Mechanisms of Portal Hypertension-Induced Alterations in Renal Hemodynamics, Renal Water Excretion, and Renin Secretion

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ABSTRACT Clinical states with portal venous hypertension are frequently associated with impairment in renal hemodynamics and water excretion, as well as increased renin secretion. In the present investigation, portal venous pressure (PVP) was increased in anesthetized dogs undergoing a water diuresis. Renal arterial pressure was maintained constant in all studies. As PVP was increased from 6 to 20 mm Hg, decreases in cardiac output (2.5–2.0 liter/min, $P < 0.05$) and mean arterial pressure (140–131 mm Hg, $P < 0.05$) were observed. Increases in PVP were also associated with decreases in glomerular filtration rate (GFR, 40–31 ml/min, $P < 0.001$), renal blood flow (RBF, 267–193 ml/min, $P < 0.001$), and increases in renin secretion (232–939 U/min, $P < 0.025$) in innervated kidneys. No significant change in either GFR or RBF and a decrease in renin secretion occurred with increases in PVP in denervated kidneys. To dissociate the changes in cardiac output and mean arterial pressure induced by increased PVP from the observed decreases in GFR and RBF, studies were performed on animals undergoing constriction of the thoracic inferior vena cava. In these studies, similar decreases in cardiac output and mean arterial pressure were not associated with significant changes in GFR or RBF. Increases in PVP also were associated with an antidiuresis as urine osmolality increased from 101 to 446 mosmol/kg H_2O ($P < 0.001$). This antidiuresis was significantly blunted but not abolished by acute hypophysectomy. In hypophysectomized animals, changes in free water clearance and urine flow were linearly correlated as PVP was increased. These studies indicate that increases in PVP result in decreases in GFR and RBF and increases in renin secretion mediated by increased renal adrenergic tone. Increased PVP is also associated with antidiuresis; this antidiuresis is mediated both by vasopressin release and by diminished tubular fluid delivery to the distal nephron.

INTRODUCTION

An impairment in glomerular filtration rate (GFR),[1] renal blood flow (RBF), and renal water excretion, as well as enhanced renin secretion, have been observed during hepatic cirrhosis (1–5). The cause of these abnormalities has not been elucidated. However, the lack of consistent histopathological alterations in kidneys of cirrhotic patients with renal failure is compatible with reversible renal hemodynamic alterations (6). The demonstration of restoration of normal renal function when kidneys from cirrhotic donors with renal failure are transplanted into recipients without liver disease also suggests a functional renal hemodynamic defect (7).

In this regard, several investigators have sought to establish a relationship between renal function and elevations in portal venous pressure (PVP), a frequent accompaniment of hepatic cirrhosis (8–13). Although most of these studies suggest that increases in PVP may result in renal functional changes, PVP was usually

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[1] *Abbreviations used in this paper:* CH_2O, free water clearance; GFR, glomerular filtration rate; PVP, portal venous pressure; RBF, renal blood flow; RPP, renal perfusion pressure; TIVC, thoracic inferior vena cava; U_{osm}, urinary osmolality.

elevated by complete portal vein occlusion, a maneuver that results in marked falls in mean arterial pressure and thus renders interpretation of results difficult. Moreover, a recent study (14) did not support previous conclusions (8–13) that increased PVP per se affects renal function. Rather, the changes in renal function were attributed to a fall in renal arterial pressure (14). In contrast to these renal hemodynamic results, no data are available on the effect of increased PVP on renal renin secretion or water excretion.

The present studies were therefore undertaken to determine the effects of acute elevations in PVP on GFR, RBF, renin secretion, and renal water excretion in animals in which partial portal vein occlusion was utilized and renal perfusion pressure (RPP) was maintained constant throughout the experiments. The results in these animal studies are of particular interest in view of recent reports suggesting that lowering PVP may improve some of the renal functional abnormalities associated with cirrhosis (15, 16).

METHODS

Experiments were performed on 25 mongrel dogs of either sex weighing 25–30 kg. Food was withheld 18 h before the experiment and all animals were allowed free access to water. The animals were anesthetized with intravenous pentobarbital (20–30 mg/kg), intubated, and ventilated with a Harvard respirator (Harvard Apparatus Co., Inc., Millis, Mass.). Seven animals underwent transbuccal hypophysectomy through the hard palate on the morning of the experiment (17). After induction of anesthesia, all animals received an intramuscular injection of 5 mg deoxycorticosterone in oil and dexamethasone (0.8 mg intramuscular and 0.8 mg intravenous). Glucocorticoid hormone was administered to avoid any glucocorticoid-mediated differences in renal water excretion between intact and hypophysectomized animals. Supramaximal doses of mineralocorticoid hormone were given to avoid any aldosterone-mediated changes in cation excretion.

Portal venous hypertension was produced by constriction of a polyethylene snare around the portal vein above the entrance of the splenic vein. The portal venous snare was placed via a small hole in the peritoneum through a right flank incision, by a retroperitoneal approach. An adjustable Blalock clamp was inserted around the aorta above both renal arteries to control RPP. RPP was controlled at a level determined from a series of preliminary experiments to be near a level induced by portal venous hypertension to 15–20 mm Hg. Polyethylene catheters were placed in both ureters and renal veins through bilateral flank incisions, by a retroperitoneal approach. Catheters also were placed in the aorta via the brachial artery and via the femoral artery for continuous measurement of arterial pressure above and below the Blalock clamp. All animals also had catheters inserted into the vena cava via the femoral vein for continuous measurement of renal venous pressure. PVP was continuously measured via a catheter inserted into the main portal vein through a tributary of the splenic vein via a left flank incision. All pressures were measured with Statham transducers (Statham Instruments Div., Gould Inc., Oxnard, Calif.). Kidneys were denervated by stripping all nerves and adventitia from the renal pedicle and by applying 95% alcohol. Clearances of inulin and para-aminohippuric acid were measured by standard methods (18). Renin was measured by radioimmunoassay (19) and individual kidney renin secretory rates were calculated by multiplying the difference between renal venous and aortic renin concentrations times renal plasma flow (20). A renin unit is arbitrarily defined as the amount of plasma renin activity necessary to generate 1 ng of angiotensin I in 1 ml plasma during 1 h of incubation at 37°C (20). Animals were administered 0.5–0.8 liters of 2.5% dextrose at 10–15 ml/min before the experiments to produce stable, hypotonic urine flow rates. Thereafter 2.5% dextrose was infused at rates equivalent to urine flow. The experiments were begun 1–2 h after completion of surgery and stabilization of urine flow. During the experiments, timed urine collection periods ranged from 5 to 10 min and arterial and renal venous samples were obtained at the midpoint of alternate urine collections. Cardiac output was measured every other collection period by the dye-dilution method (17). The experiments were carried out according to the following protocols:

Portal venous hypertension in animals with intact neurohypophyseal tracts: group I. In these experiments (13 dogs) urine flow was allowed to stabilize, then three to five control periods were obtained. The portal vein then was constricted to raise PVP to 15–25 mm Hg. After 30–60 min of equilibration, another three to five urine collection periods were obtained during continued portal vein constriction. Release of the portal vein constriction was followed by another 30–60 min equilibration period, and then three to five control urine collections were obtained. In all of these studies, renal arterial pressure was maintained constant by adjustment of the suprarenal Blalock clamp. In the initial studies in four dogs, neither kidney was denervated; subsequently, in three dogs, both kidneys were denervated, and in the remaining six dogs one kidney was denervated.

For comparison, in five dogs cardiac output was lowered by constriction of the thoracic inferior vena cava to decrease cardiac output as much or more as during portal venous constriction (21). Neither kidney was denervated in these studies.

Portal venous hypertension in hypophysectomized animals: group II. The studies in this group (seven dogs) were performed in acutely hypophysectomized animals to eliminate any change in endogenous vasopressin during portal vein constriction. One kidney was denervated in each animal. Otherwise, the protocol was the same as in group I studies.

The analytical procedures and calculations used in these studies have been referred to elsewhere (18). Inulin clearance was used as an index of GFR; RBF was calculated as renal plasma flow/1 − hematocrit. Statistical analyses were performed by a two-way analysis of variance with Scheffe's test for comparison within groups (22). A P value < 0.05 was considered significant (22).

RESULTS

The effects of portal venous hypertension in intact dogs: group I (Table I). In all intact animals acute elevations of PVP from 6±1 to 20±1 mm Hg resulted in modest, reversible decrements in cardiac output (from 2.5±0.3 to 2.0±0.3 liter/min, $P < 0.05$). Mean arterial pressure decreased insignificantly (140±7 to 131±7 mm Hg) as RPP was maintained constant (126±6 to 124±6

TABLE I

Effect of Acute Increases in PVP on Systemic and Renal

	Portal venous pressure			Cardiac output			Brachial artery pressure			Glomerular filtration rate			Renal vascular resistance		
	Before	PVP elevation	After	Before	PVP elevation	After	Before	PVP elevation	After	Before	PVP elevation	After	Before	PVP elevation	After
	mm Hg			*liter/min*			*mm Hg*			*ml/min*			*mm Hg/ml/min*		
Innervated kidneys (n = 13)															
±SEM	6±1	21±2	6±1	2.6±0.3	2.1±0.3	2.9±0.4	144±8	136±9	142±7	40±3	31±3	41±3	0.55±0.07	0.74±0.09	0.51±0.04
P value	<0.001	<0.001		NS	<0.01		NS	NS		<0.001	<0.001		<0.05	<0.01	
Denervated kidneys (n = 12)															
±SEM	6±1	19±1	6±1	2.3±0.2	1.9±0.2	2.5±0.2	135±5	126±5	132±6	40±3	42±3	47±3	0.51±0.05	0.53±0.05	0.43±0.04
P value	<0.001	<0.001		<0.01	<0.001		<0.05	NS		NS	<0.001		NS	NS	

mm Hg). The effects of portal venous hypertension on GFR, RBF, and renal vascular resistance were significantly different in denervated as compared to innervated kidneys. Therefore, the results for innervated and denervated kidneys are presented separately (Table I). In innervated kidneys, PVP elevations were associated with significant and reversible decreases in GFR (40±3 to 31±3 ml/min, $P < 0.001$) and RBF (267 ±18 to 193±20 ml/min, $P < 0.001$) as renal vascular resistance increased (0.55±0.07 to 0.74±0.09 mm Hg/ml per min, $P < 0.05$). No significant alterations in GFR (40±3 to 42±3 ml/min), RBF (256±16 to 248±17 ml/min) or renal vascular resistance (0.51± 0.05 to 0.53±0.05 mm Hg/ml per min) occurred with PVP elevations in denervated kidneys, despite comparable alterations in cardiac output and mean arterial pressure. Filtration fraction did not significantly change with increases in PVP in either innervated or denervated kidneys. These systemic and hemodynamic effects of increased PVP are summarized in Table I.

Renin secretion rates were measured in the six dogs in which one kidney was denervated (Fig. 1). With increased PVP, renin secretion increased from 232±20 to 939±80 U/min ($P < 0.025$) in innervated kidneys, while renin secretion in denervated kidneys actually decreased from 224±80 to −222±30 U/min ($P < 0.05$). The negative renin secretion rates may indicate net renin extraction by the kidney. Alternatively, these values may not be significantly different from zero and only represent methodological variability since three different measurements (i.e., arterial and venous renin activity and renal plasma flow) are involved in the determination of renin secretion rate.

An antidiuresis occurred in each experiment with elevations in PVP in these intact dogs undergoing a water diuresis. PVP elevations significantly increased urinary osmolality (U_{osm}) in both innervated (104±13 to 396±51 mosmol/kg H_2O, $P < 0.001$) and denervated (98±11 to 499±77 mosmol/kg H_2O, $P < 0.001$) kidneys. The increase in U_{osm} with PVP elevations were reversible on lowering of PVP. Parallel and reversible changes in free water clearance (C_{H_2O}) also were observed. There were no significant differences in changes in U_{osm} or C_{H_2O} during PVP elevations when innervated kidneys were compared with denervated kidneys. The antidiuresis with increases in PVP was associated with a significant decrement in solute excretion rate in innervated kidneys, while no alterations in solute excretion was observed in denervated kidneys.

TABLE II

Effect of Acute Increases in PVP on Systemic and Renal

	Portal venous pressure			Cardiac output			Brachial artery pressure			Glomerular filtration rate			Renal vascular resistance		
	Before	PVP elevation	After	Before	PVP elevation	After	Before	PVP elevation	After	Before	PVP elevation	After	Before	PVP elevation	After
	mm Hg			*liter/min*			*mm Hg*			*ml/min*			*mm Hg/ml/min*		
Innervated kidneys (n = 7)															
±SEM	7±1	20±1	7±1	2.4±0.2	1.8±0.1	2.3±0.2	130±4	114±5	131±8	32±3	25±3	35±3	0.60±0.06	0.80±0.09	0.65±0.07
P value	<0.001	<0.001		<0.001	<0.001		<0.025	<0.025		<0.05	<0.005		<0.05	<0.05	
Denervated kidneys (n = 7)															
±SEM	7±1	20±1	7±1	2.4±0.2	1.8±0.1	2.3±0.2	130±4	114±5	131±8	39±2	39±2	41±2	0.47±0.02	0.48±0.02	0.49±0.02
P value	<0.001	<0.001		<0.001	<0.001		<0.025	<0.025		NS	NS		NS	NS	

Hemodynamics and Renal Water Excretion in Intact Dogs

Filtration fraction			Solute excretion			Urine osmolality			Free water clearance		
Before	PVP elevation	After	Before	PVP elevation	After	Before	PVP elevation	After	Before	PVP elevation	After
			μosmol/min			*mosmol/kg H_2O*			*ml/min*		
0.26±0.02	0.26±0.01	0.25±0.01	234±27	171±26	283±24	104±13	396±51	163±29	1.79±0.4	−0.273±0.4	1.41±0.4
	NS	NS		<0.05	<0.001		<0.001	<0.001		<0.001	<0.005
0.29±0.01	0.31±0.02	0.28±0.01	245±18	265±25	328±24	98±11	499±97	144±21	2.35±0.4	−0.443±0.1	1.63±0.5
	NS	NS		NS	<0.001		<0.001	<0.001		<0.001	<0.001

Thoracic inferior vena cava (TIVC) constriction was performed in five dogs. Renal nerves were intact in all kidneys. TIVC constriction resulted in increments in femoral venous pressure from 6 to 12 mm Hg. The mean PVP with TIVC constriction in three animals in which it was measured was 9 mm Hg, as compared to 20 mm Hg during portal vein constriction. TIVC constriction resulted in greater decrements in cardiac output (2.8±0.1 to 1.8±0.1 liter/min, $P < 0.001$) and mean arterial pressure (144±6 to 124±5 mm Hg, $P < 0.05$) than observed in animals undergoing portal vein constriction. However, no significant alterations in GFR (41±4 to 40±3 ml/min), RBF (210±25 to 179±31 ml/min), or renal vascular resistance (0.53±0.06 to 0.61±0.12 mm Hg/ml per min) were observed with TIVC constriction as RPP was maintained constant at 115 mm Hg. An antidiuresis similar to that with increases in PVP was observed as U_{osm} increased (93±19 to 546±82 mosmol/kg H_2O, $P < 0.001$) and C_{H_2O} decreased (1.5±0.2 to −0.49±0.1 ml/min, $P < 0.001$) with TIVC constriction.

The effect of increases in PVP in hypophysectomized dogs: group II (Table II). Studies on this group of animals were performed to examine the role of vasopressin release in the antidiuresis of elevated PVP. Elevations of PVP to the same degree as those measured in intact animals resulted in similar decrements in cardiac output and mean arterial pressure. As in the intact animals, PVP elevations also resulted in significant, reversible decrements in GFR and RBF and increments in renal vascular resistance in innervated kidneys, while no change in these parameters occurred in denervated kidneys (Table II).

However, in contrast to intact animals, acute elevation of PVP in acutely hypophysectomized animals was not associated with as profound an antidiuresis. The mean U_{osm} increased only from 74±6 to 116±12 mosmol/kg H_2O ($P < 0.005$) in innervated kidneys and from 63±6 to 82±9 mosmol/kg H_2O ($P < 0.01$) in denervated kidneys. Parallel changes in C_{H_2O} were observed. By the unpaired Student t test, the increment in U_{osm} and decrement in C_{H_2O} with increased PVP in the hypophysectomized dogs were significantly less ($P < 0.001$) than the changes observed in intact animals. The minimal antidiuresis of PVP elevation in hypophysectomized dogs was examined in relationship to distal delivery of fluid to the diluting segment of the nephron (Fig. 2). In the absence of vasopressin, a linear correlation between urine flow and C_{H_2O} during both control and elevated PVP periods was observed ($r = 0.971$,

Hemodynamics and Renal Water Excretion in Hypophysectomized Dogs

Filtration fraction			Solute excretion			Urine osmolality			Free water clearance		
Before	PVP elevation	After	Before	PVP elevation	After	Before	PVP elevation	After	Before	PVP elevation	After
			μosmol/min			*mosmol/kg H_2O*			*ml/min*		
0.30±0.02	0.31±0.02	0.33±0.02	146±11	115±12	192±19	74±6	116±12	90±10	1.50±0.2	0.739±0.2	1.44±0.3
	NS	NS		NS	<0.001		<0.005	<0.05		<0.001	<0.005
0.32±0.02	0.32±0.02	0.35±0.02	162±13	162±13	197±18	63±6	82±9	74±7	2.15±0.3	1.51±0.2	2.05±0.3
	NS	NS		NS	<0.01		<0.01	NS		<0.05	<0.05

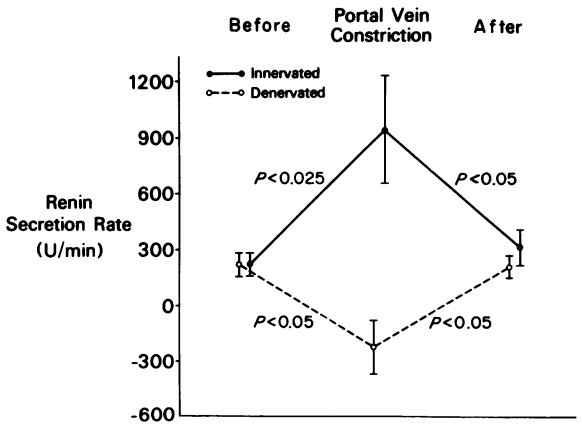

FIGURE 1 Effect of portal vein constriction on renin secretion rate.

$n = 42$, $P < 0.001$), suggesting that variations in these parameters was due to changes in distal fluid delivery.

DISCUSSION

Advanced hepatic cirrhosis with portal hypertension is generally associated with a diminished GFR and RBF, as well as impaired renal water excretion and increased renin secretion (10). The mechanisms of these abnormalities, however, have not been clarified. Several observations suggest that the alterations in renal hemodynamics associated with hepatic cirrhosis are functional (6, 7). Since elevations in PVP are nearly uniformly present when hepatic cirrhosis is associated with the above abnormalities, the present study was designed to examine the effect of acute elevations of PVP on renal function. The increases in PVP induced in the present study were similar to those measured clinically in patients with hepatic cirrhosis (23).

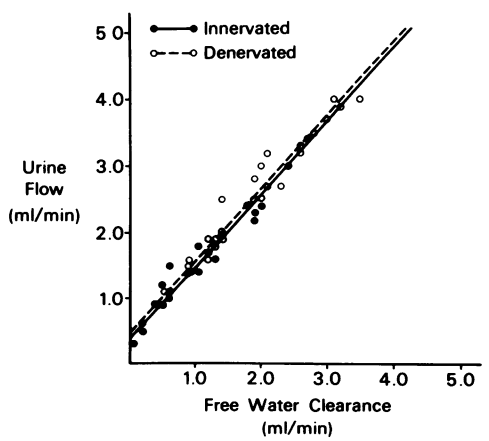

FIGURE 2 Linear correlation between urine flow rate and C_{H_2O} during control and portal vein constriction in hypophysectomized dogs undergoing a water diuresis. The open circles represent control collections and closed circles represent experimental collections during portal vein constriction.

In contrast to most other studies (8–13), the elevations in PVP in the present study were produced by partial occlusion of the portal vein, which resulted in only modest decreases in arterial pressure and cardiac output. Since changes in RPP could alter several of the parameters under study, renal arterial pressure was kept constant throughout all studies. Although RPP was constant, significant alterations in renal function were observed. These findings, therefore, do not support the previous suggestion that acute elevations in PVP in the anesthetized dog do not alter renal function per se, but rather any observed changes are due to decreases in renal arterial pressure (14).

In the present study, the acute elevations in PVP resulted in significant diminutions in GFR and RBF and increases in renal vascular resistance only in the innervated kidneys. Filtration fraction remained unchanged in these innervated kidneys, thus suggesting that the observed changes in GFR, RBF, and renal vascular resistance were due to constriction of the afferent arteriole. This interpretation is compatible with anatomical and histochemical studies that demonstrate adrenergic innervation of the afferent renal arteriole (24).

Although these results are compatible with an adrenergically mediated splanchno-renal reflex, it is possible that the reductions in arterial pressure and cardiac output induced during PVP elevations initiated the neurally mediated diminutions in GFR and RBF. For comparison, additional studies therefore were performed in which TIVC constriction resulted in decrements in cardiac output and mean arterial pressure equivalent to or greater than those produced with PVP elevations. The degree of elevation in PVP, however, was significantly less with TIVC constriction. In spite of the comparable or greater changes in systemic hemodynamics, no significant alterations in GFR, RBF, or renal vascular resistance were observed in the innervated kidney during TIVC constriction. In earlier studies from this laboratory, even greater TIVC constriction produced only minimal changes in renal hemodynamics, and renal denervation did not alter these results (21, 25). Taken together, therefore, these results indicate that the effect of PVP to diminish renal hemodynamics is mediated primarily by a splanchno-renal reflex involving adrenergic pathways. It is possible that a critical level of PVP is responsible for this reflex. An additional role of changes in arterial baroreceptor-renal reflexes, as initiated by the decreases in cardiac output and arterial pressure cannot be excluded, but in the absence of severe arterial hypotension, any such effect appears to be of secondary importance.

Elevations of PVP in the present study also were associated with increases in renin secretion. This effect

on renin secretion was demonstrable in the innervated but not denervated kidneys. Since GFR and RBF decreased in these innervated kidneys during elevations in PVP, activation of either the baroreceptor or macula densa mechanisms or both may have been involved in the enhanced rate of renin secretion. However, in a recent study from our laboratory, we have been able to dissociate the effect of renal nerve stimulation on renin secretion from changes in GFR, RBF, and solute excretion (26). This effect of renal nerve stimulation to stimulate renin secretion was abolished by *l*-propranolol, a beta adrenergic blocker, but not by *d*-propranolol, a membrane-stabilizing agent. These previous results, as well as the present results, are therefore compatible with an intrarenal beta adrenergic receptor controlling the rate of renin secretion. In any event, the present results demonstrate clearly that acute elevations in PVP are associated with an increase in renin secretion dependent on the presence of intact renal nerves.

The present study also demonstrated that acute elevations in PVP are associated with an antidiuresis. In contrast to the effects on renal hemodynamics and renin secretion, this antidiuresis occurred in both innervated and denervated kidneys. It was possible in the denervated kidneys to dissociate the antidiuresis of portal venous hypertension from renal nerves, decreases in GFR, RBF, and solute excretion, all of which are potential determinants of renal water excretion (21, 27, 28). Moreover, the absence of a profound antidiuresis with increasing PVP in acutely hypophysectomized dogs indicated that the antidiuresis was largely mediated by vasopressin. Although vasopressin release occurred in these animals, it is also possible that portal vein constriction could have affected renal water excretion by altering the metabolic clearance rate of vasopressin. Since TIVC constriction lowered cardiac output and arterial pressure at least as much as, but increased PVP less than the portal venous constriction, it seems likely that the changes in systemic hemodynamics primarily stimulated the release of vasopressin during acute PVP elevations (20). This interpretation is compatible with our previous observation that vasopressin release associated with TIVC constriction is baroreceptor mediated (21).

A slight, vasopressin-independent antidiuresis also was observed with elevated PVP in the present study. A linear correlation between changes in urine flow rate and C_{H_2O} were observed in these hypophysectomized dogs during portal vein constriction. In the absence of vasopressin, these results thus suggest that elevated PVP also diminishes renal water excretion by decreasing the rate of tubular fluid delivery to the distal nephron. This diminished fluid delivery was present in both innervated and denervated kidneys, thus suggesting an effect of enhanced proximal reabsorption in addition to any influence of a fall in GFR.

In the present study, animals were pretreated with dexamethasone and deoxycorticosterone. Since all groups of animals received these drugs, it is unlikely they accounted for the differences observed. In addition, we have previously demonstrated that dexamethasone administration does not alter the systemic or renal hemodynamic response to TIVC constriction (21). However, pretreatment with gluco- and mineral-corticoid drugs may have prevented the usual adrenocortical response to portal hypertension.

In summary, the results of the present studies indicate that acute portal venous hypertension decreases GFR and RBF, increases renin secretion, and impairs renal water excretion, independent of changes in renal arterial pressure. The results indicate that a splanchnorenal reflex causing increased renal adrenergic tone is primarily responsible for the diminution in renal hemodynamics and rise in renin secretion, while the antidiuresis is primarily vasopressin mediated. While these results have been noted during acute portal venous hypertension, additional studies will be required to determine if these effects persist during chronic portal venous hypertension.

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