Captopril Improves Impaired Endothelium-Dependent Vasodilation in Hypertensive Patients

Yoshitaka Hirooka, Tsutomu Imaizumi, Hiroyuki Masaki, Shin-ichi Ando, Seiki Harada, Michiko Momohara, and Akira Takeshita

Animal studies suggest that some angiotensin converting enzyme inhibitors augment endothelium-dependent vasorelaxation. We aimed to determine if captopril augments endothelium-dependent vasodilation in middle-aged hypertensive patients. By using strain-gauge plethysmography, forearm vasodilation evoked with intra-arterial acetylcholine (4, 8, 16, and 24 μg/min) or nitroprusside (0.2, 0.4, 0.8, and 1.2 μg/min) was examined before and after captopril administration (25 mg per os). Before captopril, forearm vasodilation with acetylcholine was less in hypertensive patients (n=12) than in age-matched (n=7) or young (n=7) normotensive subjects, but forearm vasodilation with nitroprusside did not differ among the three groups. Captopril improved forearm vasodilation in hypertensive patients (n=7) with acetylcholine but nitroprusside did not. In contrast, nifedipine (10 mg per os) did not alter forearm vasodilation with acetylcholine or nitroprusside in hypertensive patients (n=5). The decreases in mean blood pressure caused by captopril and nifedipine in hypertensive subjects were comparable. Captopril did not alter forearm vasodilation with acetylcholine or nitroprusside in young normotensive subjects (n=7). These results suggest that captopril in hypertensive patients may acutely improve impaired endothelium-dependent forearm vasodilation that does not result from reduction in blood pressure per se. (Hypertension 1992;20:175-180)

KEY WORDS • endothelium • angiotensin converting enzyme inhibitors • captopril • vascular resistance • plethysmography • acetylcholine • nitroprusside • hypertension, essential

In experimental animals, chronic hypertension is associated with attenuated endothelium-dependent relaxation to acetylcholine (ACh).1-4 The impairment of endothelium-dependent relaxation in hypertension is closely correlated with the degree of hypertension and may improve after chronic antihypertensive therapy.2,5 Recent studies in humans also have shown that endothelium-dependent forearm vasodilation to ACh is impaired in patients with essential hypertension.6,7

A recent study has suggested that lisinopril, an angiotensin converting enzyme inhibitor, increased compliance of the in situ isolated carotid arteries in the presence of the intact endothelium but did not alter it after endothelium removal in Wistar-Kyoto and spontaneously hypertensive rats.8 It also has been shown that some angiotensin converting enzyme inhibitors might augment ACh-induced vasorelaxation in the aortic rings of rats.9,10 In addition, Clozel et al11 have demonstrated that cilazapril improved but hydralazine did not improve endothelium-dependent vasorelaxation in spontaneously hypertensive rats when blood pressure was lowered similarly by the two drugs. Furthermore, they have demonstrated that improvement of endothelium-dependent vasorelaxation by cilazapril was apparent after only 4 days as well as 4 months of treatment.11

The aim of this study was to examine whether captopril acutely improves impaired endothelium-dependent vasodilation in hypertensive patients. For this purpose, we measured forearm blood flow during graded infusions of ACh and sodium nitroprusside (SNP) into a brachial artery before and after administration of captopril or nifedipine in middle-aged hypertensive patients. We also examined forearm vascular responses to ACh and SNP in two groups of normotensive subjects: age-matched and young normotensive subjects. The effect of captopril on forearm vasodilating responses to ACh was also examined in the young normotensive subjects group.

Methods

The study groups consisted of untreated middle-aged hypertensive patients (n=12, seven men and five women) and middle-aged (n=7) and young (n=7) normotensive subjects (all men). The average age of the

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hypertensive patients was 58±3 years (range, 42–66 years), and the ages of middle-aged and young normotensive subjects were 51±3 years (range, 39–60 years) and 22±1 years (range, 19–27 years), respectively. Blood pressure was measured on at least three different occasions. Hypertension was defined as systolic or diastolic blood pressure consistently in excess of 140 mm Hg or 90 mm Hg, or both. Hypertensive patients underwent physical examination, blood cell counts, urinalysis, and measurements of serum electrolytes, creatinine, fasting blood sugar, cholesterol, triglycerides, and liver enzymes. An electrocardiogram, echocardiogram, and chest x-ray were also taken. Hypertensive patients were in World Health Organization classification stage I or II. Mild proteinuria was present in three patients, hypercholesterolemia in one patient, and diabetes mellitus in one patient. Seven patients had echocardiographic and electrocardiographic findings suggestive of left ventricular hypertrophy. No patients were taking antihypertensive medications before the study. Normotensive subjects also underwent physical examination and had no cardiovascular disorders. Middle-aged normotensive subjects were drawn from hospital personnel and young subjects were volunteers. Written informed consent was obtained from each subject.

Measurements of Forearm Blood Flow and Arterial Pressure

Studies were done with the subjects in the supine position. Forearm blood flow was measured using a mercury-in-Silastic strain-gauge plethysmograph and the venous occlusion technique.2,13 The strain gauge was placed approximately 5 cm below the antecubital crease. The pressure in the venous occlusion or congesting cuff was 40 mm Hg. Circulation to the hand was arrested during determination of forearm blood flow by inflating a cuff around the wrist to a pressure that was suprasystolic. Forearm blood flow was taken as the average of at least four flow measurements made at 15-second intervals. Recording paper speed was 10 cm/min. At the end of the study, calibration of the plethysmograph was done by turning the screw of the plethysmograph a few times to shorten the silicone tube by 0.64 mm at one turn while recording the change in mercury conductance. Blood pressure was recorded by connecting the arterial line to a pressure transducer (Viggo-Spectramed, Oxnard, Calif.) with a three-way stopcock. Forearm vascular resistance was calculated by dividing mean arterial pressure (diastolic pressure plus one third of the pulse pressure in millimeters of mercury) by forearm blood flow. These values are expressed as units throughout this report.

Forearm Vascular Responses to Drugs

A brachial artery was cannulated with a 20-gauge intravascular over-the-needle Teflon catheter (QUICK-CATH, Travenol Laboratories, Inc., Deerfield, Ill.) for drug infusion. After the placement of a cannula and a strain-gauge plethysmograph, at least 15 minutes were allowed for the subjects to become accustomed to the study conditions before beginning the protocol. The arterial line was kept open by infusion of heparinized saline before drug infusion.

We examined forearm vasodilating responses to intra-arterial ACh and SNP at graded doses. ACh (4, 8, 16, and 24 μg/min) and SNP (0.2, 0.4, 0.8, and 1.2 μg/min) were infused intra-arterially for 2 minutes at each dose. The order of drug infusion was alternated. Forearm blood flow was measured continuously at 15-second intervals in the ipsilateral arm during drug infusion. Since forearm blood flow reached the steady state by 1 minute after starting infusion of each drug, we used the last 1-minute measurements during drug infusion of each dose for later analysis.

Forearm vasodilating responses to ACh and SNP were examined before and 1 hour after an oral administration of captopril (25 mg) or nifedipine (10 mg). Patients were kept in a supine position with the arterial cannula and plethysmograph in place until examination after captopril was done.

Measurements of Plasma Renin, Aldosterone, and Catecholamines

We sampled venous blood from the contralateral arm before and after captopril for measurement of plasma renin activity, plasma aldosterone, and plasma catecholamine (epinephrine and norepinephrine) concentrations. Venous blood was sampled into the tube containing EDTA-2Na (1 mg/ml) and promptly chilled in an ice bath. After plasma was removed, aliquots of the plasma sample were stored at −20°C until use. Plasma renin activity was determined by radioimmunoassay (RIA) using RIA kits obtained from Dainabot Radioisotope Laboratories, Chiba, Japan. Plasma aldosterone concentration was determined by RIA using RIA kits obtained from Daiichi Radioisotope Laboratories, Tokyo. Plasma catecholamine concentrations were determined by high-performance liquid chromatography.

Protocol

All hypertensive and normotensive subjects underwent measurement of forearm blood flow and blood pressure during intra-arterial infusion of saline, ACh, and SNP at graded doses. Measurements of forearm vascular responses to saline, ACh, and SNP were repeated 1 hour after oral administration of captopril (25 mg) in seven hypertensive patients (group 1A) or after oral administration of nifedipine (10 mg) in five hypertensive patients (group 1B). Measurements were also repeated after captopril in seven young normotensive subjects (group 2). The middle-aged normotensive subjects (group 3) did not receive captopril or nifedipine. Measurements of plasma renin, aldosterone, and catecholamines were done in hypertensive patients (group 1) and young normotensive subjects (group 2).

Preparations of Acetylcholine and Sodium Nitroprusside

Since ACh is unstable in solution, 100 mg ACh (Daiichi Seiyaku, Tokyo) was hypolozized and stored in a vial (0.4 mg ACh per vial). It was dissolved in physiological saline (10 ml) immediately before use. SNP (Wakou Junyaku Kogyo, Osaka, Japan) was dissolved in physiological saline at a concentration of 2,000 ng/ml. Special care was taken not to expose SNP to light.
TABLE 1. Control Values in Hypertensive and Normotensive Subjects Before Captopril or Nifedipine Administration

<table>
<thead>
<tr>
<th>Group 1 (hypertensive, n=12)</th>
<th>MBP (mm Hg)</th>
<th>HR (bpm)</th>
<th>FBF (ml/min per 100 ml)</th>
<th>FVR (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>119±5*</td>
<td>67±3</td>
<td>4.0±0.5</td>
<td>35.2±4.0*</td>
<td></td>
</tr>
<tr>
<td>Group 2 (Young normotensive, n=7)</td>
<td>82±2</td>
<td>64±6</td>
<td>4.4±0.9</td>
<td>23.2±3.6</td>
</tr>
<tr>
<td>Group 3 (Middle-aged normotensive, n=7)</td>
<td>91±5</td>
<td>63±3</td>
<td>5.9±0.7</td>
<td>17.1±2.2</td>
</tr>
</tbody>
</table>

Values are mean±SEM. MBP, mean blood pressure; HR, heart rate; bpm, beats per minute; FBF, forearm blood flow; FVR, forearm vascular resistance.

*p<0.01 vs. group 2 and group 3.

Statistical Analysis

Values at rest were compared by one-way analysis of variance (ANOVA). Two-way ANOVA was used to compare forearm vascular responses to the drugs among groups before and after captopril or nifedipine. When analysis by ANOVA was significant, the location of difference was determined by unpaired or paired t test. All values are expressed as mean±SEM. A value of p<0.05 was considered statistically significant.

Results

Table 1 summarizes variables at rest in the three groups. Mean blood pressure and resting forearm vascular resistance were higher in hypertensive patients (group 1) than in the two groups (groups 2 and 3) of normotensive subjects (p<0.01). Heart rate and resting forearm blood flow did not differ among the three groups. Mean blood pressure, heart rate, resting forearm blood flow, and forearm vascular resistance did not differ between the two groups of normotensive subjects.

Intra-arterial infusions of ACh and SNP did not alter mean blood pressure and heart rate in either group (data not shown). Graded doses of ACh and SNP caused progressive increases in forearm blood flow and progressive decreases in forearm vascular resistance in hypertensive patients as well as in normotensive subjects (p<0.01) (data not shown). Figure 1 shows percent changes in forearm vascular resistance during infusions of the drugs at the graded doses in hypertensive patients and in the two groups of normotensive subjects. Percent decreases in forearm vascular resistance in response to ACh at the lower doses (4 and 8 μg/min) were attenuated (p<0.01) in hypertensive patients compared with those in either group of normotensive subjects, but responses to ACh at the higher doses (16 and 24 μg/min) did not differ between hypertensive patients and normotensive subjects. Forearm vascular responses to SNP at the graded doses did not differ between hypertensive patients and normotensive subjects. Forearm vascular responses to ACh and SNP did not differ between the two groups of normotensive subjects.

In seven hypertensive patients (group 1A), captopril lowered resting mean blood pressure from 122±8 to 110±8 mm Hg (p<0.05) but did not significantly alter heart rate (69±6 versus 67±6 beats per minute, before and after captopril), resting forearm blood flow (4.5±0.7 versus 3.7±0.6 ml/min per 100 ml), or resting forearm vascular resistance (32.8±5.9 versus 37.3±8.0 units). Captopril augmented percent decreases in forearm vascular resistance evoked with the lower doses of ACh (4 and 8 μg/min) but did not alter responses to ACh at the higher doses (16 and 24 μg/min) (Figure 2). In particular, infusion of 4 μg/minute of ACh caused forearm vasodilation only after captopril. Captopril did not alter forearm vascular responses to SNP (Figure 2). In young normotensive subjects (group 2), captopril did not alter resting mean blood pressure (82±2 versus 82±2 mm Hg, before and after captopril), heart rate (64±6 versus 68±6 beats per minute), forearm blood flow.

![FIGURE 1](http://hyper.ahajournals.org/)

**FIGURE 1.** Line graphs show responses of forearm vascular resistance to intra-arterial infusion of acetylcholine (ACh) or sodium nitroprusside (SNP) in hypertensive patients (group 1, n=12), middle-aged normotensive subjects (group 3, n=7), and young normotensive subjects (group 2, n=7). Forearm vascular responses to ACh at 4 and 8 μg/min were attenuated in hypertensive patients compared with those in the two groups of normal subjects (**p<0.01).

![FIGURE 2](http://hyper.ahajournals.org/)

**FIGURE 2.** Line graphs show responses of forearm vascular resistance to intra-arterial infusion of acetylcholine (ACh) or sodium nitroprusside (SNP) before and after captopril administration in hypertensive patients (group 1A, n=7). Forearm vascular responses to ACh at 4 and 8 μg/min were augmented (**p<0.05) after captopril but those in response to SNP did not differ before and after captopril.
Forearm vascular responses to both ACh and SNP did not differ before and after captopril administration in young normotensive subjects (group 2, n=7). Forearm vascular resistance to intra-arterial infusion of acetylcholine (ACh) or sodium nitroprusside (SNP) before and after captopril administration in young normotensive subjects (group 2, n=7).

In five hypertensive patients (group 1B), nifedipine lowered resting mean blood pressure from 115±5 to 99±4 mm Hg (p<0.05) and resting forearm vascular resistance from 38.5±4.6 to 23.8±2.6 units (p<0.05). Nifedipine increased resting heart rate from 64±1 to 68±2 beats per minute (p<0.05) and resting forearm blood flow from 3.3±0.5 to 4.4±0.5 ml/min per 100 ml (p<0.05). Nifedipine did not alter percent decreases in forearm vascular resistance evoked with graded doses of either ACh or SNP (Figure 4).

In hypertensive patients (group 1A), plasma renin activity increased from 1.7±0.9 to 2.5±1.0 ng/ml per hr (p<0.05), and plasma aldosterone concentration decreased from 7.8±1.8 to 4.9±0.6 ng/dl (p<0.05) after captopril was administered to hypertensive patients. Plasma epinephrine and norepinephrine concentrations did not differ before and after captopril (epinephrine, 0.03±0.01 versus 0.03±0.02 ng/ml; norepinephrine, 0.20±0.07 versus 0.20±0.07 ng/ml, before versus after captopril, respectively). In normotensive subjects (group 2), plasma renin activity increased from 1.6±0.6 to 6.9±2.9 ng/ml per hr (p<0.05), and plasma aldosterone concentration decreased from 7.1±0.6 to 5.4±0.5 ng/dl (p<0.05) after captopril. Plasma epinephrine and norepinephrine concentrations did not differ before and after captopril (epinephrine, 0.03±0.01 versus 0.05±0.01 ng/ml; norepinephrine, 0.23±0.04 versus 0.26±0.04 ng/ml, before versus after captopril, respectively).

Plasma renin activity, plasma aldosterone concentration, and plasma epinephrine concentration did not differ before and after nifedipine in hypertensive patients (group 1B) (renin, 1.3±0.4 versus 1.9±0.7 ng/ml per hr; aldosterone, 6.7±1.5 versus 4.4±0.8 ng/dl; epinephrine, 0.03±0.01 versus 0.03±0.01 ng/ml). Plasma norepinephrine concentration tended to increase from 0.25±0.08 before to 0.37±0.12 ng/ml after nifedipine (0.05<p<0.1).

**Discussion**

The results of the present study lead to the following conclusions: First, endothelium-dependent forearm vasodilation evoked with ACh is impaired in middle-aged hypertensive patients as compared with that in age-matched as well as young normotensive subjects. Second, an hour after oral administration captopril augmented endothelium-dependent forearm vasodilation in middle-aged hypertensive patients but did not alter it in young normotensive subjects. Third, augmentation of endothelium-dependent forearm vasodilation by captopril in hypertensive patients did not result from reduction in blood pressure per se.

Recent studies in humans have demonstrated that endothelium-dependent forearm vasodilation in response to ACh is attenuated in patients with essential hypertension as compared with that in normotensive subjects.6'7 The reason for this difference is not known. Ages, resting mean blood pressure, and resting forearm vascular resistance of the patients and the doses of ACh administered were similar between this and a previous study.6 Further studies are needed to clarify the reason for this difference. However, a previous study in rats has suggested that vasodilating responses to ACh at the lower concentrations (10^-4 to 10^-7 M) were impaired in resistance arteries of spontaneously hypertensive rats compared with those in resistance arteries of Wistar-Kyoto rats, but maximal dilatation at the higher concentrations of ACh were comparable in the two groups.3

The most important finding of the present study is that captopril augmented forearm vasodilation to ACh.

**Figure 3.** Line graphs show responses of forearm vascular resistance to intra-arterial infusion of acetylcholine (ACh) or sodium nitroprusside (SNP) before and after captopril in hypertensive patients (group IB, n=5). Forearm vascular responses to both ACh and SNP did not differ before and after captopril.

**Figure 4.** Line graphs show responses of forearm vascular resistance to intra-arterial infusion of acetylcholine (ACh) or sodium nitroprusside (SNP) before and after nifedipine in hypertensive patients (group 1B, n=5). Forearm vascular responses to both ACh and SNP did not differ before and after nifedipine.
but not to SNP in middle-aged hypertensive patients. Both ACh and SNP cause cyclic guanosine monophosphate–mediated vascular smooth muscle relaxation, but vasodilation evoked with ACh is endothelium-dependent and that with SNP is endothelium-independent. Thus, these results suggest that captopril improved impaired endothelium-dependent forearm vasodilation evoked with ACh toward normal in middle-aged hypertensive patients. Captopril improved impaired forearm vasodilating responses to ACh only at the lower doses in hypertensive patients (Figure 2). We believe that captopril did not augment forearm vasodilating responses to the higher doses of ACh because forearm vasodilation evoked with ACh at the higher doses was close to maximal before captopril. This consideration is based on the finding that percent decreases in forearm vascular resistance evoked with ACh at the higher doses were similar in hypertensive and normotensive subjects (Figure 1). Absolute forearm vascular resistance during infusions of ACh at the higher doses was higher in hypertensive patients (10.8±2.9 units) than in normotensive subjects (3.7±0.8 units). However, the latter findings might have resulted from reduced maximal vasodilator capacity caused by structural vascular changes in hypertensive patients.

In contrast to hypertensive patients, captopril did not alter forearm vasodilating responses to ACh or SNP in young normotensive subjects (Figure 3). We consider it unlikely that the difference in age between hypertensive patients and normotensive subjects accounts for the difference in the effect of captopril on endothelium-dependent forearm vasodilation, since forearm vasodilating responses to ACh and SNP did not differ between middle-aged and young normotensive subjects in the present study or in a previous study from our laboratory. It is also unlikely that the difference in the effect of captopril resulted from the difference in inhibition of angiotensin converting enzyme, since changes in plasma renin activity and aldosterone did not differ between the two groups. Thus, our results suggest that captopril augmented endothelium-dependent forearm vasodilation evoked with ACh in hypertensive patients but not in normotensive subjects. Previous studies in rats have shown that angiotensin converting enzyme inhibitors such as lisinopril potentiate endothelium-dependent vasorelaxation in normotensive rats. The reason for the difference in the results between humans and experimental animals is not known.

We also examined the effect of nifedipine on forearm vasodilating responses to ACh and SNP in hypertensive patients. Although nifedipine and captopril caused comparable decreases in blood pressure, nifedipine did not alter forearm vasodilation evoked with ACh and SNP (Figure 4). These results suggest that reduction in blood pressure per se does not account for the effect of captopril on forearm vasodilating responses to ACh in hypertensive patients. Ages, blood pressure, resting forearm vascular resistance, and forearm vascular responses to ACh and SNP before captopril or nifedipine did not differ between hypertensive patients treated with captopril and those treated with nifedipine. Thus, it appears unlikely that the difference in the effects of captopril and nifedipine on forearm vasodilating responses to ACh resulted from the group difference such as the difference in the severity of hypertension.

Obviously we do not know the mechanisms by which captopril augmented forearm vasodilation to ACh in hypertensive patients. However, based on animal experiments, we speculate that captopril might have facilitated the release of endothelium-derived relaxing factors (EDRF) in response to ACh or might have protected the breakdown of EDRF by acting as a scavenger for oxygen radicals. It is also possible that inhibition of the breakdown of bradykinin, a potent releaser of EDRF, may be involved in this effect of captopril. It is unlikely that captopril augmented responses of vascular smooth muscles to EDRF since it did not alter responses to SNP, which causes relaxation of vascular smooth muscle by activation of guanylate cyclase as does EDRF. It has been shown that vasorelaxation evoked with ACh may involve the facilitated release of prostacyclin. However, a recent study has suggested that prostaglandins do not play a major role in forearm vasodilatation evoked with ACh in humans, since aspirin does not alter forearm vascular response to ACh. It has been suggested that captopril may enhance flow-mediated responses that may be involved in dilation to ACh. However, this possibility is also unlikely because captopril did not alter resting forearm blood flow. In addition, nifedipine did not alter forearm vascular response to ACh, although it increased resting forearm blood flow. Captopril may modulate effects of sympathetic nerves on blood vessels of the forearm due to the local changes in angiotensin II levels and the effects on adrenergic terminals. However, this possibility is also unlikely because captopril did not alter resting forearm vascular resistance. Furthermore, we cannot exclude the possibility that captopril may attenuate endothelium-dependent contraction to ACh via a cyclooxygenase pathway that has been observed in spontaneously hypertensive rats. Further studies are needed to clarify the mechanisms by which captopril improved endothelium-dependent forearm vasodilation in hypertensive patients.

In previous studies with rat aortic rings, it has been suggested that antihypertensive treatment for 2 or 8 weeks normalizes decreased endothelium-dependent relaxation. Although we did not see the acute improvement of forearm vasodilating responses to ACh by nifedipine, chronic antihypertensive therapy might improve impaired endothelium-dependent vasodilation in humans. Our hypertensive patients included two patients with diabetes mellitus or hypercholesterolemia, diabetes mellitus and hypercholesterolemia are known to be associated with impaired endothelium-dependent vasodilation. However, we believe that impaired endothelium-dependent forearm vasodilation in our patients resulted from hypertension since 10 of 12 patients had no cardiovascular or metabolic abnormalities other than hypertension that might cause impaired endothelium-dependent vasodilation.

In summary, the results of the present study suggest that captopril improves impaired endothelium-dependent vasodilation in hypertensive patients. It is possible that this effect of captopril may contribute to its antihypertensive action. We do not know the role of endothelial dysfunction in the development of hypertensive vascular disease. The significance of this effect of captopril in the long-term treatment of hypertension awaits future study.
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References

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