

## Effect of Chronic Bile Duct Obstruction on Renal Handling of Salt and Water

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### Research Article

Renal sodium reabsorption and the concentrating and diluting abilities of the kidney were evaluated in the same trained mongrel dogs before and after chronic common bile duct ligation (BDL). Glomerular filtration rate (GFR) and  $C_{PAH}$  were not altered by BDL. The natriuretic response to a standardized infusion of 0.45% solution of NaCl was markedly blunted by BDL ( $P < 0.01$ ); calculated distal sodium delivery was significantly less in experiments after BDL than in control studies. Furthermore, the fractional reabsorption of sodium at the diluting segment for any given rate of distal delivery was enhanced by BDL. Similarly,  $C_{H_2O}/100$  ml GFR for a given sodium delivery was higher after BDL than control values. Maximal urinary concentration (Uosm-max) was lower after BDL, and the mean Uosm-max for the whole group of animals was 60% of the control value ( $P < 0.001$ ). Mean maximal  $T_{H_2O}/100$  ml GFR after BDL was not different from control values; however,  $T^c_{H_2O}/100$  ml GFR for a given  $C_{osm}/100$  ml GFR was lower after BDL in three dogs only. The sodium content of the inner part of renal medulla after BDL was significantly lower than the values obtained in control animals. The excretion of an oral water load in the conscious state was impaired after BDL; although all animals excreted hypotonic urine, urinary osmolality was usually higher after BDL [...]

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# Effect of Chronic Bile Duct Obstruction on Renal Handling of Salt and Water

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**ABSTRACT** Renal sodium reabsorption and the concentrating and diluting abilities of the kidney were evaluated in the same trained mongrel dogs before and after chronic common bile duct ligation (BDL). Glomerular filtration rate (GFR) and  $C_{PAH}$  were not altered by BDL. The natriuretic response to a standardized infusion of 0.45% solution of NaCl was markedly blunted by BDL ( $P < 0.01$ ); calculated distal sodium delivery was significantly less in experiments after BDL than in control studies. Furthermore, the fractional reabsorption of sodium at the diluting segment for any given rate of distal delivery was enhanced by BDL. Similarly,  $C_{H_2O}/100$  ml GFR for a given sodium delivery was higher after BDL than control values. Maximal urinary concentration (U<sub>osm-max</sub>) was lower after BDL, and the mean U<sub>osm-max</sub> for the whole group of animals was 60% of the control value ( $P < 0.001$ ). Mean maximal  $T^c_{H_2O}/100$  ml GFR after BDL was not different from control values; however,  $T^c_{H_2O}/100$  ml GFR for a given  $C_{osm}/100$  ml GFR was lower after BDL in three dogs only. The sodium content of the inner part of renal medulla after BDL was significantly lower than the values obtained in control animals. The excretion of an oral water load in the conscious state was impaired after BDL; although all animals excreted hypotonic urine, urinary osmolality was usually higher after BDL than in control studies. Maximal urinary concentration and the excretion of an oral water load were not affected by sham operation.

These studies demonstrate that chronic, common bile duct ligation is associated with (a) enhanced sodium

reabsorption both in the proximal and diluting segments of the nephron, (b) a defect in attaining maximal urinary concentration, (c) diminished sodium content in the renal papilla, and (d) impaired excretion of a water load. The results suggest that decreased distal delivery of sodium may underlie the abnormality in the concentrating mechanism and in the inability to normally excrete a water load. In addition, antidiuretic activity despite adequate hydration, may contribute to the impaired water diuresis. Chronic, common bile duct ligation appears to provide a readily available and reproducible model for the study of liver-kidney functional interrelationship.

## INTRODUCTION

Available data indicate that liver damage may affect renal function (1-3). Enhanced renal tubular sodium reabsorption, impaired renal concentrating ability, and abnormal water diuresis have been reported in patients with cirrhosis of the liver (4-8), and liver failure may be associated with renal failure as in the hepatorenal syndrome (9, 10). The exact mechanisms of these renal abnormalities in patients with liver disease are poorly understood.

Evidence also exists suggesting that obstructive jaundice may increase the risk of postoperative acute renal failure in humans (11), and it may predispose the kidney to ischemic damage in rodents (1, 2). In these studies, however, the various parameters of renal function during obstructive jaundice were not evaluated. Gliedman, Carroll, Popowitz, and Mullane (12) and Mullane and Gliedman (13) found that, in the dog, liver damage produced by ligation or division of the common bile duct was associated with sodium retention by the kidney and formation of ascites. These studies did not

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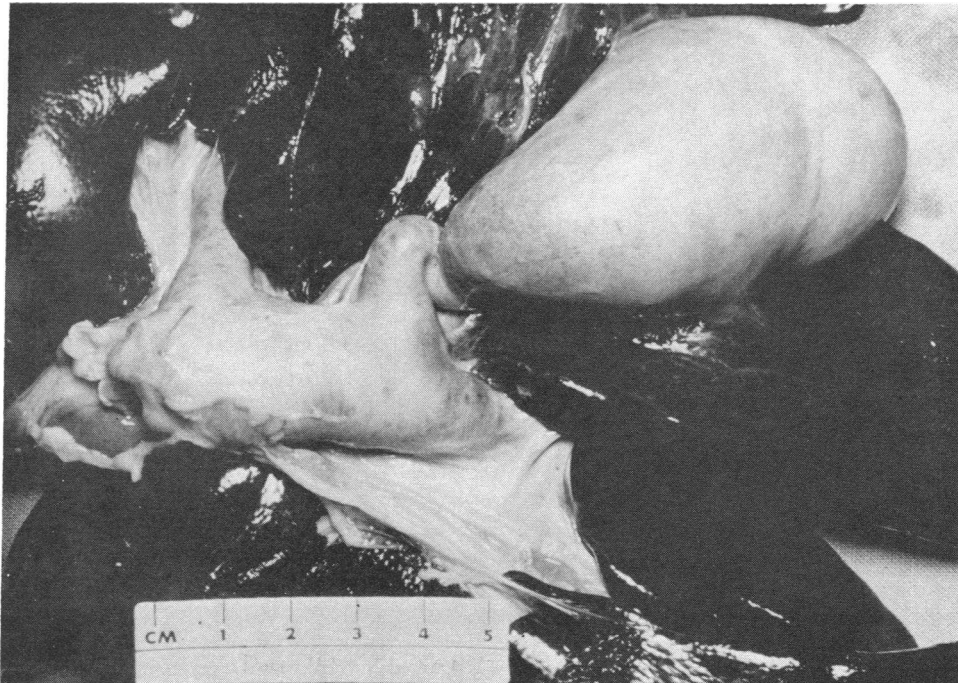


FIGURE 1 Dilatation of the gall bladder and biliary ducts as seen 19 days after the ligation of the common bile duct.

elucidate the tubular site of increased sodium reabsorption; also data on the effect of biliary tract obstruction on the concentrating and diluting abilities of the kidney are not available. Such information may help us to understand the mechanisms of sodium retention in these circumstances.

The present study was undertaken to investigate the characteristics of the renal concentrating and diluting mechanisms in dogs with chronic obstruction of the biliary tract, and to elucidate the site(s) in the nephron where enhanced sodium reabsorption occurs.

## METHODS

Studies were performed in nine female mongrel dogs weighing from 19–25 kg before and during a period of 2–7 wk after a double ligation of the common bile duct. These animals, therefore, served as their own control. 3–4 days were allowed between various studies in the same dog. The animals were maintained on a constant diet throughout the study; the dogs received 100 g of protein, 80 mEq of sodium, and 45 mEq of potassium per day. Before the study, all dogs were subjected to episiotomy, and they were trained to undergo experimental procedures while conscious. After the ligation procedure, jaundice developed in all dogs, and marked dilatation of the common bile and hepatic ducts and the gallbladder was found in all dogs on postmortem examination (Fig. 1). Some experiments were performed under anesthesia which was achieved with pentobarbital. In such studies, respiration was controlled by a Harvard respirator pump (Harvard Apparatus Co., Millis, Mass.), which was adjusted to a stroke volume of 10 ml/kg body

weight with a rate of 28 strokes/min. Glomerular filtration rate (GFR)<sup>1</sup> was measured by exogenous creatinine clearance and renal plasma flow by *p*-aminohippurate (PAH) clearance utilizing the standard techniques of priming and equilibration. Urine was collected from a retention catheter in the bladder, and complete emptying of the bladder was assured at the end of each period by an air wash. Blood samples were obtained with heparin at the midpoint of each clearance period from an indwelling needle in the jugular vein. The plasma was separated by centrifugation immediately after the blood specimens were drawn. The following studies were done:

*Water deprivation (eight dogs).* Measurements of urinary osmolality were done after 24 hr of fluid deprivation on two to four separate occasions before as well as after common bile duct ligation.

*Hypertonic saline infusion (eight dogs).* These studies were performed after 24 hr of fluid deprivation. After the induction of anesthesia, a priming dose of vasopressin, 30 mU/kg body weight, was given and this was followed by a sustaining infusion of vasopressin delivering 50 mU/kg per hr. After 45 min of equilibration of the priming dose of creatinine, PAH, and vasopressin, an infusion of 3% NaCl in water was started. The infusion was administered at increasing rates of 5, 10, and 15 ml/min with each rate given for 30 min. Urine was collected every 10 min during the entire period of the experiment.

<sup>1</sup> *Abbreviations used in this paper:* ADH, antidiuretic hormone; BDL, bile duct ligation;  $C_{H_2O}$ , free water clearance; *Cosm*, osmolal clearance; ECVE, extracellular fluid volume expansion; GFR, glomerular filtration rate; RPF, renal plasma flow; SGOT, glutamic oxalacetic transaminase;  $T_{H_2O}^a$ , free water absorption; *Uosm-max*, maximal urinary concentration.

*Hypotonic saline diuresis (eight dogs).* 1 hr before anesthesia, each animal received via an orogastric tube, a water load equivalent to 5% of body weight. After an equilibration period of 45 min, an infusion of hypotonic saline (0.45%) was administered intravenously at a rate which was progressively increased until a level of 1.5 ml/kg per min was reached; the infusion was then maintained until urine flow was stabilized. Urine was collected every 15 min. In each dog, the amounts of hypotonic saline per kilogram body weight infused before and after the ligation of the common bile duct were similar.

*Water diuresis.* This was carried out in five dogs while awake, standing, and loosely supported with a canvas sling. The animals were deprived of food but not water for 16 hr before the study. A water load equivalent to 5% of body weight was given via an orogastric tube. Urine was collected from an indwelling catheter every 30 min for a period of 4 hr. At the end of the experiment, venous blood was drawn and used for the determination of endogenous creatinine clearance.

In 10 normal dogs and in 4 dogs with the ligation of the common bile duct, the water and sodium content of the renal cortex, and of the outer, middle, and inner medulla were measured after 24 hr of water deprivation. The kidneys were removed and immediately immersed in a mixture of acetone and dry ice for 2–3 min. The frozen kidneys were cut into halves and tissue specimens were obtained from the cortex and the various parts of the medulla. After wet weight was determined, the samples were dried in an oven at 105°C for 48 hr, and then reweighed to determine water content. The specimens were then digested with 0.75 N nitric acid for 24 hr. Sodium was determined in the supernate by flame photometry.

In five additional dogs, the abdomen was opened and the common bile duct was exposed and manipulated. The concentrating ability of the kidneys (five dogs) and the excretion of the standard oral water load (four dogs) were evaluated before and after the sham operation. The temporal relationships of the studies after the sham operation were similar to those after the bile duct ligation.

Plasma and urine samples were analyzed for osmolality by measuring the depression of the freezing point with the Precision osmometer model 2007 (Precision Instrument Co., Palo Alto, Calif.), for sodium and potassium by the Instrumentation Laboratory flame photometer (Instrumentation Laboratory Inc., Lexington, Mass.), for alkaline phosphatase (14) for glutamic oxalacetic transaminase (SGOT) (15), and for the bilirubin (16). Creatinine, PAH, and urea nitrogen were determined with the Technicon Auto-Analyzer, (Technicon Instruments Corp., Ardsley, N. Y.). Osmolal clearance ( $C_{osm}$ ), free water clearance ( $C_{H_2O}$ ), and free water reabsorption ( $T_{H_2O}^c$ ) were calculated as follows:  $C_{osm} = U_{osm}/P_{osm} \times V$ ;  $C_{H_2O} = V - C_{osm}$ ; and  $T_{H_2O}^c = C_{osm} - V$ ; where  $U_{osm}$ ,  $P_{osm}$ , and  $V$  denote urinary osmolality, serum osmolality, and urine volume, respectively. Distal sodium delivery was approximated by  $C_{H_2O} + C_{Na}$  where  $C_{Na}$  represents sodium clearance. Although it could be argued that  $C_{Na} + C_{H_2O}$  may underestimate distal sodium delivery, since it is possible that some sodium and water may be reabsorbed by the collecting duct even during water diuresis. However, back diffusion of water under such circumstance is probably not substantial, and  $C_{Na} + C_{H_2O}$  is of practical use to approximately estimate distal sodium delivery. The per cent of sodium reabsorbed distal to the proximal tubule was calculated as  $C_{H_2O}/(C_{H_2O} + C_{Na}) \times 100$ . All the values for  $C_{osm}$ ,  $C_{H_2O}$ ,  $T_{H_2O}^c$ ,  $C_{Na}$ , and distal delivery of sodium were corrected for GFR of 100 ml/min.

## RESULTS

The animals tolerated the surgical procedure without complications, and the abdominal wound healed promptly. In the first few days after surgery some of the dogs had decreased appetite but the animals ate well and ingested their food completely thereafter. Ascites developed in two dogs approximately 2 months after surgery. Clinical jaundice appeared within the first few days after surgery; the blood levels of bilirubin increased to their highest levels of 2.5–9.1 mg/100 ml within the first 2 wk, and gradually fell to 0.8–4.5 mg/100 ml, thereafter. SGOT increased from control levels of 8–17 U to 93–185 U within the first 2 wk after the bile duct ligation; the SGOT levels remained elevated, thereafter. The levels of alkaline phosphatase in serum increased from control values of 0.9–2.3 Bessy-Lowry U to 60–322 U within the first 3 wk after the ligation procedure. Total proteins in serum estimated by refractometry did not show consistent changes after the bile duct ligation; the values were within the normal range in most measurements. The blood levels of BUN were within the normal range before and after the ligation procedure; urea nitrogen excretion in the urine during studies under normal hydration was  $6.6 \pm 1.6$  mg/min in control studies and  $6.8 \pm 1.6$  mg/min in experiments after bile duct ligation. The results of the liver function tests in this study are in agreement with those reported after bile duct ligation by Gliedman et al. (17).

The ligation of the bile duct did not appear to alter glomerular filtration rate and renal plasma flow (RPF). The mean values of several measurements of GFR and RPF performed in each dog before the ligation procedure were  $75 \pm 15$  and  $226 \pm 56$  ml/min, respectively. Similar evaluation of these two parameters over a period of up to 8 wk after the ligation of the bile duct yielded values of  $78 \pm 16$  ml/min for GFR and  $239 \pm 71$  ml/min for RPF.

In the normal animals, the mean maximal urinary osmolality ( $U_{osm-max}$ ) after 24 hr of water deprivation was  $1855 \pm 362$  (sd) mOsm/kg  $H_2O$ . It fell to  $1053 \pm 214$  ( $P < 0.001$ ) after the ligation of the bile duct. The inability to maximally concentrate the urine usually became apparent on 4–7 days after the surgical procedure; earlier measurements of  $U_{osm-max}$  were not done. Although  $U_{osm-max}$  in the same animal displayed considerable variations of up to 500 mOsm/kg  $H_2O$ , all values of  $U_{osm-max}$  before the ligation of the bile duct were higher than those observed after surgery (Fig. 2).

Fig. 3 depicts the data obtained during the measurement of free water reabsorption in each individual dog before and after the ligation of the common bile duct. In three animals after the ligation procedure, the levels of  $T_{H_2O}^c/100$  ml GFR for any given level of osmolal clearance were distinctly less than control values. In the

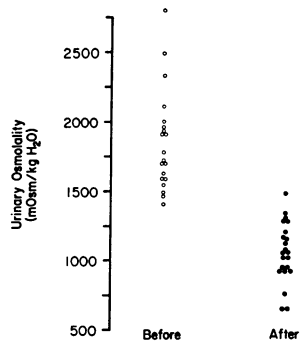


FIGURE 2 Maximal urinary osmolality after 24 hr of dehydration before (○) and after (●) the ligation of the common bile duct ( $P < 0.001$ ).

remainder of the animals,  $T^c_{H_2O}$  did not change or was even higher after ligation. The mean maximal  $T^c_{H_2O}/100$  ml GFR for the whole group of animals was  $5.8 \pm 0.97$  before ligation and  $5.3 \pm 1.19$  ml/min per 100 ml GFR after ligation.

Table I presents data of the sodium content of the renal cortex and medulla observed in 4 dogs after common bile duct ligation and in 10 other normal dogs. The mean values for sodium content of the inner part of the renal medulla in dogs with bile duct ligation was significantly lower than that of the control animals (mean  $\pm$ SD,  $900 \pm 120$ ,  $1538 \pm 58$  mEq/kg dry weight, respectively,  $P < 0.001$ ).

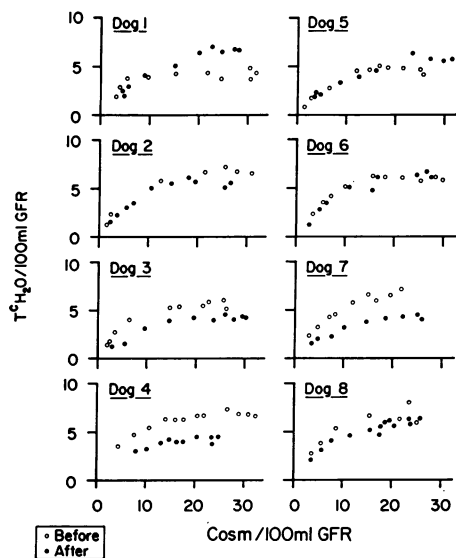


FIGURE 3 The relation between free water reabsorption ( $T^c_{H_2O}/100$  ml GFR) and osmolal clearance (Cosm/100 ml GFR) as observed during hypertonic saline infusion (3%). Open circles represent values before bile duct ligation and closed circles denote values after the ligation procedure.

TABLE I  
Sodium Content of the Renal Cortex and Medulla

Dog	Cortex	Medulla		
		Outer	Middle	Inner
		<i>mEq/kg dry weight</i>		
2	353	637	943	897
4	319	665	989	843
5	272	624	—	794
8	356	698	945	1069
Mean $\pm$ SD	$325 \pm 39$	$656 \pm 33$	$959 \pm 26$	$900 \pm 120$
Control dogs, n = 10	$307 \pm 10$	$674 \pm 58$	$1114 \pm 58$	$1538 \pm 54$
P	NS	NS	NS	<0.001

The effects of a standardized infusion of 0.45% saline on sodium clearance, distal sodium reabsorption, and free water generation for the periods of maximal free water clearance are presented in Table II and Fig. 4. As indicated above, the clearances of creatinine and PAH and the filtration fraction were not altered after the ligation of the bile duct. A striking and statistically significant decrease in the excretion and clearance of sodium ( $P < 0.01$ ) occurred after the ligation procedure. Mean  $C_{Na}/100$  ml GFR was  $7.7 \pm 2.7$  in the control studies and  $1.7 \pm 1.2$  ml/min per 100 ml GFR in the dogs with the obstruction of bile duct. After ligation, the values of distal sodium delivery were also significantly lower than the control levels ( $14.6 \pm 3.4$  and  $23.2 \pm 4.3$  ml/min per 100 ml GFR, respectively,  $P < 0.01$ ). After the bile duct ligation the calculated fractional reabsorption of sodium at the diluting segment was higher than control values for a given rate of sodium delivery (Fig. 5). During peak free water clearance,  $C_{H_2O}/100$  ml GFR was lower than control values in four animals after ligation, and the mean levels were  $15.5 \pm 3.0$  ml/min per GFR before ligation and  $12.9 \pm 2.7$  ml/min per 100 ml GFR after. However, the clearance of free water for a given rate of distal sodium delivery was higher in studies after bile duct ligation than in the control experiments; this was particularly evident at high rates of distal sodium delivery (Fig. 6).

The ability of the animals with bile duct ligation to excrete an oral water load was impaired. The mean fraction of the ingested water load excreted during the first 4 hr was significantly lower in studies after bile duct ligation than in the control experiments, Fig. 7 ( $35 \pm 15$  and  $76 \pm 5\%$ , respectively,  $P < 0.01$ ). The time of appearance of this abnormality after bile duct ligation varied from one dog to another, and it may be observed between 13–42 days. In Table III, data on the highest urine volume and lowest urinary osmolality achieved during the oral water load before and after bile duct ligation are shown. In every dog, the highest urine

TABLE II  
Data from Period of Maximal Free Water

Dog	V	C <sub>Cr</sub>	V/C <sub>Cr</sub> ×100	C <sub>PAH</sub>	FF	U <sub>osm</sub>
	<i>ml/min</i>	<i>ml/min</i>		<i>ml/min</i>		<i>mOsm/kg</i> <i>H<sub>2</sub>O</i>
Before ligation of common bile duct						
1	16.2	86.8	18.7	324.0	0.27	71
2	21.9	83.0	26.4	283.5	0.29	77
3	21.0	89.2	23.5	289.7	0.31	109
4	17.2	56.0	30.7	198.9	0.28	120
5	21.2	92.1	23.0	252.8	0.36	139
6	16.7	81.3	20.5	319.0	0.25	92
7	27.5	110.3	24.9	401.9	0.27	122
8	20.7	78.9	26.2	238.8	0.33	88
Mean	20.3	84.7	24.2	288.6	0.30	102
±SD	±3.6	±15.1	±3.7	±61.9	±0.03	±24
After ligation of common bile duct						
1	13.9	74.8	18.6	402.0	0.19	60
3	9.2	94.7	9.7	358.8	0.26	57
4	12.3	77.1	15.9	251.8	0.31	88
5	12.7	72.3	17.6	321.7	0.22	37
6	13.5	73.0	18.5	247.5	0.29	72
7	10.1	81.3	12.4	247.1	0.33	62
8	15.1	76.5	19.7	213.0	0.36	57
9	13.6	88.8	15.4	289.0	0.31	65
Mean	12.6	79.8	16.0	291.4	0.29	62
±SD	±2.0	±8.0	±3.4	±64.7	±0.05	±14
<i>P</i>	<0.01	NS	<i>P</i> < 0.01	NS	NS	<0.02

V, urine volume; C<sub>Cr</sub>, exogenous creatinine clearance; C<sub>PAH</sub>, *p*-aminohippuric acid clearance; U<sub>osm</sub>, urinary osmolality; C<sub>H<sub>2</sub>O</sub>, free water clearance; U<sub>Na</sub>V, urinary sodium; C<sub>Na</sub>, sodium clearance; U<sub>k</sub>V, urinary potassium; P<sub>Na</sub>, plasma sodium; and BDL, bile duct ligation.

Dog 2 died during the induction of anesthesia and therefore data after bile duct ligation is not available.

Dog 9 was studied only after bile duct ligation.

volume was lower after bile duct ligation. Although in all animals the urine was hypotonic during the water load, the minimal urinary osmolality was significantly higher after bile duct ligation in four of the five animals. However, dog 4 was able to achieve after bile duct ligation a minimal urinary osmolality similar to that observed in its control study. The complete study in this dog is presented in Fig. 8.

The results from the sham-operated animals are presented in Table IV. This procedure did not affect the concentration and dilution capacities of the kidney. The maximum urinary osmolality was 1895 ±209 mOsm/kg H<sub>2</sub>O before and 2004 ±244 mOsm/kg H<sub>2</sub>O after sham operation. The fraction of ingested water load excreted during the first 4 hr was 70 ±14% before and 73 ±14% after sham surgery. Also the highest urine flow and

lowest urinary osmolality were not altered by the sham procedure.

## DISCUSSION

The results of the present study demonstrate that chronic ligation of the bile duct in dogs is associated with (a) impaired excretion of intravenous saline load, (b) diminished ability to maximally concentrate the urine, and (c) impaired water diuresis after an oral water load.

Our results confirm the data of Mullane and Gliedman (13) who found that bile duct ligation in dogs is associated with sodium retention, and extend their observations by providing information regarding the site(s) in the nephron where the excessive sodium reabsorption occurs. At periods of peak free water clearance during

Clearance during the Infusion of 0.45% Saline

$C_{H_2O}$	$U_{NaV}$	$C_{Na}$	$C_{H_2O} + C_{Na}$	$\frac{C_{H_2O}}{C_{Na} + C_{H_2O}} \times 100$	$U_{kV}$	$P_{Na}$	Time after BDL
ml/min per 100 ml GFR	$\mu\text{Eq}/\text{min}$	ml/min per 100 ml GFR		%	$\mu\text{Eq}/\text{min}$	mEq/liter	wk
13.8	437	3.8	17.6	78.4	39	134	
19.0	613	5.4	24.4	78.2	74	137	
14.8	903	7.4	22.2	66.7	59	137	
19.6	877	11.6	31.2	62.8	72	135	
11.3	1166	9.4	20.7	54.6	66	134	
13.8	568	5.3	19.1	72.3	34	132	
13.9	1568	10.6	24.5	57.7	124	134	
17.9	890	8.2	26.1	68.4	39	137	
15.5	878	7.7	23.2	67.4	63	135	
$\pm 3.0$	$\pm 363$	$\pm 2.7$	$\pm 4.3$	$\pm 8.8$	$\pm 29$	$\pm 2$	
14.6	181	1.8	16.4	89.0	56	136	7
9.7	18	0.1	9.8	99.0	29	134	4
11.1	253	2.4	13.5	81.6	43	135	4
16.0	64	0.7	16.7	95.9	33	130	5
13.5	338	3.5	17.0	79.0	23	132	5
9.6	94	0.9	10.5	92.3	31	133	5
15.6	294	2.8	18.4	85.2	36	138	4
11.6	307	2.6	14.2	81.7	37	135	4
12.7	193	1.8	12.7	87.9	36	134	
$\pm 2.6$	$\pm 122$	$\pm 1.2$	$\pm 2.6$	$\pm 7.2$	$\pm 10$	$\pm 3$	
NS	$P < 0.01$	$< 0.01$	$< 0.01$	$< 0.01$	NS	NS	

hypotonic saline infusion,  $C_{Na}/100$  ml GFR in experiments performed after bile duct ligation was less than one-third of the values observed in control studies indicating that the natriuretic response to extracellular fluid volume expansion (ECVE) is blunted in dogs with bile duct obstruction.<sup>2</sup> Since ECVE decreases proximal reabsorption of sodium (18, 19), it is reasonable to assume that the biliary obstruction affects renal sodium reabsorption in the proximal tubule. This postulate is

<sup>2</sup> This phenomenon occurred despite greater degree of ECVE in animals with bile duct ligation. During hypotonic saline infusion after bile duct ligation, the animals excreted less urine than in control studies; therefore, the magnitude of ECVE was greater after bile duct ligation than in controls despite equal amount of saline infused.

further supported by the finding that distal sodium delivery was markedly reduced ( $P < 0.01$ ) after bile duct ligation. Sodium reabsorption in the diluting segment of the nephron appears to be altered as well. As demonstrated in Fig. 6, free water clearance for a given rate of distal delivery of sodium was higher in experiments after bile duct ligation than in control studies. This observation strongly indicates that a greater fraction of the sodium delivered to the diluting segment is being reabsorbed at this site.

Although careful measurements of basal sodium excretion were not carried out, numerous random determinations of sodium excretion in the morning hours showed values of less than  $5 \mu\text{Eq}/\text{min}$ . This observation and the development of frank ascites in two of our dogs and in several dogs of Gliedman et al. (12) indicates

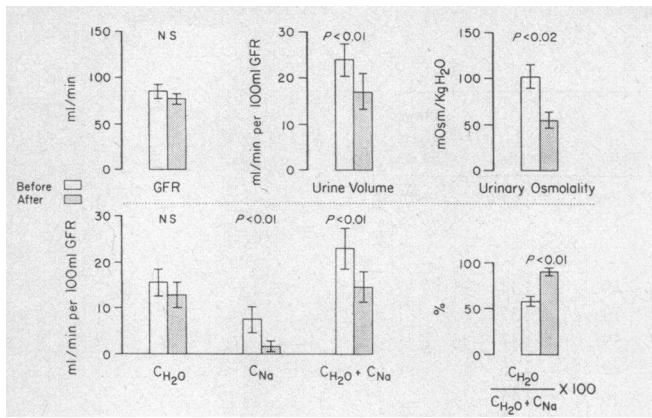


FIGURE 4 Summary of data during peak water clearance from all dogs receiving hypotonic saline infusion (0.45%). Open bars represent values for control studies and solid bars represent data from experiments after bile duct ligation. Brackets denote  $\pm 1$  SD.

that even under basal conditions, mild sodium retention may occur after bile duct ligation.

The dogs with bile duct ligation had a mean maximal urinary osmolality which was less than 60% of values observed in controls ( $P < 0.001$ ). This defect in urinary concentration could not be attributed to changes in dietary intake of protein and salt, GFR, excretion of urea, or serum potassium since these parameters were not altered after bile duct ligation. A reduction in medullary

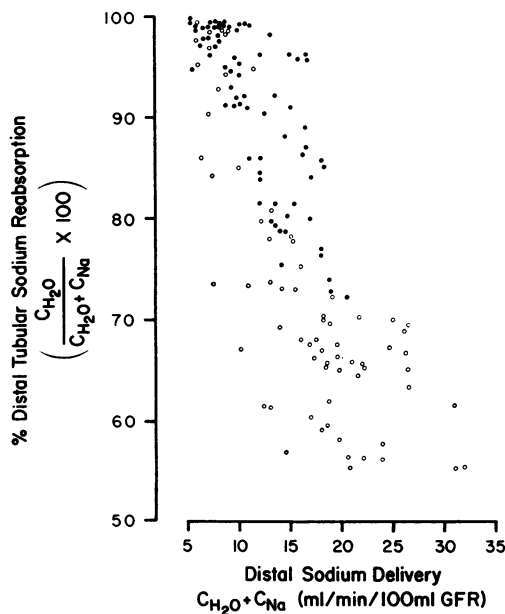


FIGURE 5 The relation between distal sodium delivery and the fractional reabsorption of sodium at the distal sites. Open circles are values from control studies and closed circles are values from studies after bile duct ligation.

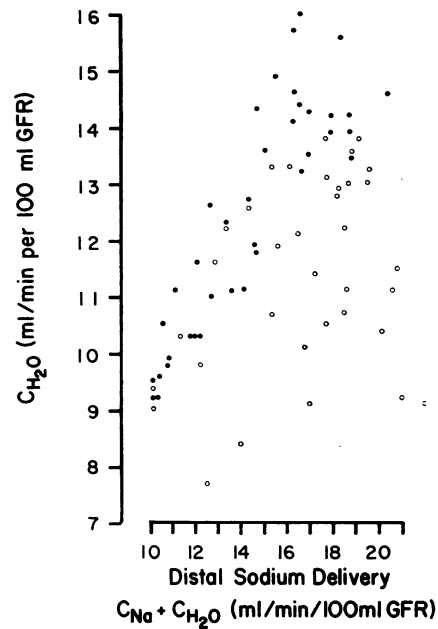


FIGURE 6 The relation between free water clearance ( $C_{H_2O}$ ) and distal sodium delivery. Open circles represent data from control studies and closed circles denote data from experiments after bile duct ligation.

hypertonicity may underlie this abnormality. Indeed, in 4 dogs the content of sodium in the papilla of the renal medulla was lower than that observed in 10 control animals (Table I). The mechanisms responsible for the reduction in medullary hypertonicity in animals with biliary obstruction are not clear. Diminished supply of sodium to the ascending loop of Henle, a decrease in the capacity to reabsorb sodium in this segment, or medullary washout of solutes may each or all contribute to lower medullary sodium content. Several lines of evidence discussed earlier indicate that in these animals sodium delivery to the loop of Henle is reduced but the capacity to transport sodium in this segment is enhanced.

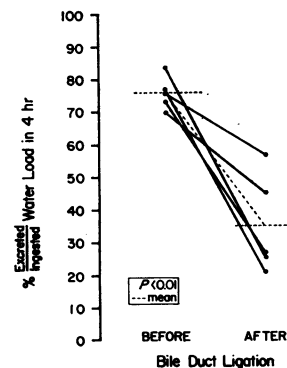


FIGURE 7 The per cent of the ingested water load excreted.



TABLE III

Highest Urine Volume and Lowest Urinary Osmolality Observed during a Standardized Oral Water Load before and after the Ligation of Common Bile Duct

Dog	Highest urine volume		Lowest urinary osmolality		C <sub>Cr</sub>	
	Before	After	Before	After	Before	After
	ml/min		mOsm/kg H <sub>2</sub> O			
1	4.4	2.7	65	153	70.4	73.2
3	5.3	3.9	81	131	81.5	84.3
4	5.9	4.6	46	53	61.3	70.7
6	4.8	4.5	65	126	72.1	68.8
8	9.4	3.8	46	149	77.5	71.9

The number of dogs are the same as in Table II. Paired statistical analysis of the data indicates that the value of highest urinary volume and the lowest urinary osmolality after common bile duct ligation are significantly different from values before ligation ( $P < 0.05$ ,  $< 0.01$  respectively). The means of creatinine clearance (C<sub>Cr</sub>) before and after bile duct ligation were not statistically different.

The mean maximal  $T^{\circ}_{H_2O}/100$  ml GFR for the whole group of animals determined during hypertonic saline infusion was not altered by bile duct ligation suggesting that sufficient sodium could be reabsorbed if sodium supply is adequate. Furthermore, the three dogs (3, 4, 7, Fig. 3) which had distinctly low  $T^{\circ}_{H_2O}/GFR$  after bile duct ligation were the same animals which had the lowest rate of distal delivery of sodium as evaluated during hypotonic saline infusion (Table II).

Impairment in the urinary concentrating ability has been found in patients with cirrhosis of the liver (5, 6).

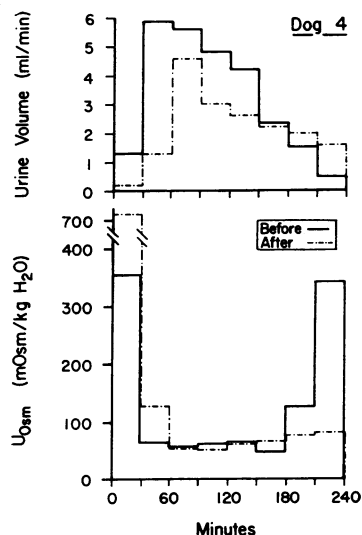


FIGURE 8 Urine volume and urinary osmolality during the first 4 hr after the ingestion of an oral water load in dog 4.

TABLE IV

Data on Urinary Dilution and Concentration before and after Sham Operation

Dog	Ingested water excreted		Highest urine volume		Lowest urinary osmolality		C <sub>Cr</sub>	
	Before	After	Before	After	Before	After	Before	After
	%		ml/min		mOsm/kg H <sub>2</sub> O			
Dilution								
A	65	61	3.7	3.9	42	53	41.8	49.3
B	91	73	5.1	4.3	48	48	49.2	42.7
D	61	93	4.1	4.3	47	45	39.2	41.0
E	64	64	3.0	3.2	38	36	41.2	40.3
Maximal urinary osmolality								
	Dog		Before	After				
Concentration								
	A		1811	1880				
	B		2036	2174				
	C		1887	2210				
	D		2140	2125				
	E		1600	1633				
	Mean		1895	2004				
	SD		±209	±244				

Several investigators have suggested that an increase in renal medullary circulation, by reducing medullary hypertonicity, may be responsible for the urinary concentrating defect in cirrhosis (5, 6, 20). Although renal cortical and medullary circulations were not evaluated in our studies, it is possible that chronic bile duct ligation may be associated with alterations in renal medullary circulation which may be partly responsible for the decrease in U<sub>osm</sub>-max observed in our dogs. Finally, an altered permeability of the collecting ducts to water could theoretically diminish back diffusion of water and cause a low U<sub>osm</sub>-max; the finding that maximal free water reabsorption was normal after bile duct ligation in five of the eight dogs does not support this contention.

The dogs after bile duct ligation excreted about 35% of a standard oral water load within 4 hr as compared with the excretion of approximately 76% of a similar load in the control studies. At least two factors may be responsible for this abnormality: a decrease in sodium delivery to the diluting segment and/or an increase in anti-diuretic hormone (ADH) activity. Evidence has already been presented demonstrating diminished sodium delivery to the diluting segment in dogs with chronic bile duct ligation. The results from dog 4 (Fig. 8) demonstrate that despite the inability to normally excrete the oral water load urinary osmolality fell after biliary obstruction to levels similar to those observed in the con-

trol experiment. This finding indicates that at least in this animal increased ADH activity was not responsible for the impaired water diuresis. However, in the other animals (1, 3, 6, and 8; Table III), an increase in ADH activity may have partly contributed to the inability to excrete the oral water load; although in these animals hypotonic urine was achieved, the lowest urinary osmolality was always higher after bile duct ligation than in the control studies.

The results of the present study clearly demonstrate that chronic ligation of the bile duct is associated with distinct alterations in the renal handling of sodium, namely an enhanced reabsorption both at the proximal and diluting segments of the nephron. Patients with cirrhosis of the liver (4, 21) and caval dogs (22, 23) which would have congestion of the liver (24), may display similar abnormalities in renal sodium reabsorption. These observations suggest that a normal liver with intact circulation and biliary drainage is essential for normal sodium homeostasis. Limited data are already available supporting this postulate. It has been reported that the natriuretic response to saline load in dogs is greater when the infusion is administered into the portal vein than into a systemic vein (25, 26). Also the exclusion of the liver from the circulation in dogs diminishes or abolishes the natriuretic response to saline load (27). It should be emphasized, however, that certain features of the abnormal renal function after bile duct ligation do not always resemble alterations of renal function in patients with cirrhosis. In some of these patients, and in contrast with dogs with bile duct ligation, glomerular filtration rate and renal plasma flow may be reduced; also, sodium and water excretion may be normal in patients with compensated cirrhosis (28).

The present study does not provide evidence as to how chronic bile duct obstruction affects renal sodium reabsorption. A fall in the concentration of serum albumin may play a role in some of the abnormalities observed. In dog 6 in Table II, serum albumin was 2.90 mg/100 ml before bile duct ligation and 2.70 mg/100 ml at the day of the study with hypotonic saline after the ligation procedure, and in dog 9, Table II, serum albumin was normal (3.15 mg/100 ml) 4 wk after bile duct ligation when his response to hypotonic saline was evaluated. It is evident that in these two dogs the response to saline infusion was blunted when the levels of serum albumin were normal. Gliedman et al. (17) reported a transient fall in the concentration of serum albumin around the 3rd wk after bile duct ligation with the values returning to normal around the 5th wk after surgery. Our studies with saline infusion were performed 7 wk after bile duct ligation in one dog, 5 wk after surgery in three dogs, and 4 wk after the ligation procedure in four dogs. It is reasonable to assume that the levels of serum albumin

at the day of the saline infusion were either normal or near normal in the six dogs where the concentrations of serum albumin were not measured. It seems, therefore, that hypoalbuminemia is not a major factor underlying the abnormalities in renal handling of sodium observed after bile duct ligation.

Finally, dogs with bile duct ligation appear to provide a reproducible and readily available experimental model for further evaluation of the liver-kidney functional interrelationship.

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