

# Attenuation of pressor responses to norepinephrine and pitressin and potentiation of pressor response to angiotensin II by captopril in human subjects

著者	Imai Y, Abe K, Seino M, Haruyama T, Tajima J, Sato M, Goto T, Hiwatari M, Kasai Y, Yoshinaga K, Sekino H
journal or publication title	Hypertension
volume	4
number	3
page range	444-451
year	1982
URL	<a href="http://hdl.handle.net/10097/51526">http://hdl.handle.net/10097/51526</a>

# Hypertension

American Heart  
Association® 

*Learn and Live*<sup>SM</sup>

JOURNAL OF THE AMERICAN HEART ASSOCIATION

**Attenuation of pressor responses to norepinephrine and pitressin and  
potentiation of pressor response to angiotensin II by captopril in human  
subjects**

Y Imai, K Abe, M Seino, T Haruyama, J Tajima, M Sato, T Goto, M Hiwatari, Y  
Kasai, K Yoshinaga and H Sekino

*Hypertension* 1982, 4:444-451

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX  
72514

Copyright © 1982 American Heart Association. All rights reserved. Print ISSN: 0194-911X. Online  
ISSN: 1524-4563

The online version of this article, along with updated information and services, is  
located on the World Wide Web at:

<http://hyper.ahajournals.org/content/4/3/444>

Subscriptions: Information about subscribing to Hypertension is online at  
<http://hyper.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters  
Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050.

Fax: 410-528-8550. E-mail:  
[journalpermissions@lww.com](mailto:journalpermissions@lww.com)

Reprints: Information about reprints can be found online at  
<http://www.lww.com/reprints>

# Attenuation of Pressor Responses to Norepinephrine and Pitressin and Potentiation of Pressor Response to Angiotensin II by Captopril in Human Subjects

YUTAKA IMAI, M.D., KEISHI ABE, M.D., MASAHIDE SEINO, M.D.,  
TOSHIKI HARUYAMA, M.D., JIRO TAJIMA, M.D., MAKITO SATO, M.D.,  
TOSHIKAZU GOTO, M.D., MASAO HIWATARI, M.D., YUTAKA KASAI, M.D.,  
KAORU YOSHINAGA, M.D., AND HIROSHI SEKINO, M.D.

**SUMMARY** The present study was conducted to investigate the influence of captopril on cardiohemodynamic responses in 38 normal volunteers (20- to 35-year-old men) to exogenously administered vasopressor substances. Norepinephrine (NE), 0.05, 0.1, and 0.2  $\mu\text{g}/\text{kg min}^{-1}$ ; angiotensin II (AII), 5, 10, and 20  $\text{ng}/\text{kg min}^{-1}$ ; and pitressin (2 mU/kg  $\text{min}^{-1}$ ) were infused for 10 minutes. Each infusion was repeated twice, and the responses were reproducible. Captopril (50 mg by mouth) significantly attenuated the pressor responses to NE and pitressin, but the decrease in heart rate in response to NE and pitressin was almost the same before and after captopril treatment, suggesting that captopril potentiates reflex slowing of the heart. Captopril significantly potentiated the pressor response to AII. Attenuation of pressor response and potentiation of reflex slowing of the heart, in response to NE and pitressin, disappeared when a subdepressor dose of AII (1  $\text{ng}/\text{kg min}^{-1}$ ) was infused in addition to captopril. Infusion of a subdepressor dose of bradykinin (BK), 0.1  $\mu\text{g}/\text{kg min}^{-1}$ , had no influence on the pressor response to NE. In the subjects treated with indomethacin (225 mg/54 hrs), captopril still attenuated the pressor response to NE. These results suggest that captopril attenuates the pressor responses to NE and pitressin primarily by depletion of endogenous AII; decreased AII may desensitize the contraction of arterial smooth muscle and may potentiate the compensatory reflex mechanism. (Hypertension 4: 444-451, 1982)

**KEY WORDS** • blood pressure • heart rate • bradykinin • angiotensin • indomethacin • vascular reactivity • baroreflex • plasma renin activity

**C**APTOPRIL (SQ 14,225), an orally active angiotensin-converting enzyme inhibitor, has been shown to be effective in lowering the blood pressure of hypertensive patients.<sup>1,2</sup> It is generally assumed that the hypotensive effect of captopril may be due to either suppression of angiotensin II (AII) formation or potentiation of bradykinin (BK), or a combination of both,<sup>2-4</sup> since angiotensin converting enzyme is identical to kininase II.<sup>5</sup> However, the precise role of the renin-angiotensin and the kallikrein-kinin systems in mediating the hypotensive effect of captopril still remains to be determined. There is documented evidence that captopril lowers

blood pressure in some patients with low renin hypertension<sup>2,6,7</sup> and in some anephric patients.<sup>8</sup> Additional studies are needed to uncover the mechanism of action of this important therapeutic agent. Okuno et al.<sup>9</sup> recently reported that captopril attenuated the contractile response to norepinephrine (NE) in the rat mesenteric artery. In view of these reports, we put forward a hypothesis that the hypotensive action of captopril is due to a change in vascular reactivity to vasopressor substances and modulation of the baroreflex mechanism. To test this hypothesis, we examined the effect of captopril on cardiohemodynamic responses to several vasoactive substances in normal volunteers.

## Materials and Methods

The present study was conducted on 38 male volunteers from 20 to 35 years of age, who were normotensive without any known renal or cardiovascular disease. They gave informed consent before the study.

From the Second Department of Internal Medicine, Tohoku University School of Medicine and Sendai Insurance Hospital, Sendai, Japan.

Supported in part by a research grant for cardiovascular disease (Grant 54-A-2) from the Ministry of Health and Welfare, Japan.

Address for reprints: Yutaka Imai, M.D., Monash University Department of Medicine, Prince Henry's Hospital, St. Kilda Road, Melbourne, Victoria 3004, Australia.

Received May 4, 1981; revision accepted December 4, 1981.

All subjects were allowed an unrestricted diet (including sodium intake), and underwent the studies either in the morning or the afternoon after a light breakfast or lunch. Each subject was investigated in the recumbent position; blood pressure was measured with an automatic blood pressure recorder (Roche, Arteriosonde Type 1210) and heart rate by a cardiometer, at 1-minute intervals throughout the study. Blood pressure and heart rate of all the subjects became stable during 1 hour of bedrest in the recumbent position. An intravenous infusion of isotonic glucose solution was started via an indwelling venous cannula at a rate of 1 ml/min and continued until the end of the study. Without disturbing the subjects, the drug solution was then infused by constant infusion pump (ATOM, Type 201) superimposed on the glucose infusion.

Drugs used in this study were NE (Noradrenalin, Sankyo), AII (Hypertensin, Ciba), pitressin (Parke-Davis), BK (BSR 640, Sandoz), captopril (Squibb-Sankyo), and indomethacin (Inteban SP, Sumitomo). We had previously determined that 1  $\mu$ U of pitressin (Parke-Davis) was equivalent to 2.5 to 2.7 pg of synthesized arginine vasopressin (unpublished data).

The term "basal" used in the present study refers to a value obtained just prior to the administration of vasopressor substances (average of five readings). The term "control" used in the present study refers to responses to vasoactive substances before captopril treatment or BK infusion. The response was defined as the difference between the "basal value" and the average of five readings for each dose of vasoactive substance given. In the cases of NE and AII, the final five readings were averaged, while in the case of pitressin, the five readings from the 3rd to 7th minute in the course of a 10-minute infusion were averaged, since tachyphylaxis easily occurred during the infusion of pitressin. Blood samples for the measurement of plasma renin activity (PRA) were taken just prior to the infusion of vasopressor substances with and without captopril treatment; PRA was measured radioimmunologically as described previously.<sup>10</sup>

#### Study Groups

Ten groups for 10 different studies were designed. One-half of the subjects were studied twice in different study protocols. The second study was performed at least 1 week after the first one. In all groups except Groups 3, 6, and 9, the changes in heart rate in response to vasopressor substances were expressed as the value obtained with the highest dose.

#### *Reproducibility of Cardiohemodynamic Responses to Norepinephrine (Group 1), Angiotensin II (Group 2), and Pitressin (Group 3)*

Norepinephrine in doses of 0.05, 0.1, and 0.2  $\mu$ g/kg  $\text{min}^{-1}$ ; AII in doses of 5, 10, and 20 ng/kg  $\text{min}^{-1}$ ; and pitressin in a dose of 2 mU/kg  $\text{min}^{-1}$  were infused into three different groups (Groups 1, 2, and 3, each with five subjects). These infusions were repeated two times to determine the reproducibility of the responses to

these vasoactive substances. Norepinephrine, AII, and pitressin solutions were diluted to concentrations of 50  $\mu$ g/ml, 5  $\mu$ g/ml, and 0.5 U/ml, respectively, using physiological saline. At least 1 hour was allowed to elapse between the first and the second infusion. Three doses of NE or AII were infused for 10 minutes each. The effects of pitressin were studied using only one dose, since tachyphylaxis and urge for defecation occurred.

#### *Effect of Captopril on the Cardiohemodynamic Responses to Norepinephrine (Group 4), Angiotensin II (Group 5), and Pitressin (Group 6)*

Seven (Group 4), six (Group 5), and five (Group 6) normal volunteers were examined to determine the effect of captopril on the responses to vasopressor substances. A control response to the vasopressor substances was first obtained, and 1 hour later captopril in a dose of 50 mg was administered orally. One hour later, the vasopressor substances were infused again. Doses of the drugs were the same as in Groups 1, 2, and 3.

#### *Effect of Combined Treatment with Captopril and a Subdepressor Dose of Angiotensin II on the Cardiohemodynamic Responses to Norepinephrine (Group 7) and Pitressin (Group 8)*

Five normal volunteers were examined in Groups 7 and 8. The subdepressor dose of AII was determined by extrapolation of the dose-response curve obtained in Group 2. One hour after obtaining the control pressor responses to NE and pitressin, infusion of AII at a rate of 1 ng/kg  $\text{min}^{-1}$  was started in addition to the oral administration of captopril in a dose of 50 mg. The second responses to NE and pitressin were tested during the infusion of AII at a low rate. Doses of the drugs were the same as in Groups 1 and 3.

#### *Effect of Infusion of Subdepressor Dose of Bradykinin on the Cardiohemodynamic Responses to Norepinephrine (Group 9)*

Five normal volunteers were examined in Group 9. The responses to NE were examined with only one dose (0.1  $\mu$ g/kg  $\text{min}^{-1}$  for 10 minutes). One hour after the control responses to NE were obtained, BK was infused in a dose of 0.1  $\mu$ g/kg  $\text{min}^{-1}$  for 20 minutes; the BK solution was diluted to a concentration of 50  $\mu$ g/ml using physiological saline. Ten minutes after the start of BK infusion, NE in a dose of 0.1  $\mu$ g/kg  $\text{min}^{-1}$  was infused.

#### *Effect of Combined Treatment with Indomethacin and Captopril on the Cardiohemodynamic Responses to Norepinephrine (Group 10)*

Five normal volunteers were examined in Group 10. Indomethacin in a dose of 25 mg was administered orally every 6 hours for 54 hours; then, 1 hour after the final administration, the control responses to NE were examined. One hour later, captopril in a dose of 50 mg was administered orally. After another hour, the responses to NE were examined again to deter-

mine the effect of the combined treatment with indomethacin and captopril on the responses to NE.

#### Calculation and Analytical Methods

The mean arterial blood pressure (MAP) was calculated from systolic and diastolic blood pressure in the conventional way. The values in the text, table, and figures are means  $\pm$  SEM. The dose response curves for NE and AII within a group and those between groups were analyzed by one-way analysis of covariance. It was determined whether the slopes of the linear regression and the corrected means for a few groups of data on pressor response to vasopressor substance were different from each other.<sup>11</sup> The pressor responses to pitressin within a group were analyzed by Student's *t* test for paired comparison, and those between groups were analyzed by analysis of variance.

### Results

Table 1 shows the basal MAP and heart rate before and after captopril or BK administration. In all studies, no statistically significant difference was found between the MAP before and after captopril or BK administration.

#### Pressor Responses to Norepinephrine, Angiotensin II, and Pitressin

Figure 1 (*upper*) shows changes in MAP produced by NE infusion in 17 subjects before captopril. Arterial pressure was increased by NE with time and with doses. Figure 1 (*center*) shows similar changes in MAP produced by infusion of AII in 11 normal subjects. With infusion of pitressin (fig. 1 *lower*), MAP in-

creased rather rapidly and attained a peak 4 minutes after the start of infusion, but failed to remain elevated and returned toward preinfusion level.

#### Reproducibility of the Cardiohemodynamic Responses to Norepinephrine, Angiotensin II, and Pitressin (Groups 1, 2, and 3)

As shown in figures 2 *left*, 3 *left*, and 4 *left*, the pressor response to each dose of vasopressor substances obtained from the first administration was not significantly different from that obtained from the second administration. The pressor responses to NE, AII, and pitressin were reproducible. The reflex slowing of the heart in response to NE and pitressin was also reproducible. The decrease in heart rate with NE was  $-10.9 \pm 1.8$  bpm (first administration) and  $-8.7 \pm 2.9$  bpm (second administration), and  $-4.9 \pm 1.5$  and  $-6.5 \pm 1.1$  bpm with pitressin. The chronotropic effect of AII was also reproducible, the change in heart rate being  $-2.9 \pm 1.8$  and  $-1.2 \pm 1.5$  bpm respectively, although the chronotropic effect of AII was variable depending upon individuals in such a way that the heart rate was increased in one, decreased in three, and unchanged in the remaining subject.

#### Effect of Captopril on the Cardiohemodynamic Responses to Norepinephrine, Angiotensin II, and Pitressin (Groups 4, 5 and 6)

Captopril did not reduce MAP in normal men (table 1). However, the dose-response curve for NE after captopril was located on the right of the control curve (fig. 2 *center*); the slopes of both curves were not significantly different from each other. There was a significant difference between the corrected means of data on pressor responses to NE before and after captopril ( $p < 0.005$ ); in other words, captopril

TABLE 1. Basal Data in Ten Groups

Group no.	No. of subjects	Age (yrs)	Weight (kg)	Basal MAP (mm Hg)		Basal heart rate (beats/min)	
				Control period	Second period	Control period	Second period
1	5	22.2 $\pm$ 1.3	62.4 $\pm$ 2.1	84.2 $\pm$ 2.3	81.6 $\pm$ 2.6	55.5 $\pm$ 3.5	54.4 $\pm$ 2.7
2	5	23.8 $\pm$ 3.4	67.2 $\pm$ 3.0	83.9 $\pm$ 5.1	84.8 $\pm$ 5.3	62.3 $\pm$ 4.0	61.4 $\pm$ 4.2
3	5	22.4 $\pm$ 1.3	62.4 $\pm$ 2.1	84.3 $\pm$ 1.3	83.9 $\pm$ 1.3	60.6 $\pm$ 2.4	57.8 $\pm$ 2.2
4	7	25.7 $\pm$ 2.1	62.5 $\pm$ 2.3	85.9 $\pm$ 2.6	83.9 $\pm$ 3.1	65.5 $\pm$ 3.6	64.8 $\pm$ 2.9
5	6	23.8 $\pm$ 1.5	67.2 $\pm$ 3.0	84.9 $\pm$ 2.9	81.6 $\pm$ 3.3	65.3 $\pm$ 4.3	62.4 $\pm$ 2.7
6	5	22.2 $\pm$ 1.3	62.4 $\pm$ 2.1	84.7 $\pm$ 1.8	90.2 $\pm$ 3.4	57.6 $\pm$ 3.2	60.0 $\pm$ 1.5
7	5	26.8 $\pm$ 2.9	61.4 $\pm$ 2.3	83.2 $\pm$ 2.2	82.8 $\pm$ 2.6	64.4 $\pm$ 3.0	54.7 $\pm$ 2.0
8	5	28.2 $\pm$ 2.6	62.8 $\pm$ 0.5	86.5 $\pm$ 2.2	88.6 $\pm$ 2.0	64.8 $\pm$ 1.1	63.3 $\pm$ 1.0
9	5	31.2 $\pm$ 1.5	63.4 $\pm$ 2.1	83.9 $\pm$ 5.0	85.6 $\pm$ 5.2	64.4 $\pm$ 3.6	65.0 $\pm$ 3.6
10	5	23.8 $\pm$ 1.5	67.2 $\pm$ 3.0	82.1 $\pm$ 5.6	80.1 $\pm$ 2.9	63.9 $\pm$ 5.0	64.0 $\pm$ 4.6

In Groups 1, 2, and 3, no pretreatment was carried out in the second period. In Groups 4, 5, 6, and 10, captopril was given in the second period. In Groups 7 and 8, captopril and a suppressor dose of angiotensin II were given in the second period. In Group 9, bradykinin was infused in the second period. In Group 10, indomethacin was given in the control and the second periods.

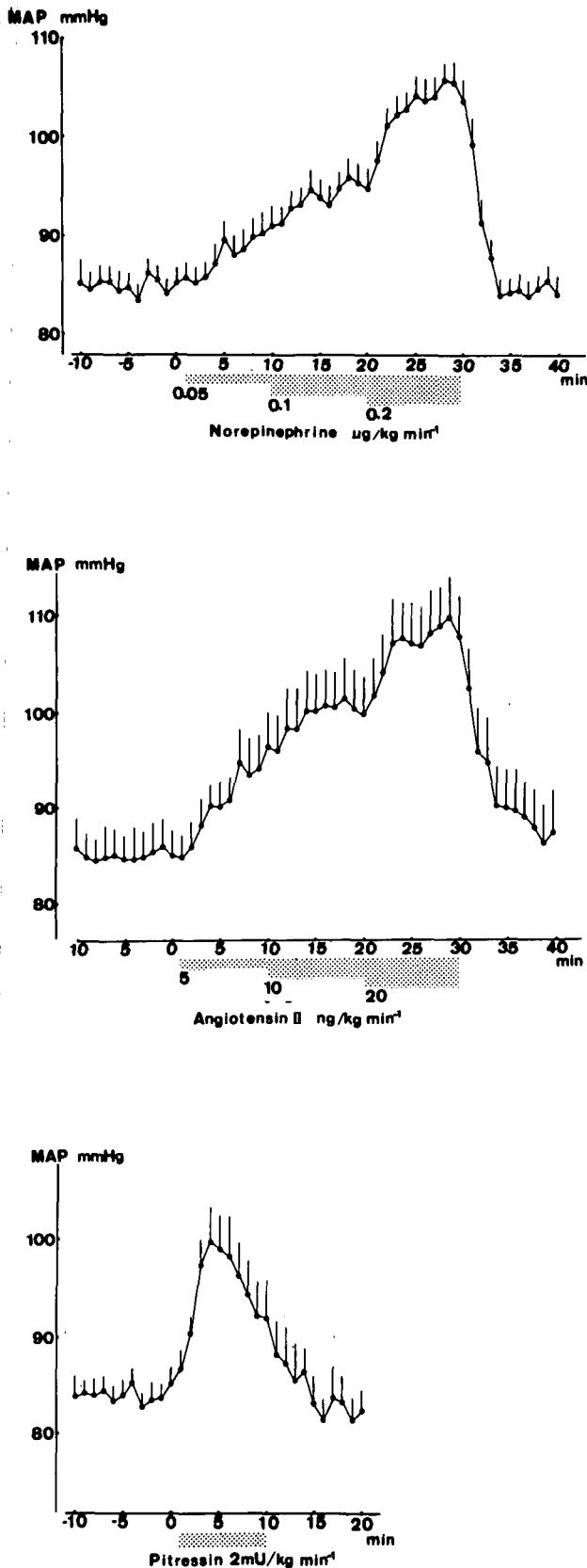


FIGURE 1. Pressor responses to norepinephrine (upper), angiotensin II (center), and pitressin (lower). Dotted columns represent the period of infusion of vasopressor substances. MAP = mean arterial pressure.

significantly attenuated the pressor response to NE. The control dose-response curves in Groups 1, 4, and 7 were not significantly different from each other. The dose-response curve after captopril in Group 4 was significantly different from the control curves in Groups 1 and 7 ( $p < 0.01$ ).

Contrariwise, captopril slightly but significantly ( $p < 0.01$ ) potentiated the pressor response to AII, as shown in figure 3 right. The control dose-response curves in Groups 2 and 5 were significantly different from each other. The dose response curve after captopril in Group 5 was significantly different from the control curve in Group 2.

As shown in figure 4 center, captopril significantly attenuated the pressor response to pitressin ( $p < 0.01$ ). The control pressor responses to pitressin in Groups 3, 6, and 8 were not significantly different from each other. The pressor responses in control in Groups 3, 6, and 8 were pooled and compared with that after captopril in Group 6. There was significant difference between these responses ( $p < 0.02$ ).

Although the increases in blood pressure caused by NE and pitressin were significantly attenuated by captopril, the decreases in heart rate caused by these pressor substances after captopril were similar to those before captopril. With NE, the decrease in heart rate was  $-11.0 \pm 1.2$  bpm before and  $-11.4 \pm 1.5$  bpm after captopril. With pitressin, the decrease in heart rate was  $-4.0 \pm 1.4$  bpm before and  $-5.5 \pm 1.1$  bpm after captopril. The change in heart rate caused by AII after captopril ( $-5.2 \pm 2.4$  bpm) was almost similar to that before ( $-4.6 \pm 3.3$  bpm).

#### Effect of Captopril on the Cardiohemodynamic Responses to Norepinephrine and Pitressin during Infusion of Subdepressor Dose of Angiotensin II (Groups 7 and 8)

Infusion of AII in a dose of  $1 \text{ ng/kg min}^{-1}$  in addition to captopril caused no significant change in MAP or heart rate (table 1). With the infusion of AII, the attenuation by captopril of the pressor responses to NE (fig. 2 right) and pitressin (fig. 4 right) disappeared.

The changes in heart rate caused by NE ( $-8.8 \pm 1.3$  bpm) and pitressin ( $-4.5 \pm 1.3$  bpm) during combined treatment with captopril and AII were not significantly different from those in the control period ( $-10.1 \pm 1.7$  bpm and  $-2.9 \pm 0.8$  bpm respectively).

#### Effect of Infusion of a Subdepressor Dose of Bradykinin on the Cardiohemodynamic Responses to Norepinephrine (Group 9)

Infusion of BK in a dose of  $0.1 \text{ } \mu\text{g/kg min}^{-1}$  did not decrease the MAP (table 1). In three of the five subjects, BK infusion in a dose of  $0.1 \text{ } \mu\text{g/kg min}^{-1}$  caused a slight tachycardia and burning sensation. The pressor response to NE during BK infusion ( $14.1 \pm 4.7 \text{ mm Hg}$ ) was almost identical to the control pressor response ( $15.0 \pm 2.8 \text{ mm Hg}$ ). The bradycardia caused by NE was significantly less during BK infusion ( $-3.3 \pm 0.8$  bpm) than in the control ( $-6.8 \pm 1.0$  bpm,  $p < 0.05$ ).

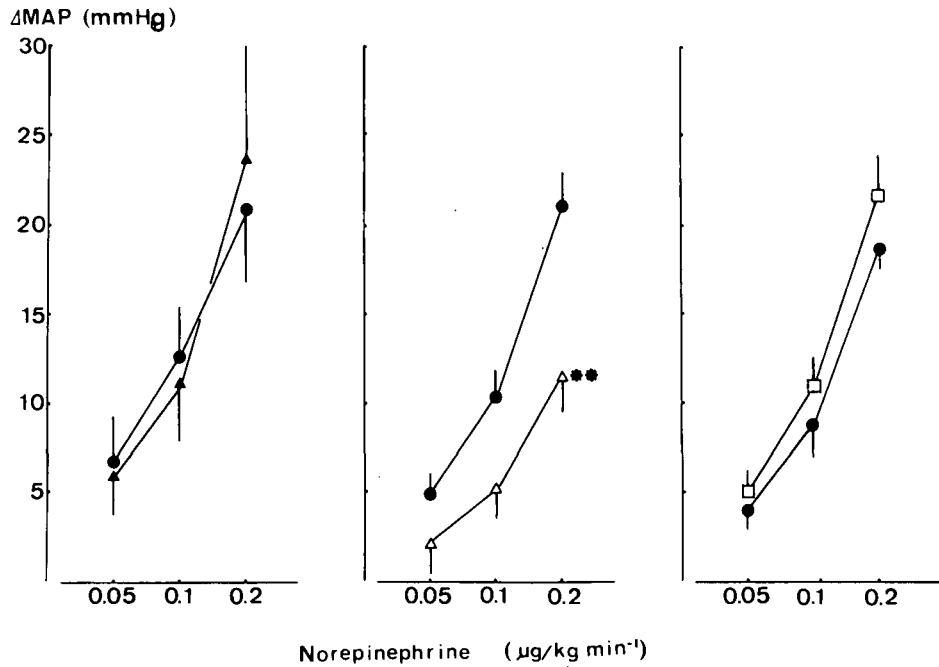


FIGURE 2. Reproducibility of the pressor response to norepinephrine (left), modification of the pressor response to norepinephrine by captoril (center), and the effect of combined treatment with captoril and a subdepressor dose of angiotensin II on the pressor response to norepinephrine (right). ●—● control pressor response; ▲—▲ pressor response to the second administration (left graph); Δ—Δ pressor response after captoril (center); □—□ pressor response during combined treatment (right). ΔMAP = change in mean arterial pressure. \*\*Significant difference from control dose-response curve ( $p < 0.01$ ).

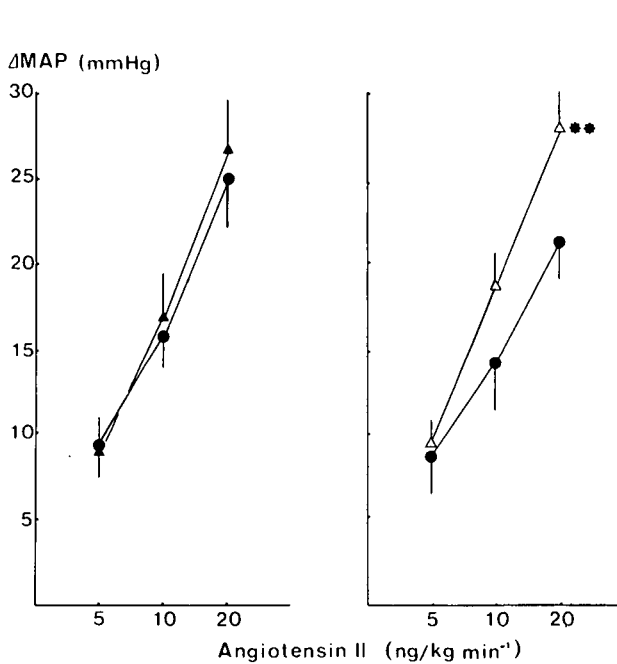


FIGURE 3. Reproducibility of the pressor response to angiotensin II (left), and modification of the pressor response to angiotensin II by captoril (right). ●—● control pressor response; ▲—▲ pressor response to the second administration (left); Δ—Δ pressor response after captoril (right). Otherwise the same as figure 2.

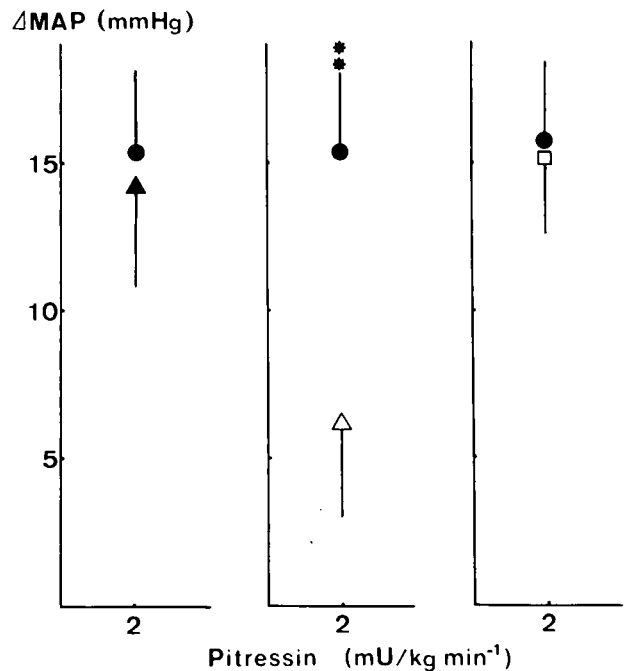


FIGURE 4. Reproducibility of the pressor response to pitressin (left), modification of the pressor response by captoril (center), and the effect of combined treatment with captoril and a subdepressor dose of angiotensin II (right). ● control pressor response; ▲ pressor response to the second administration (left); Δ pressor response after captoril (center); □ pressor response during combined treatment (right). ΔMAP = change in mean arterial pressure. \*\*Significant difference from control ( $p < 0.01$ ).

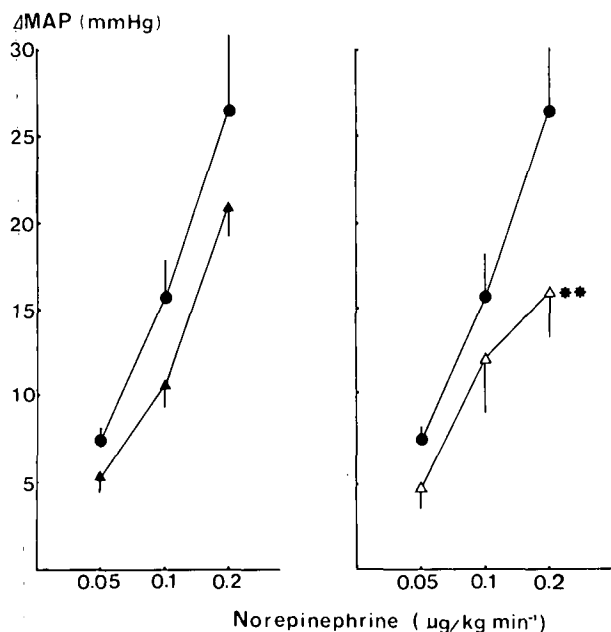


FIGURE 5. Effect of indomethacin on the pressor response to norepinephrine (left), and the effect of combined treatment with indomethacin and captopril on the pressor response to norepinephrine (right). ▲—▲ control pressor response obtained from 17 subjects who were not treated with indomethacin (left); ●—● pressor response obtained from five subjects who were treated with indomethacin; △—△ pressor response during the combined treatment (right). Otherwise the same as figure 2.

#### Effect of Captopril on the Cardiohemodynamic Responses to Norepinephrine during Indomethacin Treatment (Group 10)

The pressor response to each dose of NE in the group treated with indomethacin was not significantly different from that of the group without indomethacin (fig. 5 left). However, as shown in figure 5 right, the dose-response curves for NE was still attenuated by captopril ( $p < 0.01$ ) even in the presence of indomethacin. The reflex bradycardia during combined treatment with captopril and indomethacin ( $-11.0 \pm 2.5$  bpm) was similar to that in the control ( $-10.8 \pm 1.8$  bpm).

#### Effect of Captopril on Plasma Renin Activity

The PRA recorded just prior to the second infusion of NE ( $3.1 \pm 0.9$  ng/ml  $\cdot$  6 hrs $^{-1}$ ,  $n = 5$ ) was not significantly different from that obtained just prior to the first infusion of NE ( $3.0 \pm 0.8$  ng/ml  $\cdot$  6 hrs $^{-1}$ ). The PRA obtained 1 hour after captopril administration and just prior to the infusion of NE ( $15.5 \pm 5.2$  ng/ml  $\cdot$  6 hrs $^{-1}$ ,  $n = 7$ ) was significantly higher than that obtained just prior to the infusion of NE in the control period ( $3.8 \pm 0.7$  ng/ml  $\cdot$  6 hrs $^{-1}$ ,  $p < 0.05$ ).

#### Discussion

The influence of captopril on the pressor response to NE has been investigated in animal experiments. However, the results are conflicting. In vivo experiments showed that captopril scarcely affected the pressor response to NE in rabbits<sup>12</sup> and rats.<sup>13</sup> Recently, Spertini et al.<sup>14</sup> reported that in normotensive anesthetized rats acute converting enzyme blockade by captopril did not blunt the pressor response to NE and vasopressin, although chronic blockade blunted the pressor response to NE. Rubin et al.<sup>15</sup> reported that captopril, in vitro, had little effect on the contractile response of NE in the rat portal vein and rabbit thoracic aorta, whereas some authors reported that captopril attenuated the vasoconstrictor effect of NE in the rat mesenteric artery<sup>9</sup> or rat isolated kidney.<sup>16</sup> Our investigation presented here is the first report that describes the effect of an angiotensin converting enzyme inhibitor on the responses to exogenous vasopressor substances in humans. In the present study, captopril, 50 mg by mouth, attenuated the pressor responses to NE and pitressin in normal human subjects. The question arises as to what mechanism is involved for the attenuation of pressor responses to vasopressor substances. Since captopril attenuated the pressor responses to two vasopressor substances (NE and pitressin), it is unlikely that the attenuation was brought about by some specific mechanisms such as adrenergic alpha-receptor blockade. Since AI converting enzyme and kininase II are the same enzyme,<sup>5</sup> captopril potentiates a vaso-depressor or a vasodilator action of BK. Thus, it is possible that the attenuation of the pressor responses to NE and pitressin might be due to counteraction of endogenous BK. However, the pressor response to NE was not attenuated by a subdepressor dose of BK, even though this dose was sufficient to cause symptoms such as slight tachycardia and/or a burning sensation.<sup>18</sup> Therefore, it is unlikely that the attenuation of pressor responses to the two vasopressors by captopril was caused by an accumulation of BK.

Bradykinin is well known to promote the synthesis of prostaglandins.<sup>17, 18</sup> It is proposed that a decrease in blood pressure after captopril treatment in the rat was the result of vasodilation produced through the interaction of angiotensin-bradykinin-prostaglandin system.<sup>19</sup> Recently, some authors have suggested that the potentiation of the prostaglandin system may contribute to the antihypertensive action of captopril.<sup>7, 20</sup> Therefore, it is also possible that a prostaglandin system activated by increased BK might attenuate the pressor responses. However, attenuation of the pressor response to NE by captopril also occurred during indomethacin treatment. Therefore, it is unlikely that a bradykinin-prostaglandin system might contribute to the attenuation. The present results do not completely rule out the contribution of an endogenous bradykinin-prostaglandin system to the effect of captopril, since the dose of indomethacin used in the present study may not be enough to inhibit completely the prostaglandin synthesis.<sup>21</sup>



The attenuation of pressor responses to NE and pitressin does not depend on the specific change in the arteriole by captopril, since it did not occur with the other pressor agent, AII. In the present study, the attenuation of the pressor responses to NE and pitressin by captopril was abolished by infusion of a subdepressor dose of AII. This suggests that the depletion of endogenous AII by captopril may have some relationship to the attenuation of the pressor responses to vasopressor substances. Recently, Moulds and Worland<sup>22</sup> reported that AII potentiated vasoconstrictor effects of NE, KCl, BaCl<sub>2</sub>, and 5-HT in human vasculature. Thoenen et al.<sup>23</sup> reported that AII enhanced excitation-contraction coupling of vascular smooth muscle. Day and Moore<sup>24</sup> provided evidence that AII may potentiate the effects of NE and other vasopressor substances by inhibiting the active extrusion of sodium from the vascular smooth muscle cells, thereby causing a nonspecific sensitization. If so, depletion of endogenous AII by captopril may lead to the diminution of pressor responses to vasopressor substances. The attenuation of the pressor responses to NE and vasopressin by captopril observed in the present study could be an expression of the loss of the sensitizing effect of endogenous AII.

In our present study, the pressor response to AII was potentiated after captopril. It is reported that the nonapeptide teprotide<sup>25, 26</sup> and captopril<sup>7, 27, 28</sup> potentiate the pressor response to exogenous AII. Thurston and Laragh<sup>25</sup> postulated that the potentiation of the pressor response to exogenous AII observed during converting enzyme inhibition results from decreased competition for receptor sites to endogenous AII and increased availability of vascular receptor site to exogenous AII.

Reflex compensation mediated through the baroreceptors to acute elevation of arterial pressure could be an important contributor to the homeostasis of blood pressure. In the present study, the decrease in heart rate in response to NE and pitressin after captopril was almost similar to that in control, while the pressor responses to both vasopressor substances were lower with captopril than in control, indicating that reflex slowing of the heart was potentiated by captopril. This potentiation would be due to depletion of endogenous AII, since the potentiation of reflex bradycardia disappeared during infusion of AII. Conversely, the attenuation of the pressor response to NE also disappeared during infusion of AII. Thus, it is likely that potentiation of baroreflex mechanism by captopril may lead to the attenuation of pressor responses to vasopressor substances. It is known that angiotensin has access to the central nervous system at sites where the blood-brain barrier is deficient, such as the area postrema. Joy and Lowe<sup>29</sup> reported that a centrally mediated cardiovascular effect elicited by vertebral artery infusion of AII is suppression of cardiac vagal tone. Recently, Lee et al.<sup>30</sup> demonstrated that AII showed a dose-dependent positive chronotropic action through dose-dependent reduction in vagal tone but not through activation of the central and peripheral sympathetic system. Recently, we

reported that captopril caused instantaneous drop of blood pressure without compensatory tachycardia or with a mild degree of bradycardia. Hypotensive and chronotropic effects of captopril were almost the same in untreated and treated patients with sympatholytic and/or adrenergic  $\beta$ -receptor blocking agents. Furthermore, we observed a significant negative correlation between the change in heart rate and PRA obtained immediately before captopril administration.<sup>31</sup> The present study and some other studies cited here might suggest that depletion of endogenous AII by captopril might cause potentiation of reflex slowing of the heart in response to vasopressor substances through potentiation of centrally mediated vagal tone.

In our present study, the initial increase in blood pressure was unsustainable and returned to the basal level during pitressin infusion; this unsustainable initial increase after a high dose of pitressin or vasopressin has also been observed by several authors.<sup>32-34</sup> As a possible mechanism, Montani et al.<sup>35</sup> recently suggested that vasopressin induces the reduction of cardiac output is through a cardiovascular reflex. During pitressin or vasopressin infusion, the rising plasma vasopressin concentrations specifically increase the feedback gain of the cardiovascular reflex system, so that the vasopressor effect of vasopressin will be buffered more than that of other pressor agents.

Finally, we should justify the dose of captopril used in the present study. In our previous study, we found that in hypertensive patients captopril (50 mg by mouth) caused a significant decrease in MAP, which reached a maximum level at 1 hour after administration and stayed at that level for 1 hour.<sup>36, 37</sup> Furthermore, Ferguson et al.<sup>3</sup> reported that oral administration of 20 mg of captopril completely inhibited the pressor response to 10 ng/kg of AI for 2.5 hours in human subjects. Therefore, the dose of captopril, 50 mg by mouth, used in the present study could be sufficient to block angiotensin converting enzyme. In our present study, we measured neither the plasma level of AII nor the effect of AI. After captopril treatment, however, the PRA was clearly increased. This reflects the blocking of the negative short-feedback mechanism of AII by angiotensin converting enzyme inhibitor.<sup>3, 38</sup>

In conclusion, the attenuation of pressor responses by captopril may be explained by its inhibition of angiotensin formation; decreased AII may desensitize the contraction of arterial smooth muscle and may potentiate the compensatory reflex mechanism.

#### Acknowledgments

We are grateful to Ciba Geigy Japan, Sandoz AG Switzerland, Sankyo Japan, and Parke-Davis Japan for supplying hypertensin, bradykinin, captopril, and pitressin, respectively.

#### References

1. Case DB, Atlas SA, Laragh JH, Sealey JE, Sullivan PA, McKinstry DN: Clinical experience with blockade of the renin-angiotensin-aldosterone system by an oral converting-enzyme inhibitor (SQ 14,225, captopril) in hypertensive patients. *Prog Cardiovasc Dis* 21: 195, 1978

2. Gavras H, Brunner HR, Turini GA, Kershaw GR, Tift CP, Cattelod S, Gavras I, Vukovich RA, McKinstry DN: Anti-hypertensive effect of the oral angiotensin converting-enzyme inhibitor SQ 14225 in man. *N Engl J Med* **298**: 991, 1978
3. Ferguson RK, Turini GA, Brunner HR, Gavras H: A specific orally active inhibitor of angiotensin-converting enzyme in man. *Lancet* **1**: 775, 1977
4. Laragh JH: The renin system in high blood pressure, from disbelief to reality: converting-enzyme blockade for analysis and treatment. *Prog Cardiovasc Dis* **21**: 159, 1978
5. Erdős EG: Angiotensin I converting enzyme. *Circ Res* **36**: 247, 1975
6. Brunner HR, Gavras H, Waerber B, Kershaw GR, Turini GA, Vukovich RA, McKinstry DN, Gavras I: Oral angiotensin-converting enzyme inhibitor in long-term treatment of hypertensive patients. *Ann Intern Med* **90**: 19, 1979
7. Abe K, Itoh T, Imai Y, Sato M, Haruyama T, Sakurai Y, Goto T, Otsuka Y, Yoshinaga K: Implication of endogenous prostaglandin system in the antihypertensive effect of captopril, SQ 14225, in low renin hypertension. *Jpn Circ J* **44**: 422, 1980
8. Man In't Veld AJ, Wenting GJ, Schalekamp MADH: Does captopril lower blood pressure in anephric patients? *Br Med J* **2**: 1110, 1979
9. Okuno T, Kondo K, Konishi K, Saruta T, Kato E: SQ14,225 attenuates the vascular response to norepinephrine in the rat mesenteric arteries. *Life Sci* **25**: 1343, 1979
10. Abe K, Otsuka Y, Saito T, Siang CB, Aoyagi H, Irokawa N, Seino M, Miyazaki S, Miura Y, Ono I, Minai K, Seki K, Kobayashi K, Sato T, Yoshinaga K: Measurement of plasma renin activity by angiotensin I radioimmunoassay. A modification of Haber's method. *Jpn Circ J* **36**: 741, 1972
11. Snedecor GW, Cochran WG: *Statistical Methods*, 6th ed. Ames, Iowa: Iowa State University Press, 1967
12. Murthy VS, Waldron TL, Goldberg ME: The mechanism of bradykinin potentiation after inhibition of angiotensin-converting enzyme by SQ 14,225 in conscious rabbits. *Circ Res* **43** (suppl 1): I-40, 1978
13. Rubin B, Laffan RJ, Kotler DG, O'Keefe E, Demasio DA, Goldberg ME: SQ14,225 (d-3-mercapto-2-methylpropanoyl-l-proline), a novel orally active inhibitor of angiotensin I-converting enzyme. *J Pharmacol Exp Ther* **204**: 271, 1978
14. Spertini F, Brunner HR, Waerber B, Gavras H: The opposing effects of chronic angiotensin-converting enzyme blockade by captopril on the responses to exogenous angiotensin II and vasopressin vs. norepinephrine in rats. *Circ Res* **48**: 612, 1981
15. Casellas D, Mimran A, Dupont M, Chevillard C: Attenuation by SQ14,225 (captopril) of the vascular response to noradrenaline in the rat isolated kidney. *Br J Clin Pharmacol* **10**: 621, 1980
16. deFreitas FM, Faraco EZ, deAzebedo DF: General circulatory alterations induced by intravenous infusion of synthetic bradykinin in man. *Circulation* **29**: 66, 1964
17. McGiff JC, Terragno NA, Malik KU, Lonigro AJ: Release of a prostaglandin E-like substance from canine kidney by bradykinin. Comparison with eledoisin. *Circ Res* **31**: 36, 1972
18. Needleman P, Marshall GR, Sobel BE: Hormone interactions in the isolated rabbit heart. Synthesis and coronary vasomotor effects of prostaglandins, angiotensin, and bradykinin. *Circ Res* **37**: 802, 1975
19. Provoost AP: The effect of prostaglandin synthesis inhibition of the acute blood pressure reduction by captopril in pentobarbital-anaesthetized rats. *Eur J Pharmacol* **65**: 425, 1980
20. Mullane KM, Moncada S, Vane JR: Prostacyclin release induced by bradykinin may contribute to the antihypertensive action of angiotensin converting-enzyme inhibitors. *In Advances in Prostaglandin and Thromboxane Research*, vol 7, edited by Samuelsson B, Ramwell PW, Paoletti R. New York: Raven Press, 1980, p 1159
21. Colina-Chourio J, McGiff JC, Nasjletti A: Effect of indomethacin on blood pressure in the normotensive unanesthetized rabbit: possible relation to prostaglandin synthesis inhibition. *Clin Sci* **57**: 359, 1979
22. Moulds RFW, Worland PJ: Potentiation of human vascular smooth muscle contraction by angiotensin. *J Cardiovasc Pharmacol* **2**: 377, 1980
23. Thoenen H, Hürlimann A, Haefely W: The effect of angiotensin on the response to postganglionic sympathetic stimulation of the cat spleen; lack of facilitation of norepinephrine liberation. *Med Pharmacol Exp* **13**: 379, 1965
24. Day MD, Moore AF: Interaction of angiotensin II with noradrenaline and other spasmogens on rabbit isolated aortic strips. *Arch Int Pharmacodyn Ther* **219**: 29, 1976
25. Thurston H, Laragh JH: Prior receptor occupancy as a determinant of the pressor activity of infused angiotensin II in the rat. *Circ Res* **36**: 113, 1975
26. Jaeger P, Ferguson RK, Brunner HR, Kirchertz EJ, Gavras H: Mechanism of blood pressure reduction by teprotide (SQ 20881) in rats. *Kid Intern* **13**: 289, 1978
27. Marks ES, Thurston H, Bing RH, Swales JD: Pressor responsiveness to angiotensin in renovascular and steroid hypertension. *Clin Sci* **57** (suppl): 47, 1979
28. Millar JA, Casley DJ, Johnston CI: Adrenal angiotensin II receptors and vascular reactivity to angiotensin II in the rat during continuous inhibition of angiotensin converting enzyme. *Clin Sci* **59** (suppl): 65, 1980
29. Joy MD, Lowe RD: The site of the cardiovascular action of angiotensin II in the brain. *Clin Sci* **39**: 327, 1970
30. Lee WB, Ismay MJ, Lumbers ER: Mechanisms by which angiotensin II affects the heart rate of the conscious sheep. *Circ Res* **47**: 286, 1980
31. Imai Y, Abe K, Sato M, Haruyama T, Hiwatari M, Goto T, Sato K, Kasai Y, Tajima J, Yoshinaga K: Chronotropic effect of captopril, an orally active converting enzyme inhibitor, in several types of hypertensive patients. *Am Heart J* (in press)
32. Graybiel A, Glendy RE: Circulatory effects following the intravenous administration of pitressin in normal persons and in patients with hypertension and angina pectoris. *Am Heart J* **21**: 481, 1941
33. Kitchin AH: The effect of pitressin on hand and forearm blood flow. *Clin Sci* **16**: 639, 1957
34. Möhring J, Glänzer K, Maciel JA Jr, Düsing R, Kramer HJ, Arbogast R, Koch-Weser J: Greatly enhanced pressor response to antidiuretic hormone in patients with impaired cardiovascular reflexes due to idiopathic orthostatic hypotension. *J Cardiovasc Pharmacol* **2**: 367, 1980
35. Montani JP, Liard JF, Schoun J, Möhring J: Hemodynamic effects of exogenous and endogenous vasopressin at low plasma concentrations in conscious dogs. *Circ Res* **47**: 346, 1980
36. Imai Y, Abe K, Otsuka Y, Sakurai Y, Ito T, Sato M, Haruyama T, Omata K, Hiwatari M, Yoshinaga K: Exaggerated response of renin secretion of captopril (SQ 14225) in renovascular hypertension. *Jpn Heart J* **21**: 793, 1980
37. Imai Y, Abe K, Yoshinaga K: The effect of captopril on heart rate in several types of hypertension. *Tohoku J Exp Med* **133**: 243, 1981
38. Bing J: Rapid marked increase in plasma renin in rats treated with inhibitors of the renin system. Effects of l-sar-8-ala-angiotensin II and of a synthetic converting enzyme inhibitor (nonapeptide, SQ 20.881) on normal and adrenalectomized rats. *Acta Pathol Microbiol Scand [A]* **81**: 376, 1973