartan did not differ significantly between the subjects with normal-to-high renin activity and those with low renin activity.

Aldosterone concentrations decreased significantly after the administration of captopril (from  $17.5 \pm 1.3$  to  $8.6 \pm 1.0$  ng per deciliter [ $485.4 \pm 36.1$  to  $238.6 \pm 27.7$  pmol per liter],  $P<0.001$ ), captopril plus icatibant (from  $19.7 \pm 2.0$  to  $9.1 \pm 1.3$  ng per deciliter [ $546.5$



**Figure 3.** Mean ( $\pm$ SE) Changes in Renal Vascular Resistance after the Administration of Oral Drugs in All 27 Subjects. The decreases in renal vascular resistance after the administration of captopril ( $F=19$ ,  $P<0.001$ ), captopril plus icatibant ( $F=9.1$ ,  $P=0.007$ ), and losartan ( $F=6.2$ ,  $P=0.024$ ) were significantly greater than that after placebo.



**Figure 4.** Mean ( $\pm$ SE) Changes in Plasma Renin Activity from Base Line to Four Hours after the Administration of Oral Drugs in 15 Subjects with Normal-to-High Renin Activity and 12 Subjects with Low Renin Activity.

$\pm 55.5$  to  $252.4 \pm 36.1$  pmol per liter],  $P<0.001$ ), losartan (from  $17.7 \pm 1.6$  to  $6.4 \pm 0.7$  ng per deciliter [ $491.0 \pm 44.4$  to  $177.5 \pm 19.4$  pmol per liter],  $P<0.001$ ), and placebo (from  $22.1 \pm 2.8$  to  $12.9 \pm 1.8$  ng per deciliter [ $613.1 \pm 77.7$  to  $357.8 \pm 49.9$  pmol per liter],  $P<0.001$ ). There were no significant differences among treatments in the decrease in aldosterone, nor was there any effect of race, disease status, or re-

nin status on the response of aldosterone concentrations to treatment.

### DISCUSSION

This study provides evidence that bradykinin contributes substantially to the hypotensive effects of ACE inhibition. Coadministration of the bradykinin-receptor antagonist icatibant decreased the average response of blood pressure to captopril by 53 percent (95 percent confidence interval, 29 to 76 percent), and the decrease in blood pressure after the administration of an ACE inhibitor and bradykinin-receptor antagonist combined was similar to that after the administration of the angiotensin-receptor antagonist losartan. This effect was observed in subjects with mild hypertension as well as in normotensive subjects and in both black subjects and white subjects.

These data confirm observations made in studies in animals that bradykinin plays a part in the hemodynamic effects of short-term ACE inhibition. For example, in 1981 Carretero et al.<sup>23</sup> reported that pretreatment with antikinins blocked the hypotensive effect of ACE inhibition in two-kidney, one-clip rats. More recent studies of icatibant have shown that this specific receptor antagonist attenuates the hypotensive response to ACE inhibition in aortic-banded rats,<sup>11</sup> spontaneously hypertensive rats,<sup>12</sup> and dogs with congestive heart failure.<sup>13</sup>

Previous studies have demonstrated a blunted hypotensive response to both ACE inhibition<sup>24</sup> and angiotensin-receptor antagonism<sup>25</sup> in blacks as compared with whites and a blunted acute response to ACE inhibition in patients with low-renin essential hypertension as compared with those with normal-to-high-renin<sup>26</sup> essential hypertension. The lack of an effect of either race or renin status on the hypotensive response to captopril or losartan in our study probably results from the fact that subjects were studied while they were salt depleted. Sodium depletion resulting from the administration of a diuretic drug has been shown to eliminate differences due to race in the hypotensive response to ACE inhibition.<sup>27</sup>

Because the kallikrein-kinin system, like the renin-angiotensin system, is activated under conditions of salt depletion,<sup>15</sup> the design of our study may have obscured an effect of race or renin status on the contribution of bradykinin to the hypotensive effects of ACE inhibitors. Indeed, data that urinary kallikrein excretion is decreased in blacks<sup>28</sup> and in hypertensive patients with low renin levels<sup>29</sup> and that the level of urinary kallikrein excretion predicts the hypotensive response to ACE inhibition<sup>26</sup> suggest that both race and renin status should affect the contribution of bradykinin to the antihypertensive effects of ACE inhibitors. Studies in hypertensive patients whose salt intake is normal are needed to test this hypothesis further.

The short-term renal hemodynamic effects of ACE

inhibitors and angiotensin-receptor antagonists have been studied in predominantly white populations. ACE inhibitors decrease renal vascular resistance, usually without altering glomerular filtration.<sup>3-5</sup> However, under conditions of decreased perfusion, glomerular filtration may fall during ACE inhibition.<sup>30</sup> Data from studies in rats suggest that this decrease in glomerular filtration may be mediated through selective efferent arteriolar vasodilation by bradykinin.<sup>31</sup> Losartan also decreased renal vascular resistance without affecting glomerular filtration in most studies,<sup>32</sup> although Doig et al. observed a decrease in creatinine clearance in salt-depleted subjects.<sup>33</sup>

In our study, the short-term renal effects of an ACE inhibitor and an angiotensin-receptor antagonist were studied in both black subjects and white subjects. Strikingly, base-line renal vascular resistance was higher in the black subjects than in the white subjects. Increased renal vascular resistance has been reported previously in blacks with hypertension,<sup>28</sup> and our study extends this observation to normotensive subjects. In both racial groups, renal vascular resistance decreased to a similar extent after the administration of captopril alone, captopril plus icatibant, or losartan. The glomerular filtration rate did not change significantly from the base-line value during any treatment.

As observed in previous studies, both captopril<sup>3-5</sup> and losartan<sup>32,33</sup> caused natriuresis. However, losartan caused significantly greater natriuresis than captopril, particularly in the black subjects. The reason for this differential effect of captopril and losartan on sodium excretion, in the face of similar changes in renal vascular resistance, is not clear. Nevertheless, the administration of both icatibant and captopril did not alter urinary sodium excretion significantly from that observed after captopril alone. Taken together, these data suggest that bradykinin does not contribute importantly to the renal effects of ACE inhibition in normotensive or hypertensive subjects, regardless of race. This hypothesis is consistent with data from a recent clinical trial that showed no difference in the rates of renal insufficiency between elderly patients with congestive heart failure who were randomly assigned to receive an ACE inhibitor and those assigned to receive an angiotensin-receptor antagonist.<sup>34</sup>

Numerous investigators have demonstrated that short-term ACE inhibition or administration of an angiotensin-receptor antagonist causes an increase in plasma renin activity.<sup>2,35</sup> As in our study, Abe et al.<sup>36</sup> reported an increase in renin activity after the administration of captopril in subjects with normal-to-high levels of renin activity but not in subjects with low levels. The renin response to ACE inhibition and angiotensin-receptor antagonism has been attributed to decreased feedback inhibition by angiotensin II.<sup>37</sup> However, our findings suggest that increased bradykinin also plays a part in the renin response to the short-term administration of captopril. Thus, the ad-

ministration of both icatibant and captopril eliminated the increase in plasma renin activity observed after captopril alone.

The finding of Azizi et al. that the addition of captopril enhances the plasma-renin-activity response to losartan also suggests an effect of bradykinin on renin.<sup>38</sup> The mechanism by which bradykinin increases renin activity is not clear. Bradykinin stimulates the production of prostacyclin,<sup>9</sup> a potent stimulus to renin release.<sup>39</sup> The coadministration of a cyclooxygenase inhibitor blunts the renin response to short-term ACE inhibition.<sup>36</sup> However, urinary excretion of the prostacyclin metabolite 2,3-dinor-6-keto-prostaglandin-F<sub>1α</sub> was not increased after short-term administration of captopril in our study, suggesting that the effects of captopril-induced changes in bradykinin on renin activity were not mediated by prostaglandins. Beierwaltes has reported a prostaglandin-independent effect of bradykinin on renin activity in isolated rat glomeruli.<sup>40</sup>

In summary, our study demonstrates that bradykinin contributes to the hypotensive and endocrine effects of short-term ACE inhibition with captopril in normotensive and hypertensive subjects while they are salt depleted. The role of bradykinin during long-term ACE inhibition requires study. Investigators have demonstrated that angiotensin II concentrations increase toward base-line values during long-term ACE inhibition.<sup>41</sup> Conversely, the antihypertensive effect of angiotensin-receptor antagonists appears to increase gradually with long-term administration.<sup>42</sup> Thus, the results of our study should not be extrapolated to the long-term treatment of hypertensive patients whose salt intake is normal with ACE inhibitors or angiotensin-receptor antagonists.

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