ROLE OF THE KININ-KALLIKREIN SYSTEM IN THE VASODILATOR ACTION OF AN ANGIOTENSIN CONVERTING ENZYME INHIBITOR (CAPTOPRIL) ON THE SYSTEMIC RESISTANCE AND CAPACITANCE VESSELS OF DOGS

HIROYASU ITO, M.D., TERUCHIKA SAHASHI, M.D., ISAO HIROSE, M.D.
KIJUN NAGATA, M.D., HISAYASU WADA, M.D., KUNIYUKI TAKAI, M.D.
AND SENRI HIRAKAWA, M.D.

We investigated the vasodilator effects of captopril (CAP) on the systemic capacitance and resistance vessels by measuring changes in the mean circulatory pressure (MCP) and total peripheral resistance (TPR) that occurred in response to the intravenous injection of CAP (1 mg/kg) in open-chest dogs. The following five groups of dogs received CAP: (1) Group of untreated dogs, (2) TSA Group in which the dogs were subjected to total spinal anesthesia (TSA), (3) Ang II Group in which the dogs received a continuous intravenous infusion of angiotensin II (Ang II), (4) APR+Ang II Group in which the dogs received a continuous intravenous infusion of Ang II after pretreatment with aprotinin (APR, 25,000 K.I.E.), a kallikrein inhibitor, and (5) IND+APR+Ang II Group in which the dogs received a continuous intravenous infusion of Ang II after pretreatment with indomethacin (IND, 5 mg/kg), a prostaglandin synthesis inhibitor, and APR.

- 1) CAP significantly decreased TPR and MCP in the untreated Group.
- 2) CAP significantly decreased TPR and MCP in the TSA Group. There were no significant differences in percentage change of TPR ($\% \Delta$ TPR) and percentage change of MCP ($\% \Delta$ MCP) between the untreated and TSA Groups.
- 3) In the Ang II Group, CAP decreased the elevated TPR significantly, but hardly affected the elevated MCP.
- 4) CAP significantly decreased TPR without significant change in MCP in the APR+Ang II Group. The $\% \Delta$ TPR was significantly smaller in this Group than in the Ang II Group.
- 5) CAP significantly decreased TPR without significant change in MCP in the IND+APR+Ang II Group. The $\% \Delta$ TPR was significantly smaller in this Group than in the Ang II Group.

When one compares the arterial system with the venous system, this study

Key words:

Captopril
Systemic resistance vessels
Mean circulatory pressure
Total peripheral resistance
Kinin-kallikrein system

(Received November 2, 1990; accepted January 12, 1991)

The 2nd Department of Internal Medicine, Gifu University School of Medicine, Gifu, Japan

Mailing address: Hiroyasu Ito, M.D., The 2nd Department of Internal Medicine, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu 500, Japan

suggests that the kinin-kallikrein system activating action of CAP partly contributes to its vasodilator action on the systemic resistance vessels.

THE antihypertensive action of captopril (CAP), an angiotensin converting enzyme inhibitor, is exerted through (1) inhibition of the renin-angiotensin system and (2) activation of the kinin-kallikrein system!¹⁻³ CAP is used not only as an antihypertensive drug but also as a vasodilator in the treatment of congestive heart failure⁴⁻⁶ However, it remains unclear whether CAP dilates the systemic capacitance vessels in the whole animal.

In the present study, we measured mean circulatory pressure (MCP) before and after an intravenous injection of CAP in anesthetized open-chest dogs, and deduced dilation or constriction of the systemic capacitance vessels from the changes in MCP in response to CAP. Thus venodilation was deduced from a decrease in MCP and venoconstriction was deduced from an increase in MCP. In addition, dilation or constriction of the systemic resistance vessels was deduced from simultaneous changes in total peripheral resistance.

The aim of this study was twofold: to examine the action of CAP on the systemic resistance and capacitance vessels and to clar-

ify whether the kinin-kallikrein activating action of CAP contributes to the dilator action of CAP on the systemic resistance or capacitance vessels.

MATERIALS AND METHODS

We have described the methods for mean circulatory pressure (MCP) measurement in detail elsewhere^{7,8} so only an outline will be given here.

(1) Methods

Thoracotomy was performed on mongrel dogs, weighing 7.4 to 17.8 kg (mean $\pm$ SE: 11.7 ± 0.4 kg), anesthetized with intravenous pentobarbital (30 mg/kg), and heparinized (300 U/kg, i.v.). The dogs were ventilated with a respirator (AKOMA IKAKOGYO Co., Ltd., frequency 20/min, tidal volume 20 ml/kg) through an endotracheal tube (Fig. 1). Mean blood pressure (MBP) and mean right atrial pressure (RAP) were measured using Courmand catheters. Cardiac output was measured with an electromagnetic flow probe (NIHON KODEN Co., Ltd.) placed at the root of the aorta. A pair of electrodes

Fig.1. Experimental arrangements for measuring the mean circulatory pressure

was placed on the cardiac apex and right auricle for inducing ventricular fibrillation, when necessary, using a fibrillator (20 volts, 10 Hz). Two arterio-venous (A-V) shunts were produced by connecting bilateral femoral arteries to veins with two vinyl tubes. A constant flow pump was placed midway in these circuits so that blood could be translocated rapidly from the arterial to the venous sides.

(2) MCP measurement

Following induction of ventricular fibrillation, the previously closed A-V shunts were then opened and blood was translocated rapidly from the arteries into the veins by means of the constant flow pump. This procedure led to a fall in MBP and a rise in RAP, with the pressures soon reaching equilibrium. The equilibrium pressure is the MCP? After MCP was obtained, defibrillation was produced by a defibrillator (25 watts-sec), restoring the heart to a normal beat. The time from induction of ventricular fibrillation to MCP measurement was within 5 sec. Hemodynamic parameters except MCP were measured immediately before ventricular fibrillation. All of the parameters were recorded simultaneously using a polygraph (RMC-1100, NIHON KODEN Co., Ltd.).

MCP is equal to the sum of systemic arterial and venous extra volumes divided by the sum of the arterial and venous compliances!¹⁰ The arterial compliance is considerably smaller than the venous compliance!¹¹ If the arterial compliance is neglected, MCP is equal to the sum of systemic arterial and venous extra volumes divided by the venous compliance. When the extra volumes remain constant, a fall in MCP indicates an increase in the venous compliance. On the other hand, when the venous compliance remains constant, a fall in MCP indicates a decrease in the extra volume (an increase in the unstressed volume). Thus, in both cases a fall in MCP implies dilation of the systemic capacitance vessels. Constriction and dilation of the systemic capacitance vessels could be estimated from the increases and decreases, respectively, in MCP? In addition, constriction or dilation of the systemic resistance vessels was estimated from the increase and decrease in total peripheral

resistance.

(3) Groups studied

(i) Untreated Group (n=10)

(ii) TSA Group (n=8)

In the TSA Group, total spinal anesthesia (TSA) was produced by injecting bupivacaine (5 mg/kg) into the subarachnoid space through a suboccipital approach. Immediately after induction of TSA, MBP was maintained at about 100 mmHg by continuous infusion of epinephrine using a microinfusion pump (STC-502, TERUMO Co., Ltd.). Captopril (CAP) was injected intravenously.

(iii) Ang II Group (n=10)

In the angiotensin II (Ang II) Group, MBP was elevated by about 30 mmHg from baseline by continuous intravenous injection of Ang II, and CAP was then injected with CAP superimposed on Ang II.

(iv) Group of Ang II alone (n=10)

MCP was measured in the absence of Ang II (control period) and after Ang II.

(v) APR+Ang II Group (n=10)

MBP was elevated by about 30 mmHg from the baseline by constant intravenous injection of Ang II 30 min after intravenous aprotinin (APR, 25,000 K.I.E.), a kallikrein inhibitor. CAP was then injected intravenously.

(vi) IND+APR+Ang II Group (n=10)

Dogs were injected first with the prostaglandin synthesis inhibitor indomethacin (IND, 5 mg/kg), then with APR (25,000 K.I.E.), and then MBP was elevated by about 30 mmHg from baseline by constant intravenous injection of Ang II 30 min after APR. Under these circumstances, CAP was injected intravenously.

(4) Drugs used

CAP at a dose of 1 mg/kg was dissolved in 5 ml physiological saline, and this was infused into a vein of the dog's forelimb in 1 min. MCP was measured when MBP fell to the lowest value (about 5 min after intravenous injection of CAP).

(5) Glossary of terms

Ang II: angiotensin II

BW (kg): body weight

CAP: captopril

CO (ml/min/kg): cardiac output (per kg body weight)

TABLE I EFFECT OF CAPTOPRIL ON HEMODYNAMIC PARAMETERS

Group	No.	MCP (mmHg)		MBP (mmHg)		TPR (dyne·sec·cm ⁻⁵)	
		before	after	before	after	before	after
Untreated	10	9.2±0.4	7.8±0.4**	107±5	79±4**	7252±755	5413±602**
TSA	8	11.0±0.2	9.0±0.6**	98±1	64±3**	6956±442	4576±329**
Ang II alone	10	8.3±0.3	11.4±0.4**	102±6	142±4**	6977±511	8357±326**
Ang II	10	11.6±0.4	11.2±0.4	150±3	127±7**	8979±710	6946±558**
APR+Ang II	10	11.0±0.2	10.8±0.3	135±4	122±4**	8688±439	7667±403**
IND+APR+Ang II	10	11.0±0.3	10.8±0.4	147±5	139±5**	9621±646	8575±552**

RBR (dyne·sec·cm ⁻⁵)		CO (ml/min/kg)		RAP (mmHg)		HR (beats/min)	
before	after	before	after	before	after	before	after
474±41	397±33**	116±10	116±10	1.8±0.1	1.7±0.2	180±7	173±7*
652±41	527±35**	114±9	114±11	1.8±0.1	1.8±0.1	161±7	157±6
424±49	513±36*	81±2	93±3**	2.3±0.1	2.5±0.2	145±6	155±6
620±58	531±48**	104±6	112±6*	1.6±0.1	1.6±0.1	178±6	192±6*
626±33	593±35	110±5	113±6	1.5±0.1	1.5±0.1	166±10	174±9
587±40	548±33	116±6	122±6	1.8±0.1	1.9±0.2	170±8	176±9

Values are expressed as mean±SE.

*= $p<0.05$; **= $p<0.01$

In Ang II alone group, CAP was not given. In this group "before" means baseline values and "after" means values recorded after the administration of Ang II.

For abbreviations see the glossary of terms.

HR (beats/min): heart rate

MCP (mmHg): mean circulatory pressure

% ΔMCP: percentage change in MCP

MBP (mmHg): mean blood pressure

RAP (mmHg): mean right atrial pressure

RVR (dyne·sec·cm⁻⁵): resistance to venous return

$$RVR = [(MCP - RAP) / (CO \times BW)] \times 8 \times 10^4$$

TPR (dyne·sec·cm⁻⁵): total peripheral resistance

$$TPR = [MBP / (CO \times BW)] \times 8 \times 10^4$$

% ΔTPR: percentage change in TPR

(6) Statistics

The values are expressed as mean±SE. Statistical analysis was done by (i) Student's t-test for comparison in the same group and (ii) Scheffe's method using one-way analysis of variance for comparison between the different groups. $p<0.05$ was considered statistically significant.

RESULTS

(1) Effect of captopril (CAP) on TPR and MCP

Table I shows the effect of CAP on various hemodynamic parameters for each group.

(i) Untreated Group

CAP decreased TPR and MCP significantly.

(ii) TSA Group

CAP decreased TPR and MCP significantly.

(iii) Group of Ang II alone

Ang II was infused. TPR and MCP increased significantly with Ang II.

(iv) Ang II Group

CAP was injected in the presence of Ang II. MCP was measured before and after the injection of CAP. TPR was increased significantly by Ang II, and MCP was 11.6±0.4 mmHg. (1) The value for MCP in this group was significantly higher than the basal value (8.3±0.3 mmHg), but (2) there was no signi-

Fig.2 Comparisons of % Δ TPR and % Δ MCP between the untreated and treated group with TSA, Ang II, APR+Ang II or IND+APR+Ang II in the presence of captopril (mean $\pm$ SE)

□ = % Δ TPR, ▨ = % Δ MCP

* = $p < 0.05$; ** = $p < 0.01$

For other abbreviations, see the glossary of terms.

ficant difference in MCP after Ang II between the Group of Ang II alone (11.4 ± 0.4 mmHg) and the Ang II Group (11.6 ± 0.4 mmHg). When CAP was injected intravenously in the presence of Ang II, TPR decreased significantly, but there was no significant change in MCP.

(v) APR+Ang II Group

When MBP was raised by continuous intravenous infusion of Ang II in the presence of APR, TPR increased significantly and MCP was high (11.0 ± 0.2 mmHg). In this group, basal MCP was not measured. MCP was significantly higher than the basal value for MCP in the Group of Ang II alone (8.3 ± 0.3 mmHg) and in the untreated Group (9.2 ± 0.4 mmHg). There was no significant difference in MCP after Ang II between the Group of Ang II alone (11.4 ± 0.4 mmHg) and the APR+Ang II Group. In the APR+Ang II Group, CAP decreased TPR significantly, but the decrease in TPR was significantly smaller in the APR+Ang II Group than in the Ang II Group. CAP did not produce a significant change in MCP.

(vi) IND+APR+Ang II Group

When MBP was raised by continuous intravenous Ang II in the presence of APR and IND, TPR increased significantly and

MCP was high (11.0 ± 0.3 mmHg). Basal MCP was not measured. The change in TPR and the value of MCP were similar to those in the APR+Ang II Group. In the IND+APR+Ang II Group, CAP decreased TPR significantly, but this decrease was smaller than that which occurred in the Ang II Group. There was no significant difference between the APR+Ang II Group and the IND+APR+Ang II Group in the decrease in TPR. CAP did not produce a significant change in MCP.

(3) Effect of CAP in terms of % Δ TPR and % Δ MCP

Figure 2 shows % Δ TPR and % Δ MCP in the 5 groups

In each group, % Δ TPR was significantly greater than % Δ MCP. There was no significant difference in % Δ TPR between the untreated Group ($-25.5 \pm 2.6\%$), the TSA Group ($-34.4 \pm 1.6\%$) and the Ang II Group ($-22.2 \pm 2.5\%$). However, % Δ TPR in the APR+Ang II Group ($-11.7 \pm 1.2\%$) and the IND+APR+Ang II Group ($-10.7 \pm 1.3\%$) was significantly smaller than in the Ang II Group.

Comparison of % Δ MCP between the 5 groups revealed no significant difference in % Δ MCP between the untreated Group

($-15.7 \pm 2.0\%$) and the TSA Group ($-18.3 \pm 4.3\%$), while $\% \Delta \text{MCP}$ of the Ang II Group ($-3.6 \pm 1.9\%$), the APR+Ang II Group ($-1.4 \pm 2.0\%$) and the IND+APR+Ang II Group ($-2.1 \pm 2.7\%$) were significantly smaller than in the untreated Group ($-15.7 \pm 2.0\%$).

DISCUSSION

CAP is a vasodilator, and belongs to the group of balanced vasodilators because it dilates both systemic resistance and capacitance vessels.¹² However, its dilator action on the systemic capacitance vessels has been estimated only from clinical data,⁹ and its effect on the human forearm vein has been studied with occlusion plethysmography.^{13,14} To our knowledge, there has been only one report¹⁵ in which the action of CAP on the systemic capacitance vessels was studied when it was administered for a long period using the whole living body (dog).

In untreated dogs, CAP lowered TPR and MCP (Table I), suggesting that CAP dilated both the systemic resistance and capacitance vessels. As reported previously,¹⁶ it was found experimentally that hypotension induced by intravenous nitroglycerin lead to a baroreceptor reflex, which resulted in a release of endogenous catecholamines, and which could counterbalance the vasodilator action of nitroglycerin on the systemic capacitance vessels. This was presumably the reason why the vasodilator action of nitroglycerin on the systemic capacitance vessels appeared to be less than that on the systemic resistance vessels. It is possible that the vasodilator action of CAP on the systemic capacitance vessels observed in the present study has also been modified by a baroreceptor reflex in the direction of vasoconstriction, because CAP produced hypotension. This prompted us to perform experiments on TSA animals. However, there was no difference in $\% \Delta \text{MCP}$ between the TSA and untreated animals (Fig. 2). This observation suggested that CAP in doses used in this study did not produce a marked baroreceptor reflex. It is possible that a decrease of plasma Ang II, due to the ACE inhibiting action of CAP, reduced the stimulation of the Ang II receptors at the sympathetic nerve terminals and decreased

norepinephrine release from the sympathetic nerve terminals.¹⁷

The antihypertensive action of CAP in patients with hypertension is considered to result from (1) inhibition of the renin-angiotensin system and (2) activation of the kinin-kallikrein system.¹⁻³ In the present study, we aimed at examining the extent to which the above mechanism (2) contributed to the vasodilator action of CAP on the systemic resistance and capacitance vessels. In order to mask the endogenous Ang II reducing effect of CAP by mechanism (1), we infused exogenous Ang II continuously. Then CAP was administered (Ang II Group). We found that TPR was lowered significantly, but the previously elevated MCP was not significantly changed by CAP (Table I).

Limiting the alleged mechanisms of the vasodilator action of CAP to mechanisms (1) and (2), and assuming that the action of CAP through mechanism (1) is masked by the continuous infusion of Ang II, we propose that the result in the Ang II Group revealed the vasodilator action of CAP on the systemic resistance vessels based on mechanism (2). Namely, CAP prompts the activation of kinins through mechanism (2), resulting in an increase in bradykinin (BK) which facilitates the synthesis of prostaglandin (PG).¹⁸ BK and PGI₂ were found to dilate an isolated artery but not to dilate an isolated vein; they were even found to constrict it.¹⁹⁻²² Next, we performed an experiment after pretreatment with APR to inhibit BK synthesis in the presence of continuous intravenous injection of Ang II (APR+Ang II Group). It has been reported that intravenous infusion of 900 K.I.E./min of APR for 25 min (total dose 22,500 K.I.E.) completely inhibited the renal artery dilation caused by CAP in the dog.²³ Judging from the report, the dose of APR used in the present study (25,000 K.I.E.) was probably sufficient to inhibit the action of CAP mediated through mechanism (2). We found that $\% \Delta \text{TPR}$ with CAP in the APR+Ang II Group was significantly less than that in the Ang II Group (Fig. 2).

Ang II is capable of directly facilitating PG synthesis.^{24,25} Therefore there is a possibility that the synthesis of PG was facilitated by Ang II administered by continuous infu-

sion. Next, we performed an experiment where CAP was administered in the presence of APR, IND and Ang II (IND+APR+Ang II Group). It has been reported that 2.5 mg/kg of IND sufficiently inhibited the vasodilator action of arachidonic acid (intrarenal artery) on the canine renal artery²⁶. The dose of IND (5 mg/kg) used in the present study appears to be large enough to inhibit the PG synthesis that is facilitated by CAP. It was found that % Δ TPR with CAP in this IND+APR+Ang II Group was significantly less than in the Ang II Group (Fig. 2), but there was no difference in % Δ TPR between the APR+Ang II and IND+APR+Ang II Groups. This suggests that facilitation of PG synthesis with Ang II was not important. These results strongly suggest that part of the vasodilator action of CAP on the systemic resistance vessels in the presence of continuous Ang II infusion was mediated by mechanism (2).

Even in the IND+APR+Ang II Group, CAP still produced a decrease of about 10% in TPR. The significance and mechanism of this action are not clear. However, it has been found that CAP has a non-specific vasodilator action, not mediated by mechanisms (1) or (2)²⁷. Therefore, it is possible that the significant decrease in TPR observed in the IND+APR+Ang II Group may result from a non-specific action of CAP, if APR and IND used in the present study sufficiently inhibited the effect of CAP mediated by mechanism (2).

From these results, we suggest that CAP dilated both systemic resistance and capacitance vessels, and that the kinin-kallikrein system activating action of CAP contributed partly to the vasodilator action of CAP on the systemic resistance vessels, but not to the vasodilator action of CAP on the systemic capacitance vessels.

REFERENCES

1. ERDÖS EG: Angiotensin I converting enzyme. *Circ Res* 1975; **36**: 247
2. SKEGGS LT, DORER FE, KAHN JR, LENTZ KE, LEVINE M: The biochemistry of the renin-angiotensin system and its role in hypertension. *Am J Med* 1976; **60**: 737
3. VIDT DJ, BRAVO EL, FOUAD FM: Drug therapy: Captopril. *N Engl J Med* 1982; **306**: 214
4. AWAN NA, EVENSON MK, NEEDHAM KE, WIN A, MASON DT: Efficacy of oral angiotensin-converting enzyme inhibition with captopril therapy in severe chronic normotensive congestive heart failure. *Am Heart J* 1981; **101**: 22
5. AWAN NA, AMSTERDAM EA, HERMANOVICH J, BOMMER WJ, NEEDHAM KE, MASON DT: Long-term hemodynamic and clinical efficacy of captopril therapy in ambulatory management of severe chronic congestive heart failure. *Am Heart J* 1982; **103**: 474
6. LEVINE TB, COHN JN: Determinants of acute and long-term response to converting enzyme inhibitors in congestive heart failure. *Am Heart J* 1982; **104**: 1159
7. ITO H, HIRAKAWA S: Effects of vasodilators on the systemic capacitance vessels, a study with the measurement of the mean circulatory pressure in dogs. *Jpn Circ J* 1984; **48**: 388
8. HIRAKAWA S, ITO H, KOTOO Y, ABE C, ENDO T, TAKADA N, FUSENO H: The role of alpha and beta adrenergic receptors in constriction and dilatation of the systemic capacitance vessels: A study with measurement of the mean circulatory pressure in dogs. *Jpn Circ J* 1984; **48**: 620
9. GUYTON AC, POLIZO D, ARMSTRONG GG: Mean circulatory filling pressure measured immediately after cessation of heart pumping. *Am J Physiol* 1954; **179**: 261
10. GUYTON AC, JONES CE, COLEMAN TG: Circulatory physiology: Cardiac output and its regulation, Second Edition. WB Sanders Co., Philadelphia, 1973, p253
11. SHOUKAS AA, SAGAWA K: Control of total systemic vascular capacity by the carotid sinus baroreceptor reflex. *Circ Res* 1973; **33**: 22
12. BRAUNWALD E, COLUCCI WS: Vasodilator therapy of heart failure. Has the promissory note been paid? *N Engl J Med* 1984; **310**: 459
13. JOHNS DW, AYERS CR, WILLIAMS SC: Dilation of forearm blood vessels after angiotensin-converting-enzyme inhibition by captopril in hypertensive patients. *Hypertension* 1984; **6**: 545
14. NISHIMURA H, KUBO S, UYEYAMA M, KUBOTA J, KAWAMURA K: Peripheral hemodynamic effects of captopril in patients with congestive heart failure. *Am Heart J* 1989; **117**: 100
15. RAYA TE, GAY RG, AGUIRRE M, GOLDMAN S: Importance of venodilatation in prevention of left ventricular dilatation after chronic large myocardial infarction in rats: A comparison of captopril and hydralazine. *Circ Res* 1989; **64**: 330
16. NAGATA K, ITO H, MINATOBUCHI S, HIROSE I, SAHASHI T, WADA H, TAKAI K, WATANABE I, HIRAKAWA S: Differential vasodilator effect of nitroglycerin on systemic capacitance and resistance vessels in anesthetized dogs, and the mechanism of its action. A study by measuring mean circulatory pressure and total peripheral resistance. *Jpn Circ J* 1989; **53**: 1371
17. PARMLEY WW: Medical treatment of congestive heart failure: Where are we now? *Circulation* 1987; **75** (Suppl IV): 4
18. MCGIFF JC, TERRAGNO NA, MALIK KU, LONIGRO AJ: Release of prostaglandin E-like substance from canine kidney by bradykinin. Comparison with edoisin. *Circ Res* 1972; **31**: 36

19. REGOLI D, MIZRAHI J, D'ORLÉANS-JUSTE P, CARANIKAS S: Effects of kinins on isolated blood vessels. Role of endothelium. *Can J Physiol Pharmacol* 1982; **60**: 1580
20. GREENBERG S, KADOWITZ PJ: Difference in prostaglandin modulation of arterial and venous smooth muscle responses to bradykinin and norepinephrine. *Methods Find Exp Clin Pharmacol* 1982; **4**: 7
21. TODA N: Responses to prostaglandins H₂ and I₂ of isolated dog cerebral and peripheral arteries. *Am J Physiol* 1980; **238**: H111
22. LEVY JV: Contractile responses to prostacyclin (PGI₂) of isolated human saphenous and rat venous tissue. *Prostaglandins* 1978; **16**: 93
23. VEMULAPALLI S, CHIU PJS: Effect of aprotinin-induced kallikrein inhibition on the cardiovascular and renal action of captopril in diuretic-treated dogs. *Arch Int Pharmacodyn* 1983; **262**: 109
24. MCGIFF JC, CROSHAW K, TERRAGNO NA, LONIGRO AJ: Release of a prostaglandin-like substance into renal venous blood in response to angiotensin II. *Circ Res* 1970; **26/27** (Suppl I): I-121
25. SHEBUSKI RJ, AIKEN JW: Angiotensin II stimulation of renal prostaglandin synthesis elevates circulating prostacyclin in the dog. *J Cardiovasc Pharmacol* 1980; **2**: 667
26. TOBIA AJ, GIARDINO EC: Renal vasodilator responses to captopril in dogs pretreated with indomethacin. *Proc Soc Exp Biol Med* 1981; **167**: 242
27. OHARA N, ONO H, HASHIMOTO K: Analysis of the mechanism of acute decrease of blood pressure induced by captopril (SQ14, 225) in dogs by the use of aprotinin, Sar¹-Ile⁸-angiotensin II and indomethacin. *Jpn Circ J* 1981; **45**: 672