Captopril Potentiates Chronotropic Baroreflex Responses to Carotid Stimuli in Humans

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SUMMARY Angiotensin II is a potent vasoconstrictor and has profound effects on autonomic neural mechanisms in experimental animals. Human carotid baroreflex control of arterial pressure and heart period was examined before and after acutely decreasing angiotensin II levels by administering 50 mg of oral captopril, an angiotensin converting enzyme inhibitor. Carotid baroreceptor stimuli were delivered by a neck chamber worn by 14 normotensive volunteers. Four subjects received placebo. Arterial pressure responses to carotid distention and tachycardia in response to carotid compression were not changed in captopril or placebo groups; however, there was an augmented bradycardic response to carotid stretch in captopril-treated subjects. These results indicate that captopril has an asymmetrical effect on carotid baroreflex function and suggest that enhanced baroreflex mediated bradycardia is due to a reduction in central nervous system angiotensin II levels by captopril, which augments vagal-cardiac responses to carotid stimuli. (Hypertension 7: 602–606, 1985)

KEY WORDS • angiotensin • baroreceptor • blood pressure • carotid sinus

ANGIOTENSIN II is a potent vasoconstrictor agent that has been shown to have an important influence on autonomic neural mechanisms. For example, intravenous infusion of pressor doses of angiotensin attenuates baroreflex-mediated bradycardia in sheep,1-3 rabbit,4 dog,5-7 and humans.8 However, decreasing plasma angiotensin II levels with converting enzyme inhibitors (e.g., captopril) does not have as consistent an effect on baroreflex function. Several studies suggest that baroreflex sensitivity is unchanged9,10 or decreased,11 while others show a potentiation11,12,13 of baroreflex sensitivity, after angiotensin converting enzyme inhibition.

Although the majority of these investigations have only examined the effects of angiotensin II (or captopril) on chronotropic baroreflex responses to pressor stimuli, several studies in experimental animals suggest that angiotensin II also attenuates sympathetic baroreflex responses.4-7,14,15 Guo and Abboud4 demonstrated that angiotensin II attenuated both the reflex bradycardia and inhibition of lumbar sympathetic nerve activity provoked by baroreceptor stimuli in rabbits. Contrasting results were obtained from humans with essential hypertension: heart rate and blood pressure responses to baroreceptor stimuli were unchanged after lowering angiotensin II levels with captopril.10

In this investigation, healthy normotensive men were studied to determine the effects of short-term reductions in plasma angiotensin II levels on baroreflex control of cardiac interval and blood pressure.

Methods

Fourteen healthy young men, 20 to 29 years of age (average, 24.2 yr), participated in the study after providing informed consent. The study was approved by the institution's human research review committee. Five subjects were instructed to follow a sodium-restricted diet (2 g/day) for 3 days before the study began. Subjects collected 24-hour urine specimens; the collection ended with the morning void on the day of investigation. To ensure the adequacy of collection, these specimens were later analyzed for sodium and creatinine content.

Subjects abstained from breakfast before arriving in the laboratory. Radial artery cannulation was performed after Allen testing. Electrocardiogram electrodes were positioned, and subjects lay supine for 30 minutes before the studies were initiated. Control carotid baroreceptor reflex data and arterial blood samples were obtained. Ten subjects ingested 50 mg of captopril (Squibb), and four ingested placebo. After 90
minutes baroreceptor stimuli and blood sampling were repeated. The testing protocol was completed 2.5 hours after ingestion of captopril or placebo. Plasma renin activity was determined by radioimmunoassay of angiotensin I generation.\(^\text{16}\)

**Baroreceptor Stimuli**

An airtight flexible lead collar was worn by volunteers. Two types of carotid stimuli were employed: 1) prolonged (5 sec), graded neck suction and pressure and 2) brief (0.4 sec), repetitive, ramped neck suction. These stimuli were delivered in random sequence to subjects during end-expiratory apnea. The specific methods have been described previously.\(^\text{17-19}\) Briefly, prolonged, graded neck suction and pressure consisted of initially applying 10 seconds of 15 mm Hg of neck pressure to unload carotid baroreceptors. During breathing, when baseline cardiac interval had stabilized, neck suction was initiated 0.8 second before the anticipated occurrence of an atrial P wave.\(^\text{20}\) The RR interval immediately before the onset of neck suction was taken as the control, and the first RR interval completed after onset of neck suction was considered the response interval. Six intensities of neck suction were employed (+15 to 0, −10, −20, −30, −40, and −50 mm Hg). The abrupt termination of each neck suction to 15 mm Hg of neck pressure produced graded decreases in carotid transmural pressure. These neck pressure stimuli were also carefully timed; the cardiac cycle occurring 4 to 5 seconds after onset of neck suction served as the control interval for determining the triggering of neck pressure and subsequent shortening of pulse interval. Thus, in the same breath- hold, pulse interval responses to neck suction and pressure could be determined.

Blood pressure progressively declines during 5-second applications of neck suction. The rate of decline is linearly related to the stimulus intensity. The mean arterial pressure at precisely 4.0 seconds after onset of neck suction was calculated by least squares regression analysis. The relationship between neck suction intensity and changes in mean arterial pressure 4 seconds after suction onset is linear and is employed in this study as an index of carotid baroreflex control of arterial pressure.

The second type of baroreceptor stimulus was brief, repetitive neck suction, which consisted of five consecutive electrocardiogram R-wave-triggered carotid stimuli of increasing intensity (−10, −20, −30, −40, −50 mm Hg). Each stimulus lasted 0.4 second and was superimposed on the natural carotid pulse. By relating each neck suction intensity to the corresponding RR interval, baroreflex slopes are obtained in one breathhold.\(^\text{18, 19}\)

Seven duplicate trials of brief, repetitive neck suction and seven duplicate trials of each prolonged neck suction and pressure intensity were applied to each volunteer before and after captopril (or placebo) ingestion. Duplicate trials for each intervention were averaged for each subject. Group data represent means ± SEM of individual averaged responses. Data were analyzed by least squares linear regression analysis and Student's t-tests.\(^\text{21}\) Regression slopes were compared by analysis of covariance. Differences were considered significant at \(p < 0.05\).

**Results**

There were no significant differences in age, height, weight, baseline cardiac interval (1120 ± 30 vs 1107 ± 21 msec), or mean blood pressure (90 ± 2 vs 92 ± 2 mm Hg) between captopril-treated and placebo groups. Treatment with captopril resulted in a significant 4.2 mm Hg fall of mean pressure \(p < 0.05\) similar to the significant 3.5 mm Hg decrease of pressure in subjects receiving placebo \(p < 0.05\). Neither captopril nor placebo altered baseline cardiac interval.

There was a significant inverse relation \(r = −0.68\) between 24-hour urinary sodium excretion and the control (pre-captopril) plasma renin activity. Control plasma renin activity of 5 ± 0.07 ng/ml/hr, increased more than threefold to 17 ± 4.2 ng/ml/hr after angiotensin I converting enzyme inhibition. This finding suggests formation of angiotensin II was effectively inhibited by captopril. Plasma renin activity fell slightly in the placebo group (from 4.2 ± 2 to 3.7 ± 1.7 ng/ml/hr).

Figure 1 demonstrates the RR interval responses to graded, prolonged neck suction. The slope of this relation is an index of carotid baroreflex sensitivity. Baroreflex slopes increased by 50% after captopril treat-
Discussion

In this study, human carotid baroreflex regulation of cardiac interval and arterial blood pressure was examined before and after inhibition of angiotensin II formation. We found that in normotensive men, 1) captopril administration resulted in enhanced baroreflex-mediated bradycardia but did not alter baroreflex-mediated hypotension and 2) baroreflex-mediated tachycardia in response to carotid compression was unchanged by captopril treatment. These data suggest that angiotensin II exerts a selective influence on baroreflex responses to hypertensive stimuli: vagal responses are enhanced while sympathetic responses are not. These conclusions are strengthened by the absence of changes in baroreflex responses after placebo administration.

Plasma angiotensin II levels were not measured in this study. Other reports have shown that plasma levels are reduced 35 to 50% after short-term administration...
of similar doses of angiotensin converting enzyme inhibitors. There was a wide variation in daily sodium intake, which was achieved by placing five subjects on a low sodium diet. Although we had hypothesized a relation between the 24-hour urinary sodium excretion or the plasma renin activity (both indirect indices of plasma angiotensin II levels) and baroreceptor reflex responses, we found none. Furthermore, there was no relation between the change in plasma renin activity and the change in baroreflex response produced by captopril. This finding does not preclude the possibility of a direct relationship between the reductions in plasma angiotensin II levels and the enhancement of baroreflex responses.

Altered Carotid Baroreflex Function

**Vagal Effects**

These data demonstrate a highly significant augmentation of carotid to cardiac reflex gain when hypertensive stimuli (carotid distention) were applied after angiotensin converting enzyme inhibition. This effect was not seen during placebo or during hypotensive stimuli (carotid compression). This differential effect of angiotensin on vagal-cardiac responses to carotid compression and distention also has been noted in animal studies. Guo and Abboud demonstrated that, during angiotensin II infusion, baroreflex inhibition of heart rate in response to phenylephrine infusion was attenuated while baroreflex increases in heart rate in response to sodium nitroprusside were unchanged.

Enhanced vagal-cardiac responses to carotid stimulation may be due to 1) a direct effect of captopril, 2) a reduction of plasma aldosterone, 3) an increase of circulating bradykinin, or 4) an increase of plasma prostaglandins. However, the most likely explanation for augmented baroreflex function after captopril is that plasma (and perhaps central nervous system) angiotensin II levels are decreased. This contention is supported by data from animal studies in which baroreflex-mediated bradycardia was decreased by intravenous angiotensin infusion. Similarly, intracarotid infusion of angiotensin II has been shown to blunt baroreflex responses. Because angiotensin converting enzyme inhibitors were not employed in these studies, bradykinin and prostaglandin levels probably were unchanged.

The mechanism of this interesting interaction between angiotensin and baroreflex function is most likely due to a central effect of angiotensin that modifies vagal-cardiac activity. Several reports have provided data supporting this contention. Carotid sinus afferent traffic is not altered by physiological variations in plasma angiotensin. Baroreflex-mediated increases in vagal efferent nerve activity are blunted by angiotensin. Angiotensin produces a central, dose-dependent reduction in vagal efferent traffic and has a peripheral inhibitory action on the cardiac vagus. Interestingly, in the absence of baroreceptor reflexes, angiotensin has a direct positive inotropic and chronotropic effect.

A second possible explanation for captopril’s effect on baroreflex function is that baroreceptor reflexes are reset. Hatton et al. have shown that captopril treatment of sodium-depleted dogs produced a rightward shift in the systolic pressure–RR interval relation (change in set point) without an alteration in sensitivity. However, these effects were not evident in dogs on normal sodium diets. In the present study blood pressure was not changed by captopril administration. Therefore, replotting Figures 1, 2, and 3 with carotid sinus transmural pressure (systolic pressure–neck suction intensity) would not demonstrate a change in set point.

**Sympathetic Effects**

In animal models, the effects of angiotensin II infusion on baroreflex control of blood pressure and sympathetic nerve activity have not been consistent. Goldstein et al. reported that angiotensin did not change the reflex vasodilator response to carotid stimulation in dogs; however, opposing findings have been reported by others. Additionally, angiotensin infusion may or may not alter sympathetic efferent nerve activity at rest. The reasons for these inconsistencies are unclear. In the present study angiotensin converting enzyme inhibition did not alter baroreflex-mediated hypotension.

**Conflicting Human Data**

Mancia et al. applied neck suction, neck pressure, and infused phenylephrine and sodium nitroprusside in hypertensive patients before and after captopril ingestion. In contrast to the results of this study, they showed that bradycardia following phenylephrine infusion was unchanged after captopril administration while tachycardia in response to sodium nitroprusside and hypertension in response to neck pressure were enhanced by captopril. Several important differences in methods should be pointed out. Mancia et al. studied only hypertensive subjects. Furthermore, they applied neck chamber stimuli for 120 seconds and demonstrated an effect of captopril only on “late” (90–120 sec after stimulus onset) blood pressure responses. It is possible that prolonged neck suction or pressure activates extracarotid reflex systems or alters cerebral blood flow. These authors were unable to show any effect of captopril on “early” reflex responses of blood pressure to carotid compression or distention. These early responses may be better indices of physiological phenomena since neural control mechanisms in humans show moment to moment fluctuations.

**Limitations**

The site and mechanism of action of captopril was not ascertained in this study, but animal studies provide strong evidence that angiotensin acts within the central nervous system to alter vagal-cardiac mechanisms. The results of this study suggest that captopril-induced reductions in angiotensin II produce opposite effects. Whether potentiation of baroreflex chronotropic responses persisted during long-term
administration of captopril was not determined; only short-term effects (within 3 hr) were examined. Blood pressure responses to carotid compression also were not examined.

In this study, angiotensin I converting enzyme inhibition did not alter peripheral sympathetic (hypotensive) responses to baroreflex activation and did not influence tachycardic responses to carotid compression. However, a short-term augmentation of baroreflex-mediated bradycardia was demonstrated in normotensive men after captopril administration. This finding is most likely due to a reduction in central nervous system angiotensin II levels, which augments vagal-cardiac responses to carotid stimuli. Baroreflex potentiation of chronotropic baroreflex responses to hypertensive stimuli by captopril may represent a contributory antihypertensive effect of this drug.

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