The Role of Renal Nerves and Prostaglandins in Control of Renal Hemodynamics and Plasma Renin Activity during Hypotensive Hemorrhage in the Dog

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ABSTRACT The effects of hypotensive hemorrhage (HH) on renal hemodynamics and plasma renin activity (PRA) during prostaglandin (PG) synthesis inhibition were examined in three groups of dogs. In each group of animals arterial blood pressure was lowered by a 30% decrement. In the first group of eight control animals, HH was not associated with a significant change in glomerular filtration rate (GFR, 42–36 ml/min, NS); renal blood flow (RBF) declined significantly, from 234 to 171 ml/min, $P < 0.05$. In the second group of eight animals, pretreated with RO 20-5720 (RO, 2 mg/kg), a competitive inhibitor of PG synthesis, HH was associated with a significant fall in GFR (43–17 ml/min, $P < 0.001$) and RBF (195–89 ml/min, $P < 0.001$). In the third group of eight animals, pretreatment with indomethacin (IN, 10 mg/kg), a chemically dissimilar PG inhibitor, HH was also associated with a significant fall in GFR (38–8 ml/min, $P < 0.001$) and RBF (150–30 ml/min, $P < 0.001$). Renal denervation attenuated this renal ischemic effect of HH in the presence of PG inhibition. In the RO group, GFR (34 vs. 17 ml/min, $P < 0.005$) and RBF (145 vs. 89 ml/min, $P < 0.025$) were significantly greater in denervated vs. innervated kidneys during HH. Similarly, in animals treated with IN, a significantly higher GFR (28 vs. 8 ml/min, $P < 0.005$) and RBF (101 vs. 30 ml/min, $P < 0.005$) occurred in denervated as compared to innervated kidneys during HH. With HH, the increase in PRA in the control group (3.34–11.68 ng/ml per h, $P < 0.005$) was no different than that observed in the RO group (4.96–18.9 ng/ml per h, $P < 0.001$) or IN group (4.71–17.8 ng/ml per h, $P < 0.001$). In summary, the present results indicate that renal PG significantly attenuate the effect of HH to decrease GFR and RBF. Furthermore, renal denervation exerts a protective effect against the enhanced renal ischemic effects which occur in the presence of PG inhibition during HH. Finally, PG inhibition does not alter the effect of HH to cause an increase in PRA.

INTRODUCTION

The factors that modulate renal hemodynamic responses to hypotensive hemorrhage (HH)[1] have not been clearly defined. Previous studies have suggested that HH results in renal nerve stimulation which directly induces renal vasoconstriction (1). However, either direct renal nerve stimulation (2) or the intrarenal infusion of the sympathetic neurotransmitter, norepinephrine (3), has been found to stimulate the renal release of prostaglandins. Furthermore, recent studies have suggested that prostaglandins may act as renal vasodilators and play a protective role against the redistribution of renal blood flow (RBF) which occurs in response to HH (4). Thus, renal nerve stimulation induced by HH could potentially result in both direct renal vasoconstriction as well as release of renal vasodilator prostaglandins. At the present time, however, such an interrelationship between renal nerves and

An abstract of this work was published in 1977. *Clin. Res.* **25:** 435A. (Abstr.)

Dr. Henrich is a recipient of a fellowship from the National Kidney Foundation. Dr. Anderson is a Teaching and Research Scholar of the American College of Physicians. Dr. Berns is the recipient of a fellowship from the Rocky Mountain Kidney Foundation.

Received for publication 25 May 1977 and in revised form 11 November 1977.

[1] *Abbreviations used in this paper*: GFR, glomerular filtration rate; HH, hypotensive hemorrhage; RBF, renal blood flow.

prostaglandins in influencing renal hemodynamic responses to HH is theoretical.

The present studies therefore were undertaken to investigate the importance of renal prostaglandins and renal nerves on glomerular filtration rate (GFR) and RBF during HH. Also, since recent studies suggest that prostaglandins play a major role in stimulating renal renin release after hemorrhage (5) the effect of prostaglandin inhibition on plasma renin activity after HH was studied. Our results demonstrate that prostaglandin inhibition significantly enhances the effect of HH to decrease GFR and RBF but does not alter the effect of HH to increase plasma renin activity. Furthermore, renal denervation exerts a protective effect against the enhanced renal ischemic effects of HH which occur in the presence of prostaglandin inhibition.

METHODS

24 mongrel dogs weighing between 20 and 30 kg were used in the study. Food was withheld 18 h before the study and the animals were allowed free access to water. On the morning of the study the animals were anesthetized with intravenous pentobarbital (30 mg/kg), intubated, and ventilated with a Harvard respirator (Harvard Apparatus Co., Inc., Millis, Mass.). Supplemental doses of pentobarbital were administered as needed throughout the experiment to maintain a stable state of anesthesia. Polyethylene catheters were placed in both ureters and renal veins through bilateral flank incisions and a retroperitoneal approach. Unilateral renal denervation was performed in all of the animals by severing and stripping the renal nerves and applying 95% alcohol to the renal pedicle. To assess the adequacy of denervation in our study, renal tissue norepinephrine content (6) was measured in four dogs 3 days after unilateral renal denervation. Innervated kidneys had a tissue norepinephrine level of 0.724 $\pm$0.12 μg/g whereas the denervated kidneys had a level of 0.019$\pm$0.018 μg/g ($P < 0.01$). Thus, denervation was associated with tissue norepinephrine depletion. An equal number of right and left kidneys were denervated in the study. A brachial artery catheter connected to a Statham transducer (Statham Instruments Inc., Oxnard, Calif.) was used to continuously monitor blood pressure; a right atrial catheter was placed via the jugular vein to allow measurement of cardiac outputs by using the dye dilution technique as previously described (7). Midway through the surgery, a 0.3% sodium chloride infusion was begun through a peripheral vein at 20 ml/min to replace fluid losses and achieve stable urine flows; this infusion was continued for 60–80 min. After stable urine flow rates were obtained the infusion rate was decreased to equal urine flows for the remainder of the study. After completion of surgery, a solution of 0.9% sodium chloride containing sufficient inulin and para-aminohippurate was infused (0.5 ml/min) into a foreleg vein to maintain plasma levels of these substances at 15–20 and 1–3 mg/100 ml, respectively.

All animals were allowed to stabilize for 1–2 h after surgery. Calculations utilized for clearance measurements were performed as previously described (8). Four periods were utilized in the protocol; in each period three to five timed urine specimens and at least two arterial and renal venous blood samples were obtained for clearance measurements and analyzed for para-aminohippurate and inulin as previously described (8). Plasma renin activity was measured in arterial blood by radioimmunoassay as previously noted (9). Cardiac outputs were performed during the middle of each clearance period. The four clearance periods were as follows:

Period 1 (precontrol). Period for base-line clearance measurements.

Period 2 (postinfusion). 15 min before the beginning of this period, each group of animals received one of three intravenous bolus infusions: (*a*) Group I (control animals), a blank bicarbonate solution equal in volume to prostaglandin inhibitor solutions (eight dogs); (*b*) Group II, RO 20-5720 (Hoffmann-La Roche Laboratories, Nutley, N. J.), an inhibitor of prostaglandin synthesis, 2 mg/kg (eight dogs); (*c*) Group III, indomethacin, 10 mg/kg, dissolved in bicarbonate buffer (eight dogs). Thus, Group I animals received the carrier solution of prostaglandin inhibitor and Groups II and III animals received chemically dissimilar prostaglandin synthetase inhibitors. The RO 20-5720 compound has been previously shown to cause a 50% reduction in renal venous prostaglandin levels when given in a dose of 1 mg/kg (10).

Period 3 (HH). All three groups of animals were hemorrhaged via the arterial catheter to a stable mean arterial pressure which was 30% less than mean blood pressure measured in Period 2. Hemorrhage was carried out over a period of 10–15 min. 10 min after hemorrhage, three 20-min urine collections were made for clearance measurements.

Period 4 (postcontrol). 30–40 min after reinfusion of the shed blood, a postcontrol clearance period was obtained.

Renal tissue prostaglandin concentrations were measured in a separate group of animals. After removal of one kidney for assay, dogs received either blank solution, indomethacin (10 mg/kg), or RO 20-5720 (2 mg/kg). Hemorrhage sufficient to lower blood pressure by 30% was then performed. The remaining kidney was removed and assayed for tissue prostaglandin 30–40 min later to correspond with the HH period of the physiologic studies. This procedure allowed each animal to serve as its own control, and any effect of nephrectomy per se would be expected to occur in all three groups. All kidneys utilized were promptly excised, bivalved and medullary tissue snap-frozen within 30–45 s in liquid nitrogen. All samples were analyzed at the University of Colorado for tissue prostaglandin content using methods previously described (11).

Statistics were performed using the Sheffe's analysis of multiple comparisons (12) between both periods and groups. Student's paired *t* test was employed when comparing innervated to denervated kidneys in the same animal. A *P* value of <0.05 was considered significant; all data are expressed as the mean$\pm$SEM.

RESULTS

Effect of hypotensive hemorrhage on systemic hemodynamics (Table I). There were no significant differences in the mean volume of blood removed from each group of animals to effect a 30% decrement in mean arterial pressure. The decrement in mean arterial pressure was equivalent in each group of animals and the mean arterial pressure also returned to prehemorrhage levels in each group of animals upon reinfusion of shed blood. HH was associated with a decrease in cardiac output in all three groups of animals. The decrease in cardiac output with HH was significant in Group I (control) and Group III (indomethacin) animals.

TABLE I

Effect of Hypotensive Hemorrhage on Systemic Hemodynamics

	Volume of hemorrhage	Mean arterial pressure				Cardiac output			
		Pre-control	Post-infusion	HH	Post-control	Pre-control	Post-infusion	HH	Post-control
	ml/kg body weight	*mm Hg*				*liters/min*			
Group I (n = 8)									
Control	25.9	150	148	104	150	3.3	3.0	1.9	3.2
SEM	3.46	7	8	4	6	0.3	0.3	0.2	0.4
P value			NS	<0.001	<0.001		NS	<0.005	<0.001
Group II (n = 8)									
RO 20-5720	27.2	151	158	108	161	3.7	3.1	2.4	3.2
SEM	3.31	10	8	4	8	0.4	0.3	0.6	0.7
P value			NS	<0.001	<0.001		NS	NS	NS
Group III (n = 8)									
Indomethacin	29.9	149	155	105	151	3.1	3.0	1.5	3.1
SEM	3.6	6	6	5	5	0.5	0.5	0.2	0.8
P value			NS	<0.001	<0.001		NS	<0.01	<0.005

Effect of hypotensive hemorrhage on glomerular filtration rate and renal blood flow (Table II). In Group I (control) animals, HH induced an insignificant reduction in GRF in both innervated and denervated kidneys. HH resulted in significant reductions in RBF in both innervated (212±21 to 163±21 ml/min, $P < 0.05$) and denervated (234±25 to 171±19 ml/min, $P < 0.05$) kidneys. No significant difference in RBF was observed when innervated and denervated kidneys were compared. Thus, in these control animals (Group I), with intact prostaglandin synthesis, the presence or absence of renal nerves did not alter detectably the renal hemodynamic response to HH.

In contrast to the Group I control animals, a comparable degree of HH resulted in significant decrements in both GFR and RBF in the prostaglandin-inhibited Group II (RO 20-5720) animals (Table II). HH resulted in a striking fall in GFR in innervated kidneys (43±4 to 17±5 ml/min, $P < 0.001$) and a slight fall in denervated kidneys (41±4 to 34±5 ml/min, $P < 0.05$) in Group II animals. The decrement in GFR induced by HH in these prostaglandin-depleted animals was significantly greater in innervated than denervated kidneys, $P < 0.005$ (Fig. 1). HH also resulted in a significant decrease in RBF in Group II animals. The decrease in RBF was significant in innervated (195±35 to 89±35 ml/min, $P < 0.001$) but not denervated (190±19 to 145±26 ml/min, NS) kidneys. The decrement in RBF with HH was significantly greater in innervated than denervated kidneys, $P < 0.025$ (Fig. 1). Thus, in the face of prostaglandin inhibition, renal denervation exerted a significant protective effect on the renal ischemic response to GFR and RBF to HH.

To confirm that the effects observed with HH in Group II animals were due to prostaglandin inhibition, HH was induced in a third group of animals (Group III) pretreated with indomethacin, a chemically dissimilar inhibitor of prostaglandin synthesis. The effect of HH on renal hemodynamics in these indomethacin-treated animals was similar to that observed in Group II animals. In the Group III animals, HH resulted in a striking decline in GFR (38±3 to 8±3 ml/min, $P < 0.001$) and RBF (150±18 to 30±11 ml/min, $P < 0.001$) in innervated kidneys. In denervated kidneys HH after indomethacin also resulted in falls in GFR (38±2 to 28±4 ml/min, $P < 0.05$) and RBF (157±21 to 101±14 ml/min, $P < 0.05$). However, this fall in GFR and RBF in denervated kidneys was significantly less than in innervated kidneys, $P < 0.005$ (Fig. 1), thus confirming the results observed in Group II animals.

Effect of hypotensive hemorrhage on plasma renin activity (Fig. 2). Basal prehemorrhage arterial plasma renin activity was comparable in all three groups of animals. Neither the administration of RO 20-5720 nor indomethacin significantly reduced basal arterial plasma renin activity before hemorrhage. HH was associated with highly significant, comparable increments in arterial plasma renin activity in all three groups of animals (Fig. 2). The increase in plasma renin activity with HH reverted toward pre-HH values upon reinfusion of blood. Because of the profound decreases observed in renal plasma flows in innervated kidneys with HH, no significant differences in renin secretory rates between innervated and denervated kidneys were observed.

TABLE II

Effect of Hypotensive Hemorrhage on Glomerular Filtration Rate and Renal Blood Flow

	Glomerular filtration rate				Renal blood flow			
	Pre-control	Post-infusion	HH	Post-control	Pre-control	Post-infusion	HH	Post-control
	ml/min				*ml/min*			
Group I (Control)								
Innervated (n = 8)	47	42	36	46	245	212	163	203
SEM	4	4	4	5	27	21	21	32
P value		NS	NS	NS		NS	<0.05	NS
Denervated (n = 8)	47	41	38	46	255	234	171	199
SEM	4	3	4	4	27	25	19	26
P value		NS	NS	NS		NS	<0.05	NS
Group II (RO 20-5720)								
Innervated (n = 8)	43	43	17*	34	248	195	89*	175
SEM	4	3	5	4	43	35	35	34
P value		NS	<0.001	<0.001		NS	<0.001	<0.001
Denervated (n = 8)	39	41	34	41	246	190	145	163
SEM	4	4	5	5	26	19	26	26
P value		NS	<0.05	<0.05		NS	NS	NS
Group III (Indomethacin)								
Innervated (n = 8)	38	38	8*	34	205	150	30*	149
SEM	3	3	3	4	20	18	11	23
P value		NS	<0.001	<0.001		NS	<0.001	<0.001
Denervated (n = 8)	39	38	28	36	210	157	101	164
SEM	2	2	4	4	26	21	14	16
P value		NS	<0.05	NS		<0.05	<0.05	<0.05

* Differs significantly from contralateral denervated kidney.

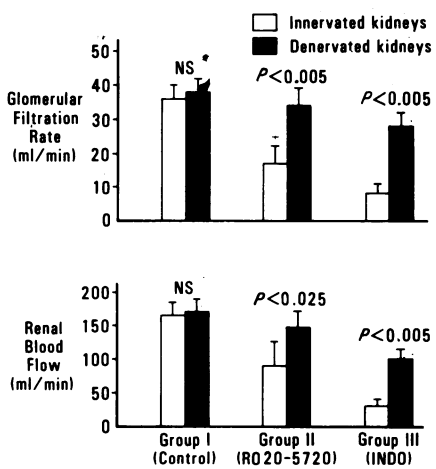

FIGURE 1 Renal hemodynamics during HH (Period 3). No significant differences in GFR and RBF were observed between innervated and denervated kidneys in Group I (control animals). In striking contrast, denervated kidneys in both prostaglandin inhibition groups (Groups II and III) had a significantly higher GFR and RBF during HH. Indomethacin, INDO.

Effect of indomethacin and RO 20-5720 on renal tissue prostaglandin. In a separate group of animals, prostaglandin tissue levels were measured in kidneys removed before HH. The animals then received either blank, indomethacin, or RO 20-5720 solutions, and HH was performed with subsequent removal of the second kidney for prostaglandin assay. In six control animals, the renal prostaglandin level in the kidneys removed before HH was 48±9 pg/ml tissue; after administration of blank solution and HH, the level was 94.4±17 pg/mg tissue ($P < 0.01$). A second group of five dogs had an initial prostaglandin tissue level of 60.9±20 pg/mg tissue; in contrast to the control group receiving the blank, after administration of indomethacin (10 mg/kg) and HH, a striking fall in tissue levels to 3.8±.5 pg/mg tissue ($P < 0.05$) was observed. A third group of six dogs had a slightly but not significantly higher base-line tissue level of 81.2±22 pg/mg tissue; after administration of RO 20-5720 (2 mg/kg) and HH the levels decreased significantly to 37.9±8 pg/mg tissue ($P < 0.05$). Interestingly, in the prostaglandin inhibition groups during HH, the more profound hemo-

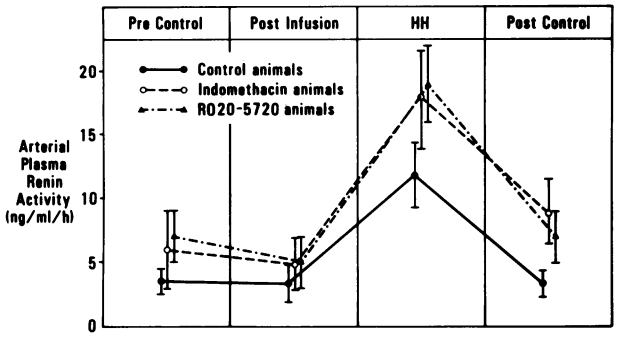

FIGURE 2 Plasma renin activity (PRA) in HH. A comparable and significant increase in PRA ($P < 0.005$) was observed in each group during HH (Period 3). Reinfusion of shed blood resulted in a decrease in PRA to pre-HH values.

dynamic effects were observed in the indomethacin-treated animals. This may be accounted for, at least in part, by a greater degree of prostaglandin depletion associated with indomethacin administration.

DISCUSSION

HH is generally accepted to be associated with renal ischemia (13, 14). The factors which may mediate, enhance or attenuate this renal ischemic effect of hemorrhage, however, are in need of further clarification. Recently, a role of renal prostaglandins has been suggested in the renal response to hemorrhage by the results of several investigations. Interestingly, Vatner (15) demonstrated that modest hemorrhage in conscious dogs was paradoxically associated with early renal vasodilatation, an effect which could be abolished by pretreatment with inhibitors of prostaglandin synthesis. This study, however, did not examine whether the fall in RBF during more severe hemorrhage may be enhanced by inhibition of prostaglandin synthesis. The recent results by Data et al. (4) also suggest a role of renal prostaglandins in the renal response to hemorrhage. Using microsphere techniques, these workers found a redistribution of blood flow from outer to inner renal cortex during hemorrhage; this redistribution during hemorrhage was abolished by inhibition of prostaglandin synthesis. However, the effect of prostaglandin inhibition on alterations in GFR during HH was not examined. Romero et al. (5) recently suggested that hemorrhage-induced rises in plasma renin activity were prostaglandin mediated, since pretreatment with prostaglandin inhibitors abolished this effect. The degree of hemorrhage, however, was difficult to assess, because changes in systemic hemodynamics were not reported. Lastly, in vitro studies have suggested that prostaglandins may inhibit norepinephrine release from nerve endings (16); thus, prostaglandin inhibition theoretically might be expected to enhance renal ischemia which occurs secondary to renal nerve stimulation. Thus, taken together, there is either in vivo or in vitro evidence which suggests that renal prostaglandins may mediate several responses to hemorrhage including early vasodilatation (15), redistribution of blood flow from outer to inner cortex (4), and attenuation of other responses such as increases in plasma renin activity (5) and possibly renal nerve stimulation (16). The present studies, therefore, were undertaken to examine whether inhibition of renal prostaglandin synthesis alters the response of total RBF and GFR to HH. The interaction between renal prostaglandins, renal innervation and renin release also were investigated.

In the present study in anesthetized dogs HH, which caused a 30% fall in mean arterial pressure, was associated with a modest but significant fall in RBF. This fall in RBF was not altered by renal denervation. This result, however, does not exclude the possibility that renal denervation with more severe hemorrhage might attenuate the fall in RBF. The cross-perfusion studies of Gill and Casper (17) indeed indicate that renal nerve stimulation in hemorrhaged dogs diminishes para-aminohippurate clearance even when the animal's kidneys are perfused by blood from nonhemorrhaged dogs. It is possible, however, that an increase in endogenous catecholamines or angiotensin may increase renal vascular resistance in denervated and innervated kidneys to a comparable degree. In any case, what is important in the present studies is that the effect of hemorrhage on RBF in the control (Group I) studies was not altered by renal denervation. As will be discussed later this result is quite different from the effect of renal denervation in animals pretreated with prostaglandin inhibitors.

In previous studies, HH has been found to increase renal prostaglandin synthesis and release (14). Similarly, in the present study HH was found to increase renal medullary prostaglandin concentration. These findings, in addition to the above mentioned results of Vatner (15) and Data et al. (4), prompted further investigation of the importance of prostaglandin synthesis during hemorrhage. Inhibition of prostaglandin synthesis with either of two chemically dissimilar agents (indomethacin and RO 20-5720) was found to have a profound effect on the renal ischemic response to HH. While RBF fell modestly in the control animals during hemorrhage, a profound diminution in RBF occurred when the animals were pretreated with either inhibitor of prostaglandin synthesis. The doses of the prostaglandin inhibitors which were used also were adequate to abolish the effect of hemorrhage to increase renal medullary prostaglandin concentration. These results, therefore, indicate that increased prostaglandin release during hemorrhage may not only cause early vasodilatation (15) and redistribution of blood

flow from outer to inner cortex (4) but also is protective against the effect of HH to lower total RBF.

While most previous studies have focused primarily on the importance of prostaglandins on RBF, the present study also examined the effect of GFR. In this regard, it could be argued that any effect on glomerular ultrafiltration rather than blood flow is of primary importance since this is the initial event in urine formation. Inhibition of prostaglandin synthesis was found in the present study to predispose to a profound fall in GFR during hemorrhage. While the HH did not cause a fall in filtration rate in the control animals, the same degree of hemorrhage caused severe reductions in filtration rate in the indomethacin-treated animals (38–8 ml/min, $P < 0.001$) and RO 20-5720–treated animals (43–17 ml/min, $P < 0.001$). Thus, inhibition of prostaglandin synthesis with either agent was associated with a significantly greater reduction in both RBF and GFR. The results in innervated kidneys in the control and prostaglandin-inhibited animals serve, therefore, to emphasize the importance of renal prostaglandins in opposing decrements in RBF and GFR associated with HH.

Although renal denervation exerted no detectable effect on either RBF or GFR during HH in the control (Group I) animals, this was clearly not the case in the prostaglandin-inhibited animals (Group II and III). In these animals renal denervation was associated with a significant protective effect against the renal ischemia of hemorrhage. The falls both in RBF and GFR during HH were significantly less in the denervated compared to the innervated kidneys in the prostaglandin-inhibited animals (Fig. 1). These findings are compatible with the in vitro results which suggest that prostaglandins may inhibit norepinephrine release from nerve endings. This association, however, cannot be considered as definitive proof since the vasodilatory effect of prostaglandins might only counter balance the vasoconstriction of renal nerve stimulation. Also, the occurrence of such a neural-prostaglandin interaction in the kidney might be expected to predominate in the cortex where most nerve endings are present, even though higher concentrations of prostaglandins are found in the medulla. In this regard, however, there is little doubt that prostaglandin synthesis does occur in the renal cortex (18).

On the background of the results of Romero et al. (5), which reported that inhibition of prostaglandin synthesis abolished the rise in plasma renin activity during hemorrhage in conscious rabbits, it could be suggested that any deleterious effect of inhibition of prostaglandin synthesis might be attenuated by the simultaneous abolishment of activation of the renin-angiotensin system. However, in the present results, the rises in plasma renin activity during hemorrhage (Fig. 2) were comparable in the control (Group I) animals and animals pretreated with prostaglandin inhibitors (Groups II and III). Moreover, in the present study one could argue that any increase in activation of the renin-angiotensin system would be associated with greater vasoconstriction in the presence of prostaglandin inhibition. Such an enhancement by prostaglandin inhibition of the vasoconstrictor effect of exogenously infused angiotensin has been demonstrated (19) so that further studies of the role of angiotensin in the renal ischemia of HH are needed. Whether differences in the degree of hemorrhage, the species, the metabolic kinetics of renin, or anesthesia account for the different results in the present study and the study of Romero et al. (5) is not clear. It is clear, however, from the present study that pathways other than, or in addition to, prostaglandin release may stimulate renin release during hemorrhage.

In conclusion, the present results demonstrate that inhibition of prostaglandin synthesis, with either of two chemically dissimilar agents, profoundly enhances the effect of HH to lower both GFR and RBF. These findings suggest that renal prostaglandins are of major importance in opposing the ischemia of HH. Prostaglandin inhibition, however, failed to alter the increase in plasma renin activity seen with HH. The results did, however, suggest an effect of prostaglandin inhibition to enhance ischemia associated with renal nerve stimulation during hemorrhage. This conclusion is based on the findings that renal denervation exerted a significant protective effect against the renal ischemia of hemorrhage in prostaglandin-inhibited but not control animals. This latter effect suggests that prostaglandin release during hemorrhage may not only directly vasodilate blood vessels but may possibly inhibit norepinephrine release from nerve endings. While such an effect of prostaglandins is compatible with results in previous in vitro studies, further studies will be necessary to confirm this possibility.

ACKNOWLEDGMENTS

We are grateful for the excellent technical assistance provided by Lowell K. Gilbert, Deborah K. Hyde, and Abby Erickson and for the expert secretarial assistance by Linda M. Benson. We also express our thanks to Dr. Roscoe M. Hersey who performed the tissue catecholamine assay.

This work was supported by a grant from the National Institutes of Health, HL 15629.

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