PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 162, 105–111 (1979)

# Interaction of Adrenergic Stimuli, Prostaglandins and Angiotensin II in the Dog Kidney (40627)

EDWARD J. ZAMBRASKI AND GERALD F. DIBONA

*Department of Internal Medicine, University of Iowa College of Medicine, Iowa City, Iowa 52242*

It has been previously shown that intraarterial infusion of angiotensin II (AII) potentiates the renal and mesenteric vascular response to adrenergic stimuli (1, 2). The cutaneous vascular response to sympathetic nerve stimulation was potentiated to a greater degree than the response to exogenous norepinephrine (NE) (3). The exact mechanism by which this potentiation occurs remains to be clarified. Previous reports have suggested that AII facilitates NE release from adrenergic nerve terminals (4), enhances NE biosynthesis (5), and inhibits neuronal uptake of NE (6). Malik and Nasjletti (7) have implicated AII receptors in this process by demonstrating that prior treatment with the angiotensin II antagonist, 1-sarcosine-8-isoleucine angiotensin II (AIIA), abolished the potentiation by AII of mesenteric vascular responses to adrenergic stimuli.

Although the potentiation by exogenous AII of renal vascular responses to adrenergic stimuli has been clearly demonstrated, the physiological role of this phenomenon is still in question. One purpose of this study was to determine if endogenous circulating levels of AII, present in the anesthetized dog, potentiate the renal vascular response to exogenous NE or renal nerve stimulation (RNS). It was reasoned that if endogenous circulating levels of AII do potentiate renal vascular responses to adrenergic stimuli then the magnitude of such responses should be decreased by renal blockade to circulating AII.

Prostaglandins (PG) have also been implicated as agents which modify the responses to adrenergic stimuli in various vascular beds (8–10). The responses, however, are species dependent and differences have been noted between the rat and rabbit renal vasculature (7). Prostaglandins, when infused into the renal artery, are capable of selectively modulating responses to adrenergic stimuli (11–13). In the dog (11), rabbit (12), and cat (13) kidney, intrarenal infusion of $PGE_2$ abolished the renal vasoconstrictor response to RNS but had little effect on the renal vasoconstrictor response to exogenous NE.

Indomethacin and meclofenemate, inhibitors of PG synthesis, have been utilized to assess the role of endogenous PG in this process. In the isolated-perfused rabbit heart indomethacin augmented NE release after sympathetic nerve stimulation (14). Zimmerman and colleagues (8) reported that, in the perfused dog paw, indomethacin potentiated the cutaneous vascular response to both NE and nerve stimulation. Chapnick and colleagues (15) demonstrated that, in the cat kidney, indomethacin enhanced the renal vascular response to exogenous NE but not RNS whereas meclofenemate had no effect on the renal vascular response to either exogenous NE or RNS.

The second purpose of this study was to evaluate the role of endogenous PG in modifying the vascular responses to RNS and exogenous NE in the canine renal vascular bed.

In anesthetized dogs systemic indomethacin administration increases mean arterial pressure (MAP), reduces renal blood flow (RBF), and increases renal vascular resistance (RVR) (16). A study of Mimran and colleagues (17) in the rat implicated the renin–angiotensin system in this process. Bilateral nephrectomy abolished the rise in MAP normally seen with indomethacin treatment and in normal rats systemic administration of AIIA prevented the indomethacin-induced increase in MAP and decreases in RBF.

The third purpose of this study was to examine the possible involvement of the renin–angiotensin and adrenergic nervous systems in the renal vasoconstrictor response to systemic administration of indomethacin and meclofenemate in the dog.



0037-9727/79/090105-07$01.00

*Materials and methods.* All studies were performed on female mongrel dogs, 15–20 kg in weight, fed a standard kennel ration. On the day prior to the study all dogs were deprived of food but water was permitted *ad libitum.* On the day of the study the animal was anesthetized with i.v. sodium pentobarbital 30 mg/kg, and supplemental doses were added throughout the experiment to maintain anesthesia. The animal was intubated with an endotracheal tube and mechanically ventilated to maintain arterial pH between 7.35 and 7.45.

Catheters were inserted into the right femoral artery, inferior vena cava via right femoral vein, and left jugular vein to permit sampling of arterial blood, arterial blood pressure measurements, and intravenous infusion of fluids. The left kidney was exposed via a left subcostal incision, cleared of perirenal tissue, and supported in a Lucite cup ring. The renal nerves were dissected free and platinum electrodes were placed on the transected distal portion. Small catheters were placed in the left and right ureters. An external flow probe was placed on the left renal artery and led to an electromagnetic flow meter (Carolina); this system was calibrated *in situ* and *in vivo* at the end of each experiment. For one series of experiments an additional external flow probe was placed on the right renal artery. A 25-gauge curved needle attached to polyethylene tubing was placed in the left renal artery against the direction of flow. The tubing was connected to an infusion pump and 0.9% NaCl was infused at 0.5 ml/min. This procedure did not affect the signal output from the external flow probe.

At the conclusion of surgery a priming dose of inulin was given followed by its constant infusion in 0.9% NaCl at 1.0 ml/min to maintain a plasma concentration of 0.02 mg/ml. At least 60 min were allowed for equilibration following surgery.

Plasma and urine samples were analyzed for inulin by the anthrone method (18). The clearance of inulin was taken to be glomerular filtration rate (GFR). MAP was measured with a pressure transducer. RBF and MAP were recorded on a direct writing recorder. RVR (mm Hg/ml/min) was calculated by dividing MAP by RBF.

In one group of studies, left kidney AII receptor blockade was achieved by the intrarenal arterial infusion of 1-sarcosine-8-isoleucine angiotensin II (AIIA) at 0.2 μg/kg/min. After 20 min of AIIA infusion, the efficacy of blockage was verified by the failure to note changes in RBF after intrarenal arterial doses of AII (1–5 μg) which prior to the infusion of AIIA reduced RBF by 30–50%. As in previous studies employing this AIIA (19), intrarenal arterial infusion of AIIA alone did not affect RBF (251 ± 29 vs 249 ± 25 ml/min, $N = 8$, see Fig. 1) nor did it abolish the systemic pressor response to intravenous administration of 10 μg AII (+ 35 ± 6 vs + 37 ± 5 mm Hg, $N = 8$) or the contralateral renal vasoconstrictor response to intrarenal arterial administration of AII (−92 ± 12 vs −96 ± 13 ml/min, $N = 8$).

In separate groups of studies indomethacin or meclofenemate were used to inhibit PG synthesis. Indomethacin (2 mg/kg), dissolved by the method of Davis and Horton (20) and meclofenemate (2 mg/kg), dissolved in 0.9% NaCl, were infused intravenously over a 10-min period. Following infusion, a 20-min equilibration period preceded all tests. Studies by Kaloyanides and colleagues (21), Dunn and colleagues (22), and Zambraski and Dunn (23) indicate that these doses of indomethacin or meclofenemate reduce renal

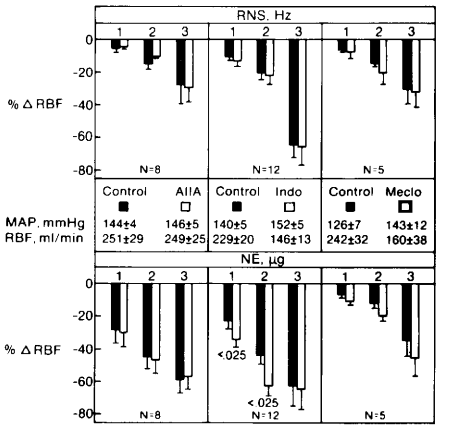


FIG. 1. Renal blood flow (RBF) responses to graded renal nerve stimulation (RNS) and doses of exogenous norepinephrine (NE) before and after intrarenal angiotensin II blockade (left panel) and systemic administration of indomethacin (middle panel) and meclofenemate (right panel).

$PGE_2$ secretion and excretion. In addition, the ability of indomethacin and meclofenemate to block the renal vasodilator response to arachidonic acid (dissolved in 0.1 *M* sodium carbonate in 10% ethanol) was taken as an indication of reduction of enzymatic conversion of arachidonic acid to vasodilator prostaglandins (24).

In another group of studies, renal α-adrenergic receptor blockage was produced by the intrarenal arterial infusion of phenoxybenzamine, 0.2 μg/kg/min. Adequacy of renal α-adrenergic receptor blockade was evaluated via renal intrarterial injections of phenylephrine 10–40 μg which produced 50–75% reductions in RBF in the absence of phenoxybenzamine. Previous studies (25, 26) have demonstrated that this dose of phenoxybenzamine infused into the renal artery does not result in systemic α-adrenergic receptor blockade.

Direct electrical stimulation of the renal nerves was performed using a Grass S9 stimulator at 10–20 V, and 1.0 msec. The frequency of renal nerve stimulation was varied in each animal to achieve approximately 10, 20, and 50% decreases in RBF. Each stimulation period lasted approximately 2 min, at which time RBF had decreased and remained constant. The different intensities of stimulation were performed in random order and a time interval sufficient for complete recovery, 5- to 10-min duration, was allowed between successive stimulations.

Norepinephrine was administered as norepinephrine bitartrate, dose in terms of base, in a constant volume into the renal artery infusion line. The different doses of norepinephrine were administered in random order and a time interval sufficient for complete recovery, 5- to 10-min duration, was allowed between successive doses.

Renal nerve stimulation and norepinephrine administration were done in the same animal before and after intrarenal angiotensin II blockade ($N = 8$ dogs), systemic administration of indomethacin ($N = 12$ dogs), and meclofenemate ($N = 5$ dogs).

The data in the text and figures are expressed as the mean ± standard error. A Student's *t* test (27) was used for statistical analysis of paired data within each group.

*Results.* The results of the studies concerning the effect of renal AII blockade and inhibition of prostaglandin synthesis on renal vascular responses to RNS and exogenous NE are shown in Fig. 1. Renal AII blockade did not significantly change baseline MAP or RBF nor did it alter the renal vascular responses to RNS or exogenous NE.

The results of the studies concerning the ability of indomethacin and meclofenemate to block the renal vasodilator response to arachidonic acid are shown in Table I. The intrarenal arterial administration of arachidonic acid produced dose-related increases in RBF. The administration of indomethacin and meclofenemate produced changes in basal MAP and RBF; indomethacin increased MAP from 142 ± 4 to 152 ± 5 mm Hg and decreased RBF from 201 ± 8 to 146 ± 23 ml/min and meclofenemate increased MAP from 121 ± 10 to 131 ± 9 mmHg and decreased RBF from 179 ± 29 to 144 ± 27 ml/min. The renal vasodilator responses to arachidonic acid were decreased by an average of 50% by both indomethacin and meclofenemate, similar to the findings of Feigen and colleagues (9).

The results of the studies concerning the effect of inhibition of prostaglandin synthesis on renal vascular responses to RNS and exogenous NE are shown in Fig. 1. Indomethacin administration increased baseline MAP by 9% ($P < 0.01$) and decreased baseline RBF by 36% ($P < 0.001$). Meclofenemate administration increased baseline MAP by 13% ($P < 0.05$) and decreased baseline RBF by 34% ($P < 0.025$). Neither indomethacin nor meclofenemate altered the renal vascular response to RNS. Indomethacin significantly increased the renal vasoconstrictor responses

TABLE I. EFFECT OF INDOMETHACIN AND MECLOFENEMATE ON RENAL VASODILATOR RESPONSES TO ARACHIDONIC ACID[a]

| Dose (mg) | *N* | Control ΔRBF (ml/min) | Indomethacin ΔRBF (ml/min) | Meclofenemate ΔRBF (ml/min) |
|---|---|---|---|---|
| 0.1 | 4 | 10 ± 3 | 6 ± 1 | |
| 0.3 | 4 | 25 ± 5 | 7 ± 1 | |
| 1.0 | 4 | 39 ± 6 | 15 ± 4 | |
| 0.1 | 4 | 8 ± 1 | | 4 ± 2 |
| 0.3 | 4 | 16 ± 2 | | 8 ± 1 |
| 1.0 | 4 | 50 ± 8 | | 23 ± 4 |

[a] Data are mean ± SE; *N* = number of animals.

to the 1- and 2-$\mu$g doses of exogenous NE ($P < 0.025$) but did not influence the response to the 3-$\mu$g dose of exogenous NE. Meclofenemate did not alter the renal vascular responses to RNS or exogenous NE.

The results of studies concerning the mechanism of the renal vasoconstrictor response following indomethacin and meclofenemate administration are shown in Figs. 2–4. In Fig. 2, the renal vascular response to systemic indomethacin is monitored bilaterally; blockade to circulating AII was produced in the left kidney while the right kidney of the same dog served as an untouched internal control. Similar decreases in RBF and GFR were observed in both left and right kidneys. Figure 3 illustrates data from similarly designed experiments with meclofenemate; again, the alterations in RBF and GFR were similar in the two kidneys. These data indicate that the renal vasoconstriction observed after systemic indomethacin or meclofenemate administration is not mediated by circulating AII. In Fig. 4, both AII and $\alpha$-adrenergic receptor blockade were produced in the left kidney. Systemic indomethacin administration produced an increase in MAP from 129 ± 3 to 140 ± 4 mm Hg, a decrease in RBF from 218 ± 33 to 170 ± 26 ml/min, and an increase in RVR from 0.712 ± 0.157 to 1.120 ± 0.376 mm Hg/ml/min (all $P < 0.01$). These responses are similar to those previously observed in our laboratory (28) when indomethacin was administered alone and to those observed in the current studies (Fig. 2, right kidney) when indomethacin was adminis-

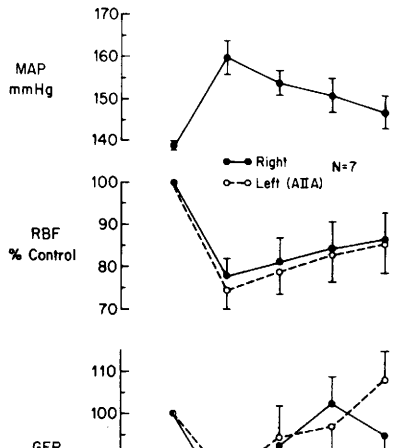


FIG. 2. Effect of left kidney angiotensin II blockade (AIIA) on the renal vasoconstrictor response to systemic indomethacin, N = 7.

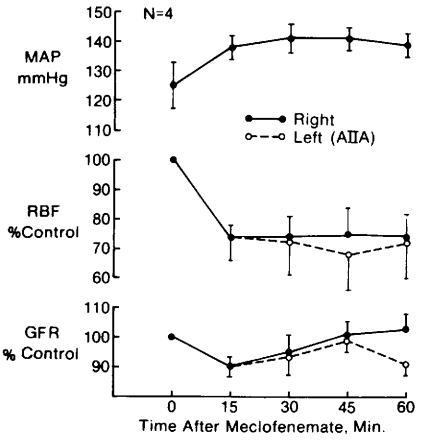


FIG. 3. Effect of left kidney angiotensin II blockade (AIIA) on renal vasoconstrictor response to systemic meclofenemate, N = 4.

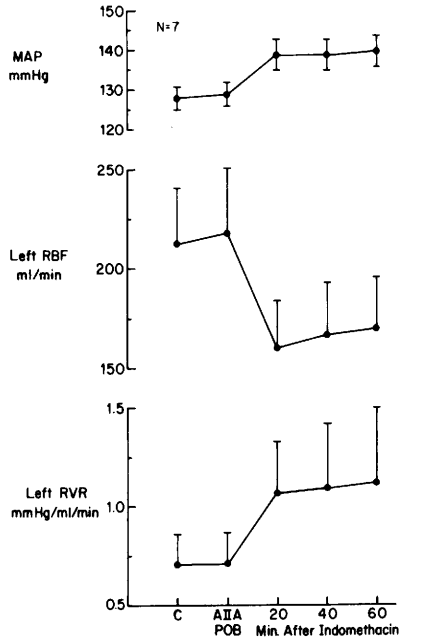


FIG. 4. Effect of combined renal $\alpha$-adrenergic receptor blockade with phenoxybenzamine (POB) and renal angiotensin II blockade (AIIA) on the renal vasoconstrictor response to systemic indomethacin, N = 7.

tered alone. Identical results were obtained in two similarly prepared dogs given meclofenemate, i.e., a renal vasoconstrictor response of magnitude similar to that observed when meclofenemate was administered alone (Fig. 3, right kidney). These data indicate that the renal vasoconstriction observed after systemic indomethacin or meclofenemate administration is not mediated by circulating catecholamines.

*Discussion.* The interactions between adrenergic stimuli and various vasoactive substances are complex. It has been well documented that renal nerve stimulation or exogenous NE causes the renal release of renin (29) and PG (30). AII administration also affects NE synthesis, release, and reuptake (4–6). AII also stimulates the renal release of PG (31).

Previous reports using exogenous AII infusions into the kidney have demonstrated potentiation of the renal vascular response to adrenergic stimuli (1). However, there are no studies dealing with the question of whether the levels of endogenous circulating AII alter the renal vascular response to adrenergic stimuli. We found that renal blockade to endogenous circulating AII did not alter the renal vascular responses to exogenous NE or RNS. These data suggest that even though exogenously administered AII can potentiate the renal vascular responses to exogenous NE or RNS, the levels of endogenous circulating AII are without effect in this regard.

The studies by Kaloyanides and colleagues in the isolated perfused dog kidney (22), by Dunn and colleagues in the intact kidney of anesthetized dogs (23), and by Zambraski and Dunn in the intact kidney of unanesthetized dogs (24) indicate that indomethacin and meclofenemate diminish renal secretion of $PGE_2$. In addition, our studies demonstrated that both indomethacin and meclofenemate markedly reduced the renal vasodilator response to arachidonic acid, a precursor of prostaglandins. This was taken to indicate a reduction in enzymatic conversion of arachidonic acid to vasodilator prostaglandin by indomethacin and meclofenemate, as was founded by Feigen and colleagues (25).

The interactions between PG and adrenergic stimuli in the renal vascular bed are species dependent. In the isolated perfused rabbit kidney, exogenous PG administration decreased the renal vascular response to RNS whereas, in the isolated perfused rat kidney, the response was increased; the renal vascular response to exogenous NE was unaffected in both species (7). Using indomethacin Zimmerman and colleagues (8) examined the role of endogenous PG in the control of vascular responses in the perfused dog paw. It was found that indomethacin potentiated the cutaneous vascular responses to both nerve stimulation and exogenous NE. In the dog (11), rabbit (12), and cat (13) kidney, intrarenal infusion of $PGE_2$ abolished the renal vasoconstrictor response to RNS but had little effect on the renal vasoconstrictor response to exogenous NE. Additional studies in the feline kidney by Chapnick and colleagues (15) demonstrated that indomethacin enhanced the renal vascular response to exogenous NE but not RNS whereas meclofenemate had no effect on the renal vascular response to either exogenous NE or RNS. In conscious dogs, Swain and colleagues (33) observed that the increase in RVP produced by intravenous methoxamine, an $\alpha$-adrenergic agonist, was increased by prior treatment with indomethacin. Our findings that renal vascular responses to exogenous NE were increased by indomethacin (Fig. 1) in anesthetized dogs are in agreement with the results of Swain and colleagues in the dog (32) and Chapnick and colleagues in the cat (15). Our findings that indomethacin did not affect renal vascular responses to RNS and meclofenemate did not affect renal vascular responses to RNS or exogenous NE are in agreement with similar observations by Chapnick and colleagues in the cat kidney (15). It is not clear why indomethacin but not meclofenemate potentiated the renal vascular responses to exogenous NE but it may be that the indomethacin effect is related to an action of the drug separate from its action to inhibit prostaglandin synthesis. These data suggest that endogenous prostaglandins do not serve to modulate the effects of the sympathetic nervous system on the canine renal vascular bed.

Mimran and colleagues (17) implicated the renin–angiotensin system as the mediator of the increase in MAP, decrease in RBF, and increase in RVR observed in the rat following

indomethacin administration. Bilaterally nephrectomized rats did not demonstrate an increase in MAP when given indomethacin. Systemic administration of AIIA attenuated the increase in MAP and prevented the decrease in RBF. Satoh and Zimmerman (33) administered indomethacin or meclofenemate into the renal artery of anesthetized dogs and did not observe an increase in MAP or renal vasoconstriction unless the renal artery was partially occluded. The renal vasoconstriction seen under these circumstances was abolished by renal blockade to angiotensin II. Our studies differ from these previous studies in that the prostaglandin synthesis inhibitors were administered systemically to anesthetized dogs. This intervention regularly produced an increase in MAP and a decrease in RBF, an observation previously made by us (28) as well as others (16, 34) in the anesthetized dog. The failure of Satoh and Zimmerman (33) to observe an increase in MAP or renal vasoconstriction in anesthetized dogs may relate to the administration of the prostaglandin synthesis inhibitors into the renal artery rather than systemically. Alternatively, they suggested that a background level (i.e., above the basal state) of circulating angiotensin II produced by the renal artery occlusion may be necessary for an increase in MAP and a decrease in RBF to occur after intrarenal administration of prostaglandin synthesis inhibitors. Our studies indicate that the renal vasoconstrictor response to systemic administration of prostaglandin synthesis inhibitors in anesthetized dogs is not mediated by the intrarenal action of the prevailing circulating levels of angiotensin II.

Since we observed that indomethacin enhanced the renal vascular response to exogenous NE, the possibility remained that the renal vasoconstriction observed after indomethacin could be mediated by the removal of endogenous PG inhibition of circulating NE. However, addition of renal $\alpha$-adrenergic receptor blockade to renal AII blockade did not alter the characteristic renal vasoconstriction observed after indomethacin. Since meclofenemate did not alter the renal vascular response to exogenous NE, it was anticipated that addition of renal $\alpha$-adrenergic receptor blockade to renal AII blockade would not alter the characteristic renal vasoconstriction observed after meclofenemate; such was the case. It is evident, however, that the anesthetized operated dog has higher levels of renal prostaglandin secretion than are observed in the unanesthetized conscious dog (35). Several studies have demonstrated that indomethacin or meclofenemate administration to unanesthetized conscious dogs does not result in renal vasoconstriction independent of changes in either renal venous prostaglandin concentrations (35) or in renal $PGE_2$ secretion or excretion (24).

In the anesthetized operated dog, not only are renal prostaglandin secretion rates elevated (35) but circulating levels of angiotensin II (36), as well as sympathetic nervous system activity, is increased. The possibility existed that the renal vasoconstrictor response to the systemic administration of indomethacin or meclofenemate to anesthetized operated dogs was due to the unopposed renal vasoconstrictor action of elevated levels of circulating angiotensin II or catecholamines. Our studies indicate that this is not the case and suggest that the renal vasoconstriction is related to the removal of endogenous prostaglandin renal vasodilator activity.

It should be emphasized that these observations pertain to the experimental circumstances of the anesthetized unstressed animal. In the anesthetized animal subjected to hemorrhage, it is clear that the resultant renal vasoconstriction, mediated by both angiotensin II and the renal sympathetic nerves, is significantly enhanced by the administration of prostaglandin synthesis inhibitors (36).

*Summary.* In the anesthetized dog, neither renal angiotensin II blockade nor systemic administration of meclofenemate altered the renal vascular response to renal nerve stimulation or exogenous norepinephrine. Systemic administration of indomethacin enhanced the renal vascular response to exogenous norepinephrine but not to renal nerve stimulation. Renal blockade to angiotensin II, alone or combined with renal $\alpha$-adrenergic receptor blockade produced by phenoxybenzamine did not affect the renal vasoconstrictor response to systemically administered indomethacin or meclofenemate. These data demonstrate that neither endogenous circulating angiotensin II nor prostaglandins significantly alter the effects of the sympathetic

nervous system on the canine renal vascular bed. The renal vasoconstriction associated with systemic indomethacin or meclofenemate administration is not due to unopposed angiotensin II or $\alpha$-adrenergic agonist vasoconstrictor action but rather to the withdrawal of endogenous prostaglandin vasodilator activity.


1. Zimmerman, B. G., and Gisslen, J., J. Pharmacol. Exp. Ther. **163,** 320 (1968).
2. Malik, K. U., and Nasjletti, A., Cir. Res. **38,** 26 (1976).
3. Zimmerman, B. G., and Gomez, J., Int. J. Neuropharmacol. **4,** 1985 (1965).
4. Zimmerman, B. G., Gomer, S. K., and Liao, J. C. Fed. Proc. **31,** 1344 (1972).
5. Roth, R. H., Fed. Proc. **31,** 1358 (1972).
6. Khairallah, P. A., Fed. Proc. **31,** 1351 (1972).
7. Malik, K. U., and Mc Giff, J. C., Circ. Res. **36,** 599 (1975).
8. Zimmerman, B. G., Ryan, M. J., Gomer, S., and Kraft, E., J. Pharmacol. Exp. Ther. **187,** 315 (1973).
9. Messina, E. J., Weiner, R., and Kaley, G., Circ. Res. **37,** 430 (1975).
10. Malik, K. U., Ryan, P., and McGiff, J. C., Circ. Res. **39,** 163 (1976).
11. Lonigro, A. J., Terragno, N. A., Malik, K. U., and McGiff, J. C., Prostaglandins **3,** 596 (1973).
12. Frame, M. H., Hedquist, P., and Astrom, A., Life Sci. **15,** 239 (1975).
13. Chapnick, B. M., Paustian, P. W., Klainer, E., Joiner, P. D., Hyman, A. L., and Kadowitz, P. J., J. Pharmacol. Exp. Ther. **196,** 44 (1976).
14. Chanh, P. H., Junstad, M., and Wennmalm, A., Acta Physiol. Scand. **86,** 563 (1972).
15. Chapnick, B. M., Paustian, P. W., Feigen, L. P., Joiner, P. D., Hyman, A. L., and Kadowitz, P. J., Circ, Res. **40,** 348 (1977).
16. Feigen, L. P., Klainer, E., Chapnick, B. M., and Kadowitz, P. J., J. Pharmacol. Exp. Ther. **198,** 457 (1976).
17. Mimran, A., Casellas, D., Dupont, M., and Barjon, P., Clin. Sci. Mol. Med. **48,** 2995 (1975).
18. Fuhr, M., Kaczmarczyk, J., and Kruttgen, C. D., Klin Wochschr. **33,** 729 (1955).
19. Prosnitz, E. H., and DiBona, G. F., Clin. Res. **25,** 445A (1977).
20. Davis, H. A., and Horton, E. W., Brit. J. Pharmacol. **46,** 658 (1972).
21. Kaloyanides, G. J., Ahrens, R. E., Shepherd, J. A., and DiBona, G. F., Circ. Res. **38,** 67 (1976).
22. Dunn, M. J., Liard, J. F., and Dray, F., Kidney Intern. **13,** 136 (1978).
23. Zambraski, E. J., and Dunn, M. J., Amer. J. Physiol. **236,** F552 (1979).
24. Feigen, L. P., Chapnick, B. M., Flemming, J. E., and Kadowitz, P. J., Amer. J. Physiol. **234,** H496 (1978).
25. Gill, J. R., Jr., and Casper, A. G. T., J. Clin. Invest. **50,** 112 (1971).
26. Slick, G. L., DiBona, G. F., and Kaloyanides, G. J., Amer. J. Physiol. **226,** 925 (1974).
27. Huntsberger, D. V., and Leaverton, P. E., "Statistical Inference in the Biomedical Sciences." Allyn and Bacon, Boston (1970).
28. DiBona, G. F., Zambraski, E. J., Aguilera, A. J., and Kaloyanides, G. J., Circ. Res. **40,** Suppl. I, 127 (1977).
29. Reid, I. A., Morris, B. J., and Ganong, W. F., Annu. Rev. Physiol. **40,** 377 (1978).
30. Dunham, E. W., and Zimmerman, B. G., Amer. J. Physiol. **219,** 1279 (1970).
31. McGiff, J. C., Crowshaw, K., Terragno, N. A., and Lonigro, A. J., Circ. Res. **27,** Suppl. I, I121 (1970).
32. Swain, J., Hendrickx, G. R., Boettcher, D. H., and Vatner, S. F., Amer. J. Physiol. **229,** 836 (1975).
33. Satoh, S., and Zimmerman, B. G., Circ. Res. **36/37,** Suppl. I, 189 (1975).
34. Terragno, N. A., Terragno, A., and McGiff, J. C., Circ. Res. **40,** 590 (1977).
35. Burger, B. M., Hopkins, T., Tullock, A., and Hollenberg, N. K., Circ. Res. **38,** 196 (1976).
36. Henrich, W. L., Berl, T., McDonald, K. M., Anderson, R. J., and Schrier, R. W., Amer. J. Physiol. **235,** F46 (1978).


Received January 25, 1979. P.S.E.B.M. 1979, Vol. 162.