Mechanisms of Renin Secretion during Hemorrhage in the Dog

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ABSTRACT The importance of renal perfusion pressure (RPP), the sympathetic beta adrenergic nervous system and renal prostaglandins (PG) on renin release during a uniform 15–17% reduction in blood pressure by hemorrhage (HH) was studied systematically in anesthetized dogs. All groups of animals had similar decrements in systemic and renal hemodynamics with HH. In control dogs (n = 7), both plasma renin activity (PRA, 4.1–9.0 ng angiotensin I/ml per h, $P < 0.05$) and renin secretory rate (RSR, 26–228 ng/ml per h·min, $P < 0.005$) increased significantly with HH. This increase in renin release during HH was not abolished by any single maneuver alone including beta adrenergic blockade with *d,l*-propranolol (n = 6), renal PG inhibition with indomethacin (n = 7), or control of RPP (n = 6). However, when beta adrenergic blockade was combined with control of RPP (n = 7) during HH, neither PRA (1.9–2.7 ng/ml per h, NS) nor RSR (16–53 ng/ml per h·min, NS) increased significantly. Similarly, a combination of beta adrenergic blockade and PG inhibition (n = 6) also abolished the increase in PRA (1.5–1.4 ng/ml per h, NS) and RSR (14–55 ng/ml per h·min, NS) during HH despite significant decreases in sodium excretion. Finally, a combination of PG inhibition and RPP control was associated with significant increases in PRA and RSR during HH. These results support a multifactorial mechanism in renin release during HH and implicate both the beta adrenergic receptors, renal baroreceptors, and possibly the macula densa as constituting the primary pathways of renin release during HH of this magnitude. Because either constant RPP or PG inhibition blunted renin release during HH in the setting of beta adrenergic blockade, the present results strongly suggest that the renal baroreceptor, and probably the macula densa mechanism are PG mediated.

INTRODUCTION

The investigation of factors involved in renin secretion has remained both a fascinating and enigmatic subject to renal physiologists during the past decade. The study of renin secretion has been particularly enigmatic when a stimulus such as hemorrhage has been employed to provoke renin release; this may be true because hemorrhage may represent a heterogenous stimulus to renin release. For example, hemorrhage may induce renin secretion through activation of arterial stretch receptors in the renal circulation when renal perfusion pressure (RPP)[1] falls (1, 2); similarly, an increase in renal sympathetic nerve activity (3, 4) or an increase in circulating catecholamines (5–7) may also induce renin secretion. Finally, a decrease in sodium delivery to the macula densa may occur with hemorrhage and thus provide another efferent mechanism for renin release (8).

Previous investigations of the renin response to hemorrhage have stressed the importance of the macula densa and renal nerve activity as important stimuli to renin release (9). The experimental model used in these earlier studies was that of the denervated, nonfiltering kidney (10). Although these studies have implicated distal sodium delivery and sympathetic nerves as factors in renin release with hemorrhage, the denervated, nonfiltering kidney may have a different renin response to hemorrhage than the in vivo kidney with a normal renal vascular resistance and renal blood flow. Furthermore, the influence of the renal prostaglandin system as a contributing factor in renin release during

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[1] *Abbreviations used in this paper*: PRA, plasma renin activity; RPP, renal perfusion pressure; RSR, renin secretory rate.

hemorrhage was not examined in these earlier studies, and has been a subject of some controversy in recent papers (11, 12).

In the present investigation the effect of a uniform 15–17% reduction in arterial blood pressure by hemorrhage was examined on both plasma renin activity (PRA) and renin secretory rate (RSR). In several groups of animals, the separate and combined importance of the renal baroreceptor, the beta adrenergic nervous system, and the renal prostaglandin system was sequentially examined.

METHODS

45 mongrel dogs weighing between 20 and 35 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 sodium (30 mg/kg), intubated and ventilated with a Harvard respirator (Harvard Apparatus Co., Inc., Millis, Mass.). Supplemental doses of pentobarbital sodium 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 using a retroperitoneal approach. A brachial artery catheter connected to a Statham transducer (Statham Instruments, Inc., Oxnard, Calif.) was used to continuously monitor systemic blood pressure. In the animals in which RPP was maintained constant, a Blalock vascular clamp was placed around the aorta above both renal arteries, so that RPP was maintained constant by clamp adjustment. The clamp was preadjusted 90 min before starting the experiments so that RPP could be maintained constant during the acute hemorrhage. In these animals, a femoral artery catheter also was inserted into the aorta below the clamp and connected to a pressure transducer so that RPP could be constantly monitored. A right atrial catheter was inserted into all animals via the jugular vein to allow measurement of cardiac outputs by using the dye dilution technique as described (13). Midway through the surgery, a 0.3% sodium chloride infusion was begun at 15 ml/min to replace fluid losses and to achieve stable urine flows; this infusion was continued for 30–45 min and then adjusted to equal urine flow rates for the remainder of the study. After the completion of the 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 used for clearance measurements were performed as described (14). Four or five clearance periods were used 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 inulin and para-aminohippurate as described (14). PRA was measured in arterial and renal venous blood by radioimmunoassay as noted (15). RSR was calculated during each period from at least two samples by the following standard formula: RSR (ng/ml per h·ml/min) = renal plasma flow × (renal venous renin − renal arterial renin). Cardiac outputs were performed in duplicate during the middle of each clearance period.

A total of seven groups of dogs were studied which were prepared in the following manner: group 1 (n = 7), control animals; group 2 (n = 6), RPP controlled during hemorrhage; group 3 (n = 6), *d,l*-propranolol infusion given before hemorrhage; group 4 (n = 7), indomethacin infusion given before hemorrhage; group 5 (n = 7), *d,l*-propranolol infusion given before hemorrhage and RPP controlled; group 6 (n = 6), *d,l*-propranolol infusion and indomethacin infusion given before hemorrhage; group 7 (n = 6), indomethacin infusion given and RPP controlled.

The four clearance periods used in the present study are outlined below.

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

Period 2 (drug infusion). 15 min before the beginning of this period the animals received one of several infusions. Groups 1 and 2 received a blank bicarbonate solution equal in volume to the prostaglandin inhibitor solution. Groups 3, 5, and 6 received *d,l*-propranolol intravenously in a dose of 1 mg/kg bolus followed by an infusion at 0.5 mg/kg per h; this dose was sufficient to block the systemic hemodynamic response to systemic isoproterenol at a rate of 0.018 μg/kg per min in a separate group of dogs. Finally, groups 4, 6, and 7 received indomethacin 10 mg/kg as an intravenous bolus; this dose has been previously associated with renal tissue prostaglandin depletion (12). Thus, only group 6 dogs received both drug infusions (*d,l*-propranolol and indomethacin) and two separate infusion periods were used in this particular group.

Period 3 (hemorrhage). All seven groups of dogs were hemorrhaged over a period of 5–10 min via the brachial arterial catheter to a stable mean arterial pressure 15–17% less than the mean blood pressure in period 2. In those groups of animals in which RPP was controlled (groups 2, 5, and 7), constant RPP was obtained by adjusting the suprarenal Blalock clamp appropriately.

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

Statistics were performed using Scheffe's (16) analysis of variance between periods and groups. A P value of <0.05 was considered significant, and all data are expressed as the mean±SE.

RESULTS

Systemic and renal hemodynamics and sodium excretion during hemorrhage. As shown in Table I, the volume of blood removed to effect the 15–17% decrement in mean arterial pressure was similar in all groups of animals. In all dogs, the fall in blood pressure induced by hemorrhage was statistically significant and was reversible when the shed blood was returned to the animals. In the three groups of animals with a suprarenal aortic clamp (groups 2, 5, and 7), RPP was maintained constant throughout the experiment. The decrement in cardiac output caused by hemorrhage was significant in all groups, and increased toward prehemorrhage levels after blood reinfusion.

The prehemorrhage glomerular filtration rates and renal blood flows were statistically similar in all groups of dogs. The 15–17% hemorrhage induced a modest fall in glomerular filtration rate that reached statistical significance in groups 1, 2, 4, and 7. Similarly, a moderate decrease in renal blood flow was also observed during the hemorrhage period in all groups of dogs; this decrease was statistically significant in all groups of dogs except groups 5 and 6. The most

striking decrement in renal blood flow occurred in group 7, in which a 42% fall in renal blood flow from 230±16 to 132±14 ml/min ($P < 0.001$) occurred with hemorrhage. In all groups, reinfusion of the shed blood resulted in small to modest increases in both filtration rate and blood flow. As shown in Table I, hypotensive hemorrhage caused a significant and reversible decrease in urinary sodium excretion in all but one group of animals (group 5).

PRA and RSR during hemorrhage (Table II). In group 1 (control) dogs, the hypotensive hemorrhage induced an increase in both PRA (4.05±1.7–9.0±2.7 ng/ml per h, $P < 0.05$) and RSR (26±41–228±74 ng/ml per h·ml/min, $P < 0.005$). This increase in renin release was reversible upon reinfusion of shed blood. Animals treated before hemorrhage with either RPP control (group 2), *d,l*-propranolol (group 3), or indomethacin (group 4) also had significant increases in both PRA and RSR during hemorrhage. Thus, the maintenance of a constant RPP, systemic beta adrenergic blockade, and inhibition of prostaglandin synthesis were insufficient as solitary maneuvers in blocking the increase in PRA and RSR noted during hemorrhage.

To test the possibility that a combination of maneuvers could blunt the rise in PRA and RSR in hemorrhage, three more groups of dogs were hemorrhaged the same amount as in the earlier studies. When control of RPP was combined with beta adrenergic blockade (group 5), no significant increase in either PRA (1.92±0.65–2.68±1.47 ng/ml per h) or RSR (15.9±12.0–53.0±25.0 ng/ml per h·ml/min) occurred. Although prostaglandin inhibition recently has been shown to blunt the increase in renin release during aortic clamping in the nonfiltering kidney (17), the possibility that prostaglandin inhibition would act similarly to RPP control in hemorrhage remained untested. Thus, another group of dogs (group 6) was hemorrhaged to determine whether or not beta adrenergic blockade and prostaglandin inhibition could ablate the rise in PRA and RSR during hemorrhage. As shown in Table II, neither PRA (1.45±0.9–1.42±0.98 ng/ml per h, NS) nor RSR (14±13–55±20 ng/ml per h·ml/min, NS) rose significantly in these animals (group 6) subjected to the same amount of hemorrhage as earlier dogs. Thus, it seemed clear that when combined with beta adrenergic blockade, prostaglandin inhibition was similar to RPP control in blocking the response of PRA and RSR to hypotensive hemorrhage.

The possibility remained, however, that this inhibition of renin release during hemorrhage was simply a result of a nonspecific combination of protective maneuvers. Therefore, in the final group of dogs (group 7), RPP control was combined with prostaglandin inhibition, thus leaving the beta adrenergic nervous system intact. In this group of animals, hemorrhage was again associated with significant increases in both PRA (1.36±0.64–3.70±1.24 ng/ml per h, $P < 0.05$) and RSR (10±7–217±39 ng/ml per h·ml/min, $P < 0.05$).

Prehemorrhage plasma potassium concentrations were similar in all groups of dogs and did not change with hemorrhage.

DISCUSSION

The enhancement of the activity of the renin-angiotensin system during hemorrhage is a well-accepted phenomena (18–20) that has stimulated physiologic investigation for a number of years. Studies in the nonfiltering kidney suggest that hemorrhage may provide a multifactorial stimulus for renin release (9). However, although use of the nonfiltering kidney model has contributed significantly to our understanding of renin release, results from this model may differ from those in the normal filtering kidney. For example, differences may occur because the nonfiltering kidney has a very low renal blood flow with increased renal vascular resistance and the animals are both hypervolemic and azotemic. In the present study, therefore, the mechanisms and mediators of renin release were studied in the normal filtering kidney.

The results of the initial three groups of studies support the conclusion, that hypotensive hemorrhage stimulates renin by more than one pathway. After the control group of studies (group 1) were performed, control of RPP was used to examine the role of baroreceptors in the renin response to hypotensive hemorrhage (group 2). Although the control of renal perfusion probably influences the macula densa as well as the baroreceptor mechanism, this approach seemed preferred to the use of intrarenal papaverine since the phosphodiesterase inhibiting activity of this drug could potentially alter the renin response independent of the vascular baroreceptor. In the present studies, control of RPP alone did not abolish the renin response to hypotensive hemorrhage.

Previous studies from our laboratory have demonstrated that *d,l*-propranolol blocks the effect of renal nerve stimulation to increase renin release in absence of alterations in renal hemodynamics. The effect of *d,l*-propranolol on renin release was demonstrated to be primarily a result of beta adrenergic blockade (3). Studies therefore were performed to examine the effect of hypotensive hemorrhage in the presence of beta adrenergic blockade with *d,l*-propranolol. As with control of RPP, beta adrenergic blockade alone failed to abolish the effect of hypotensive hemorrhage to stimulate renin release (group 3).

Although Romero et al. (11) found that inhibition of prostaglandin synthesis abolished the renin response to hemorrhage in the conscious rabbit, this was not found to be the case in the present study in the anesthetized dog. Hypotensive hemorrhage significantly

TABLE I

Systemic and Renal Hemodynamics and Sodium Excretion during Hemorrhage in the Dog

		Mean arterial pressure				RPP			
	Volume of hemorrhage	Pre-control	Post-infusion	Hemorrhage	Post-control	Pre-control	Post-infusion	Hemorrhage	Post-control
	ml/kg	*mm Hg*				*mm Hg*			
Group 1 (control)									
Mean±SE	16.9	156	156	129	162				
	1.7	7.0	6.5	6.0	5.0				
P value			NS	<0.001	<0.001				
Group 2 (RPP controlled)									
Mean±SE	17.9	163	164	137	170	128	127	126	129
	2.3	5.7	5.2	3.8	4.5	4.5	4.0	3.7	4.0
P value			NS	<0.001	<0.001		NS	NS	NS
Group 3 (*d,l*-propranolol)									
Mean±SE	18.1	169	171	143	167				
	1.45	4.3	4.0	4.0	4.6				
P value			NS	<0.001	<0.001				
Group 4 (indomethacin)									
Mean±SE	15.9	163	174	144	173				
	1.9	4.0	1.6	1.4	2.0				
P value			<0.05	<0.001	<0.001				
Group 5 (RPP controlled and *d,l*-propranolol)									
Mean±SE	15.6	156	163	139	169	126	130	131	131
	1.48	6.0	6.0	6.0	5.0	5.0	5.0	5.0	5.0
P value			NS	<0.001	<0.001		NS	NS	NS
Group 6 (*d,l*-propranolol and indomethacin)									
Mean±SE	15.0	162	168	145	171				
	1.7	2.3	1.8	1.2	1.7				
P value			NS	<0.001	<0.001				
Group 7 (RPP controlled and indomethacin)									
Mean±SE	18.9	171	178	148	176	135	136	135	135
	2.0	2.0	1.0	1.5	2.3	4.0	5.0	5.0	4.0
P value			<0.05	<0.001	<0.001		NS	NS	NS

stimulated renin release in animals pretreated with indomethacin in doses that have been demonstrated to provide blockade of prostaglandin synthesis (group 4). These results confirm the findings of earlier studies in the dog from our laboratory suggesting that renin release during hemorrhage is not dependent on intact prostaglandin synthesis (12, 23). Because the present studies were performed in anesthetized dogs, it is appropriate to indicate that renal prostaglandin release seems to be higher in anesthetized than conscious dogs (21). Hemorrhage, however, has been demonstrated to activate prostaglandin release in both conscious (22) and anesthetized (12) dogs.

The failure of RPP control, beta adrenergic blockade, or prostaglandin inhibition alone to block the renin response to hemorrhage suggested either that multiple stimuli to renin release were occurring or that stimulation of the macula densa may have provided the primary stimulus. The decrease in urinary sodium excretion during hemorrhage was comparable with this possibility. Although the results of Witty et al. (9) in the nonfiltering kidney which demonstrate an increase in renin release during the absence of detectable filtration make the macula densa unlikely to be the primary pathway, the role of this mechanism in the filtering state cannot be excluded. Studies, therefore, were undertaken to examine whether a combination of pathways are responsible for renin release during hypotensive hemorrhage.

The first possibility examined was whether a combination of stimulation of the beta adrenergic receptor and baroreceptor pathways occur in the dog during hypotensive hemorrhage. Studies in which both RPP was controlled and beta adrenergic blockade induced before hemorrhage, therefore, were performed. The results demonstrated that hypotensive hemorrhage that lowered blood pressure by 15–17% did not stimulate renin activity or renin secretion in the presence of a combination beta blockade and control of RPP. These results therefore are compatible with the proposal that with this degree of hemorrhage activation of the renin angiotensin system is due to the combination of stimulation of beta adrenergic receptors and baroreceptors. In addition, because urinary sodium did

TABLE I (*Continued*)

Cardiac output				Glomerular filtration rate				Renal blood flow				Sodium excretion			
Pre-control	Post infusion	Hemorrhage	Post-control	Pre-control	Post-infusion	Hemorrhage	Post-control	Pre-control	Post-infusion	Hemorrhage	Post-control	Pre-control	Post-infusion	Hemorrhage	Post-control
liters/min				*ml/min*				*ml/min*				*μeq/min*			
3.57	3.13	2.09	2.59	44.2	44.2	36.8	42.6	299	262	209	233	149	159	58	169
0.30	0.30	0.14	0.13	3.5	2.6	4.4	2.3	23	19	27	14	48	45	14	39
	NS	<0.005	NS		NS	<0.05	NS		NS	<0.05	NS		NS	<0.05	<0.01
3.90	3.54	2.13	2.83	46.8	46.3	32.6	42.1	320	288	176	223	55	72	26	75
0.50	0.40	0.30	0.51	3.3	3.2	2.4	3.2	26	26	17	36	16	16	7	16
	NS	<0.001	<0.05		NS	<0.001	<0.05		NS	<0.01	NS		NS	<0.05	<0.05
4.23	3.40	1.83	3.30	47.9	47.6	43.1	45.1	336	285	202	219	232	280	76	189
0.65	0.40	0.31	0.80	2.2	3.0	5.0	4.0	32	31	31	19	38	44	16	19
	NS	<0.05	<0.05		NS	NS	NS		<0.05	<0.001	NS		NS	<0.001	<0.005
3.11	2.66	1.79	2.08	40.9	41.8	37.0	37.4	314	223	160	176	122	125	60	192
0.29	0.21	0.22	0.15	2.0	2.0	3.0	2.0	27	21	14	8	24	38	15	62
	NS	<0.001	NS		NS	<0.05	NS		<0.001	<0.05	NS		NS	<0.05	<0.01
3.33	2.78	1.86	2.43	42.3	40.8	40.6	40.1	255	204	178	181	76	67	78	74
0.31	0.30	0.30	0.31	2.5	2.0	4.0	2.0	17	12	13	11	13	8	15	14
	NS	<0.005	<0.05		NS	NS	NS		<0.01	NS	NS		NS	NS	NS
3.62	2.48	1.84	2.70	32.5	40.1	38.3	39.0	363	230	187	202	151	183	99	197
0.31	0.25	0.22	0.37	2.2	1.9	2.4	2.2	36	23	20	23	21	53	35	50
	<0.05	<0.05	<0.05		NS	NS	NS		<0.001	NS	NS		NS	<0.05	<0.05
4.05	3.36	2.22	2.76	41.9	41.9	30.3	39.3	337	230	132	166	83	101	20	82
0.42	0.4	0.40	0.40	2.0	2.0	3.0	2.0	29	16	14	9	24	30	6	24
	<0.05	<0.001	<0.01		NS	<0.001	<0.001		<0.001	<0.001	NS		NS	<0.005	<0.05

not decrease in this group of animals, a failure to activate the macula densa could be also implicated.

The present results demonstrating a multifactorial mechanism for renin release in the filtering kidney also provide a potential explanation for the failure of inhibition of prostaglandin synthesis alone to block renin release during hemorrhage. Recent results by Data et al. (17), in the nonfiltering kidney, suggest that the baroreceptor pathway for renin release is primarily dependent on an intact pathway for prostaglandin synthesis. If this is the case, and the beta receptors for renin release remain intact, then prostaglandin inhibition alone would not be expected to block the renin response to hypotensive hemorrhage. This possibility provided the basis for the next series of experiments (group 6) in which beta blockade with *d,l*-propranolol was combined with indomethacin-induced inhibition of prostaglandin synthesis in the absence of control of RPP. If intact prostaglandin pathways are necessary for the integrity of the baroreceptor mechanism, then beta adrenergic blockade with *d,l*-propranolol and prostaglandin inhibition with indomethacin might be expected to block the renin response to the degree of hypotensive hemorrhage used in the present study. This indeed proved to be the case and thus provided further evidence that beta adrenergic stimulation and prostaglandin-mediated baroreceptor activation constitute the primary pathways whereby hypotensive hemorrhage of the degree used in the present study stimulate renin release. It is also of note, that in this group of animals (group 6) the abolishment of renin secretion occurred despite a significant decrease in sodium excretion and presumably a diminished delivery of sodium to the macula densa. Inasmuch as the macula densa mechanism was activated by this degree of hemorrhage then the failure to observe an increase in renin release suggests that the macula densa, as well as the baroreceptor pathway, may be prostaglandin mediated.

The possibility remained, however, that any combination of maneuvers might block in a nonspecific manner the renin release that occurs in response to hypotensive hemorrhage. Thus, studies (group 7) were performed in which control of RPP and inhibition of

TABLE II
PRA and RSR during Hemorrhage

	PRA				RSR			
	Pre-control	Post-infusion	Hemorrhage	Post-control	Pre-control	Post-infusion	Hemorrhage	Post-control
	ng/ml per h				*ng/ml per h·ml/min*			
Group 1 (control)								
Mean	4.60	4.05	9.00	3.90	114	26	228	−40
±SE	1.70	1.70	2.70	1.22	64	41	74	53
P value		NS	<0.05	<0.01		NS	<0.005	<0.001
Group 2 (RPP controlled)								
Mean	3.10	2.63	5.28	2.06	134	17.5	170	−7.3
±SE	0.70	0.54	0.41	0.19	68	24	50	10
P value		NS	<0.005	<0.001		NS	<0.05	<0.05
Group 3 (*d,l*-propranolol)								
Mean	2.73	1.92	7.68	2.06	143	39	263	5
±SE	0.95	0.51	2.84	0.55	54	18	65	12
P value		NS	<0.05	<0.05		NS	<0.01	<0.005
Group 4 (indomethacin)								
Mean	1.32	0.65	2.00	0.71	128	49	197	24
±SE	0.53	0.24	0.46	0.22	34	22	52	11
P value		NS	<0.05	<0.05		NS	<0.001	<0.001
Group 5 (RPP controlled and *d,l*-propranolol)								
Mean	3.78	1.92	2.68	1.56	178	15.9	53	74
±SE	1.00	0.65	1.47	0.74	50	12	25	37
P value		NS	NS	NS		<0.05	NS	NS
Group 6 (*d,l*-propranolol and indomethacin)								
Mean	2.43	1.45	1.42	1.15	78.4	14	55	34.1
±SE	0.80	0.90	0.98	0.95	42	13	20	13
P value		NS	NS	NS		NS	NS	NS
Group 7 (RPP controlled and indomethacin)								
Mean	2.80	1.36	3.70	1.05	285	10	217	4.7
±SE	1.15	0.64	1.24	0.36	92	7	39	9
P value		NS	<0.05	<0.01		<0.005	<0.05	<0.05

prostaglandin synthesis were present during hypotensive hemorrhage. If either of these maneuvers alone block the baroreceptor mechanism and do not alter the integrity of beta adrenergic receptors, hypotensive hemorrhage in this setting would be expected to stimulate renin release. This indeed was found to be the case and thus provided support for the earlier results (groups 5 and 6) that incriminated both the beta adrenergic receptor and baroreceptor pathways in renin release during hypotensive hemorrhage.

In summary, the present in vivo results of studies in the normal filtering kidney support the earlier proposal from studies in the nonfiltering kidney that no single pathway is responsible for the stimulation of the renin-angiotensin system during hypotensive hemorrhage in the dog. Rather a combination of factors including stimulation of the beta adrenergic receptors and baroreceptors are involved in renin release during hypotensive hemorrhage of the degree (15–17% fall in blood pressure) examined in the present study. The results also demonstrate that normal prostaglandin synthesis is necessary for the integrity of the baroreceptor but not the beta adrenergic system for stimulating renin release during hypotensive hemorrhage. Furthermore, it must be noted that in all experimental groups with the exception of group 6 (beta blockade plus prostaglandin inhibition) the changes in urinary sodium excretion during hemorrhage are compatible with the interpretation that the macula densa mechanism is one of the mediators of renin release. However, the results of group 6 studies in which renin failed to rise despite a decrease in sodium excretion suggests either that the macula densa plays a secondary role in renin secretion during hemorrhage or, alternatively, that the macula

densa itself is prostaglandin dependent. This possibility is deserving of further investigation.

It is also relevant to note that the combination of RPP control or indomethacin and beta adrenergic blockade is most effective in attenuating the effects of hypotensive hemorrhage on renal hemodynamics. This may be because this combination of maneuvers blocks both the adrenergic (perhaps by a central effect) and renin-angiotensin mediated vasoconstrictor effects on the kidney. Such an attenuation in the renal ischemic response could contribute to the abolishment of the renin response to hemorrhage. Recent studies from our laboratory with renal denervation and angiotensin antagonism during hypotensive hemorrhage, indeed support the conclusion that renal nerve stimulation and activation of the renin-angiotensin system primarily modulate the renal ischemic of hypotensive hemorrhage (23). Whereas inhibition of prostaglandin synthesis was shown to enhance the renal ischemic effect during more severe hypotensive hemorrhage (12), this effect was clearly less with the degree of hemorrhage used in the present study. Lastly, if the macula densa mechanism was activated with the degree of hemorrhage used in the present study, then it seems likely that this pathway is also prostaglandin mediated.

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