Dilation of Forearm Blood Vessels After Angiotensin-Converting-Enzyme Inhibition by Captopril in Hypertensive Patients

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SUMMARY In eight hypertensive patients, forearm vascular tone was assessed by water plethysmography following inhibition of angiotensin II-converting-enzyme (ACE) activity with captopril. Acute captopril administration increased venous distensibility (VV,) and decreased forearm vascular resistance (FVR), while it lowered systemic blood pressure (BP). Alpha-one adrenergic receptor blockade by prazosin did not prevent captopril from decreasing vascular tone or lowering blood pressure (BP). Thus, captopril dilated both veins and arterioles. The primary mechanism of captopril's acute antihypertensive action did not involve inhibition of alpha,-adrenergic receptor activity. Moreover, captopril and prazosin together produced a greater reduction in BP and peripheral resistance than occurred with either agent alone. (Hypertension 6: 545-550, 1984)

KEY WORDS • angiotensin • prazosin • veins • arterioles • plethysmography • peripheral resistance • sympathetic nervous system • hypertension

ELEVATED plasma angiotensin II (ANG II) concentration has been found in patients with severe hypertension1,2 and, in some patients, has been correlated with diastolic blood pressure.3 Although the role of ANG II in the pathophysiology of hypertension is not completely understood, inhibition of angiotensin-converting-enzyme activity (ACE) has been reported to lower blood pressure in hypertensive patients.4-8 Also, blockade of ANG II formation has been demonstrated to decrease systemic vascular resistance and left ventricular filling pressure in patients with hypertension9 and in those with severe congestive heart failure.10-12

The reduction in vascular resistance (afterload) and the decrease in left ventricular filling pressure (preload) imply a decrease in both arteriolar and venous tone. It has been suggested that the reduction in vascular tone following ANG II inhibition may be due to a decrease in sympathetic nervous system activity.13 The present study presents direct evidence of arteriolar and venous forearm dilation in patients with hypertension treated by inhibition of ACE with captopril.

Methods

Eight hypertensive patients, five men and three women, aged 38 to 70 years, voluntarily entered this two-part study. During Part 1, or the control period, antihypertensive medications were discontinued for 3 weeks. Patients returned to the University of Virginia Hypertension/Atherosclerosis Unit where plethysmographic studies were performed. A dose of captopril which produced at least a 10 mm Hg decrease in supine diastolic blood pressure (BP) (25 or 50 mg) was then administered, and plethysmography was repeated. During Part 2, patients received prazosin, which was progressively increased from 1 to 5 mg three times daily. One week later patients again underwent plethysmographic study before and after captopril. Thus, plethysmographic determinations were obtained four times in each patient: on no medications, approximately 1 hour after acute captopril administration, after 1 week of prazosin, and again 1 hour after acute captopril administration.

Patients were studied in the basal, postabsorptive state and had had no caffeine, nicotine, or venipuncture for at least 30 minutes before the start of the studies. Patients were supine, with their heads elevated 15° and were covered lightly with a sheet. Studies were performed in a quiet room that was maintained at a constant temperature of 74° to 75° F (24° C).14 Duplicate measurements of blood pressure (BP) in mm Hg and heart rate (HR) in beats per minute (bpm) were recorded from the right arm before and after each study. All values reported were recorded after the patients were supine for at least 15 minutes. The left forearm was positioned at the level of the right atrium and was enclosed in a plexiglass, single-chamber wa-
ter plethysmograph. The temperature of the water in the plethysmograph was 32°C.

The height of the water in the chamber was 23 cm above the upper surface of the left forearm and thus assured a local pressure sufficient to counterbalance natural venous pressure. To exclude the circulation of the hand, a pneumatic cuff was inflated at the wrist to supra systolic pressures during all measurements. Venous distensibility (VVw) was then calculated as described by Wood at a distending pressure of 30 mm Hg (achieved by stepwise 5 mm Hg increases of the proximal pneumatic cuff) and is expressed as ml/100 ml forearm volume. Three separate venous volume curves were recorded; a 5-minute equilibration period was observed between measurements when all cuffs were deflated. The curves were reproducible, and the three measurements were averaged in a given patient. An increase in VVw indicates an increase in venous distensibility or venous dilation.

The initial slope of the volume record obtained by rapidly inflating the congesting cuff to 30 mm Hg was used as an index of basal blood flow (BBF) and is expressed as ml/min/100 ml forearm volume. TriPLICATE measurements were obtained, and the average of these values is reported as BBF. An increase in BBF indicates arterial dilation.

Blood flow was measured during reactive hyperemia after 5 minutes of ischemia (proximal cuff inflated 50 mm Hg above systolic pressure × 5 minutes). Peak blood flow (usually approximately 15 seconds after cuff deflation) was reported in ml/min/100 ml forearm volume. An increase in peak hyperemic blood flow (PHBF) indicates an increase in maximal dilatory capacity of arterioles.

Mean arterial pressure (MAP) was calculated as the sum of the diastolic pressure plus ⅓ of the pulse pressure and is expressed in mm Hg. Forearm vascular resistance (FVR) was calculated by dividing MAP by BBF and is expressed as mm Hg/ml/min/100 ml forearm volume.

Before and after each plethysmographic study (or before and 90 to 120 minutes after captopril administration) blood was drawn for determination of ACE, plasma renin activity (PRA), and plasma aldosterone concentration (PAC). The blood was collected in iced vacutainers containing (EDTA) and centrifuged immediately. The plasma was decanted and frozen at —70°C.

Acid released after incubation for 60 minutes at 37°C was determined by the radioimmunoassay method of Wood with angiotensin I (ANG I) generated after incubation at pH 5.7 for 3 hours at 37°C. PAC was assayed in triplicate, and circulating hormonal concentrations following captopril administration. Figure 3 A demonstrates suppression of ACE activity by captopril. In the control period, ACE activity fell from 92 ± 10 to 8 ± 2 nM/min/100 ml forearm volume; p = 0.001). Similarly, following 1 week of prazosin therapy (26.3 ± 3 to 22.9 ± 4 mmHg/ml/min/100 ml forearm volume; p = 0.01), as seen in Figure 2 C.

Statistical analysis was performed using Student's paired t test. Changes were considered significant if the double-tailed p values were less than 0.05. Data are expressed as means ± 1 standard error (SE). The p values reported with systolic/diastolic BPs refer to the least significant measurement.

Results

Figure 1 depicts the supine BP and HR responses to the acute administration of captopril before and after treatment with prazosin. After discontinuation of all antihypertensive medications for 3 weeks, the average BP for the control group was 162 ± 7/97 ± 3 mm Hg. After captopril administration, BP fell acutely to 140 ± 7/79 ± 5 mm Hg (p = 0.002) while HR remained unchanged (76 ± 3 vs 73 ± 5 bpm; p > 0.05).

After 1 week of prazosin treatment, captopril still lowered BP from 147 ± 5/91 ± 5 to 134 ± 3/79 ± 4 mm Hg (p = 0.009). Again, HR did not change (80 ± 2 vs 81 ± 4 bpm; p > 0.05). The fall in BP after 1 week of prazosin therapy (162 ± 7/97 ± 3 vs 147 ± 3/91 ± 4 mm Hg; p = 0.002) established the efficacy of α1 receptor blockade.

Figure 2 represents plethysmographic responses to captopril before and after prazosin. Venous distensibility (Figure 2 A) rose acutely after captopril both in the control period (from 4.40 ± 0.3 to 4.74 ± 0.3 ml/100 ml forearm volume; p = 0.001) and after 1 week of prazosin therapy (4.37 ± 0.4 to 4.94 ± 0.6 ml/100 ml forearm volume; p = 0.01). There was no significant difference between the venous distensibility obtained on no medications and that obtained on prazosin alone.

Captopril had no effect on BBF (Figure 2 B) in the control period (3.97 ± 0.6 vs 4.17 ± 0.06 ml/min/100 ml forearm volume; p = 0.06) nor after prazosin treatment (4.57 ± 0.6 vs 4.67 ± 0.7 ml/min/100 ml forearm volume; p > 0.05). However, there was an increase in BBF after prazosin alone from 3.97 ± 0.6 to 4.58 ± 0.6 ml/min/100 ml forearm volume (p = 0.03).

Captopril reduced PHBF in the control period (from 49.5 ± 4 to 39.5 ± 2 ml/min/100 ml forearm volume; p = 0.002), but had no effect on PHBF following prazosin (45.3 ± 4 vs 40.7 ± 4 ml/min/100 ml forearm volume; p > 0.05). However, captopril decreased FVR both in the control period (from 35.3 ± 6 to 27.8 ± 5 mm Hg/ml/min/100 ml forearm volume; p = 0.001) and after 1 week of prazosin therapy (26.3 ± 3 to 22.9 ± 4 mmHg/ml/min/100 ml forearm volume; p = 0.01), as seen in Figure 2 C.

Figure 3 depicts the changes in enzymatic activity and circulating hormonal concentrations following captopril administration. Figure 3 A demonstrates suppression of ACE activity by captopril. In the control period, ACE activity fell from 92 ± 10 to 8 ± 2 nM/ml/min (p = 0.0001). Similarly, following 1 week of prazosin, captopril decreased ACE activity from 91 ± 7 to 6 ± 1 nM/ml/min (p = 0.0001).

In the control period, the PRA rose acutely after captopril before and after prazosin therapy. After discontinuation of all antihypertensive medications for 3 weeks, the average BP for the control group was 162 ± 7/97 ± 3 mm Hg.
VASODILATION BY CAPTOPRIL/Johns et al.

**Figure 1.** Blood pressure and heart rate responses to captopril before and after pretreatment with prazosin. Clear bars represent data obtained on no medications; striped bars refer to data obtained on captopril. Stippled bars represent data obtained on prazosin for 1 week. Values are means ± SEM. Dotted line = mean arterial blood pressure.

**Figure 2.** Plethysmographic responses to captopril before and after pretreatment with prazosin. Clear bars represent data obtained on no medications; striped bars depict data obtained on captopril; stippled bars refer to data obtained on prazosin. Values are means ± SEM. A. Venous volume (VV30) in ml/100 ml forearm volume. B. Basal blood flow (BBF) in ml/min/100 ml forearm volume. C. Forearm vascular resistance (FVR) in mmHg/ml/min/100 ml forearm volume.

**Figure 3.** Converting enzyme activity and circulating hormonal concentration in response to captopril before and after pretreatment with prazosin. Clear bars refer to data obtained on no medications; striped bars depict data obtained on captopril; stippled bars represent data obtained after one week of prazosin. Values are means ± SEM. A. Angiotensin-converting enzyme activity (ACE) in nmol/min/ml. B. Plasma renin activity (PRA) in ng/ml/hr. C. Plasma aldosterone concentration (PAC) in ng/dl.
Discussion

In eight hypertensive patients we found that acute ACE suppression with captopril resulted in increased venous distensibility and decreased FVR and BP. Moreover, captopril's ability to vasodilate and to lower BP was additive to the effects achieved by \(\alpha\)-adrenergic blockade with prazosin. This report extends our earlier findings of arteriolar and venous dilation following captopril administration to patients with severe hypertension.\(^{22}\) Although in this study we could not exclude the influence of acute withdrawal of previous antihypertensive medications, in the present study antihypertensive medications were discontinued 3 weeks prior to study. The association of captopril with arteriolar dilation in hypertensive humans\(^9\)\(^{23}\) and in patients with congestive heart failure\(^{24-27}\) has been inferred from the reduction in systemic vascular resistance consistently demonstrated. Captopril-induced venodilation has been a variable finding. In patients with congestive heart failure, captopril-induced venous dilation was demonstrated by Awan et al.\(^{28}\) in the forearm blood vessels and by Kayanakis et al.\(^{29}\) in calf blood vessels. However, Faxon et al.\(^{30}\) failed to demonstrate an effect on either venous capacitance or basal blood flow in calf vessels under similar circumstances. Captopril could cause vasodilation by any of several mechanisms. Captopril blocks formation of ANG II by inhibition of ACE.\(^{31}\) Angiotensin II is a potent arteriolar constrictor.\(^{32,33}\) Its effect on veins has been variable. Most authors have observed weak venous constriction in vivo\(^{34-37}\) although Emerson et al.\(^{38}\) have demonstrated that, on an equimolar basis, ANG II is a more potent small vein constrictor than is norepinephrine. The ANG II-induced venous constriction has been observed in vitro in isolated rat portal veins,\(^{39,41}\) in pulmonary, gastroduodenal, mesenteric and saphenous veins of the dog,\(^{42}\) and in the external jugular and anterior mesenteric veins of the rabbit.\(^{43}\)

Collier and Robinson\(^{44}\) have demonstrated that arteries of the forearm and veins of the hand constrict following intraarterial infusion of ANG I and ANG II. The vascular response to ANG I was abolished or greatly attenuated by infusion of the converting-enzyme inhibitor teprotide, whereas ANG II-induced vasoconstriction was unaffected. Thus, captopril may have produced vasodilation in the present experiments by inhibiting the endogenous formation of ANG II. Using forearm plethysmography, Wood\(^{45}\) observed constriction of veins and arterioles after ANG II infusion in normal subjects; however, ANG II infusion in hypertensive patients produced arteriolar constriction without further venous constriction. If the veins in hypertensive patients were maximally constricted via the influence of endogenous ANG II, further vasoconstriction with exogenous ANG II administration would not be expected. The ability of the veins and arterioles to dilate in the present experiments implies that the synthesis of ANG II contributes to the maintenance of the hypertension.

Angiotensin II stimulates sympathetic nervous system activity centrally\(^{46}\) and in the periphery.\(^{47-50}\) Elevated plasma concentrations of catecholamines have been demonstrated in patients with hypertension.\(^{51,52}\) DePasquale and Burch\(^{53}\) abolished ANG II-induced venous constriction by regional nerve block in the forearm of normal subjects.\(^{57}\) Angiotensin II is known to facilitate release of norepinephrine from sympathetic neurons at physiologic frequencies of stimulation.\(^{50}\) Thus, captopril might decrease vasomotor tone indirectly through neurogenic mechanisms induced by reduction of ANG II levels.

Antonaccio\(^{53}\) demonstrated that acute administration of captopril inhibited the pressor response to sympathetic nerve stimulation and to exogenously administered ANG I in pithed spontaneously hypertensive rats (SHR). The BP rise induced by exogenous infusion of both ANG II and norepinephrine was unaffected by captopril, which suggests that captopril acts on the presynaptic nerve terminals. If captopril's primary action is a reduction of sympathetic activity that leads to decreased activation of \(\alpha_1\) vascular receptors, one would expect to see some evidence of blunted antihypertensive activity following \(\alpha_1\)-adrenergic receptor blockade with prazosin. In our patients, prior administration of prazosin in doses sufficient to lower blood pressure did not inhibit captopril's ability to lower vascular resistance or to increase venous capacitance. However, postsynaptic \(\alpha_2\) receptors also are known to mediate vasoconstriction.\(^{51,52}\) SHR and Dahl salt-sensitive rats exhibit higher renal \(\alpha_1\)- and \(\alpha_2\)-receptor densities than their normotensive controls.\(^{54}\) A recent report suggests that postsynaptic \(\alpha_2\) receptors contribute significantly to the responses of rat tail arteries to norepinephrine in SHR but not in normotensive WKY rats.\(^{56}\) The present study does not define the relative importance of the two \(\alpha\)-adrenergic subtypes.

In the absence of a direct measurement of ANG II concentration, suppression of ANG II can be inferred from the association of an elevated PRA with a reduced PAC following acute captopril administration,\(^{4,48}\) as was found in the present study. One week of prazosin led to a rise in PRA and PAC in our patients, which implies a rise in ANG II concentration. This corroborates the findings of some authors who have reported a rise in PRA\(^{57,58}\) and differs from other reports of little or no PRA elevation\(^{59}\) following prazosin administration. The further lowering of BP obtained by adding captopril to prazosin is consistent with prazosin-induced activation of the renin-angiotensin system. Although the present study does not define the mechanism, possibilities include stimulation of the sympathetic nervous system, decreased renal perfusion pressure, or a direct action of prazosin on the juxtaglomerular cell.

ACE inhibition has been demonstrated to block degradation of bradykinin.\(^{60}\) Bradykinin elicits a dose-related lowering of BP in the normotensive rat and frequently an increased BP in the hypotensive rat.\(^{61,62}\) Bradykinin is a potent dilator of arteriolar smooth muscle,\(^{63}\) but its effect on veins differs depending on the experimental preparation. Contraction of isolated rabbit vein strips,\(^{54}\) isolated dog veins,\(^{60}\) and bovine pul-
monary veins has been demonstrated. However, venous dilation has been reported following bradykinin infusion in humans. Thus, bradykinin accumulation might directly decrease vasomotor tone or might lead to vasodilation by effects on local release of prostaglandins from blood vessels. The possible potentiation of bradykinin activity by ACE inhibition has been demonstrated in hypertensive patients, and the present studies do not exclude that hypothesis. But if bradykinin were the primary mediator of captopril’s hypotensive action, one would have expected an increase in cardiac output and HR, which was not demonstrated in the present experiments.

We have demonstrated that captopril dilates forearm veins and arterioles and lowers BP in hypertensive patients. This decrease in vasomotor tone may reflect a reduction in vasoconstrictor action of ANG II on smooth muscle directly or augmentation of the vasodilatory action of bradykinin. Alpha-one receptor blockade by prazosin did not prevent captopril’s ability to vasodilate, which suggests that inhibition of sympathetic nervous system activity is not the primary mechanism of captopril’s acute antihypertensive action. In addition, the vasodilatory and antihypertensive responses to captopril and prazosin together were greater than the responses to either agent alone.

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