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Research Article

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We conclude that saline infusion depresses proximal sodium reabsorption in acute and chronic TVC dogs. Since saline loading markedly increases distal delivery without a concomitant natriuresis, enhanced distal reabsorption must play a major role in the sodium retention exhibited by chronic caval dogs. Redistribution of filtrate does not appear to be a factor […]

Proximal Tubular Function in Dogs with Thoracic Caval Constriction

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Abstract The effect of saline infusion on proximal sodium reabsorption was compared in normal dogs and in dogs with acute or chronic partial thoracic vena cava obstruction. After acute vena cava obstruction, proximal fractional sodium reabsorption rose by 74%. During continued caval obstruction, saline loading strikingly reduced proximal reabsorption but sodium excretion remained minimal. In chronic caval dogs, saline loading reduced proximal fractional sodium reabsorption by 31% but sodium excretion in the micropunctured kidney was only 41 μEq/min. After saline infusion in normal dogs, proximal fractional sodium reabsorption fell 39% while unilateral sodium excretion rose to 584 μEq/min.

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INTRODUCTION

Dogs with partial obstruction of the thoracic inferior vena cava (TVC dogs) demonstrate renal sodium retention; in chronic preparations, ascites and peripheral edema develop. Evidence from clearance experiments (1) has indicated that decreased sodium excretion is not due either to a decrease in filtered sodium or to enhanced aldosterone secretion. Dirks, Cirksena, and Berliner (2, 3) demonstrated that saline infusion inhibits proximal sodium reabsorption in normal dogs, but not in dogs in which the thoracic inferior vena cava is obstructed acutely. They concluded that renal sodium retention in acute caval dogs is due to altered proximal reabsorption and suggested that this mechanism may be important in chronic edematous states.

Acute obstruction of the vena cava produces marked systemic and renal hemodynamic changes (1, 3) which in themselves have been shown to increase proximal fractional reabsorption (4–7). No direct evaluation of the separate effect of such hemodynamic changes was possible from the studies of Cirksena et al. (3), since observations were made only after the combination of caval obstruction and saline infusion, but not after caval obstruction alone. It seemed possible that acute caval obstruction enhanced proximal reabsorption above the control level, while saline infusion did decrease reabsorption, but that the net effect was to return reabsorption towards control. This, in fact, appears to be the case: in the present studies, we found that acute caval obstruction alone markedly increases proximal fractional reabsorption, while subsequent saline infusion inhibits reabsorption as in normal dogs.

Because the acute reductions in glomerular filtration and renal blood flow characteristic of acute caval obstruction are not found in chronic caval dogs (1), we also investigated the effect of saline infusion on proximal reabsorption in chronic caval dogs with ascites. Our experiments do not permit conclusions regarding changes in basal proximal reabsorption in chronic caval dogs. Clearly demonstrated, however, is a depression of proximal sodium reabsorption in these edematous animals in response to acute saline infusion.

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METHODS

Experiments were performed on 12–25 kg mongrel dogs of both sexes, deprived of food and water 12–16 hr before micropuncture. Most animals received vasopressin tannate in oil, 10 U, and desoxycorticosterone acetate (DOCA),[1] 10 mg, intramuscularly the evening before and again 1–2 hr before micropuncture. Anesthesia was induced with pentobarbital, approximately 60 mg/2.5 kg body weight, and smaller sustaining doses were administered as required during micropuncture. An endotracheal tube was inserted in all dogs and respiration was assisted with a small animal respiration pump. Indwelling polyethylene catheters were inserted in two foreleg veins, one for saline (except in type 1 studies) and the other for inulin and *p*-aminohippurate (PAH), which were given in 0.9% NaCl at 0.5–0.7 ml/min. Catheters were placed into the aorta via both remoral arteries, one for measuring blood pressure, the second above the renal arteries for lissamine green injections. In acute obstruction experiments, the balloon of a double lumen balloon catheter was placed in the thoracic inferior vena cava via the femoral vein. Balloon location was confirmed at the end of each experiment. Inferior vena caval pressure below the balloon was monitored by attaching the second catheter lumen to a saline-filled manometer. In normal and chronic TVC dogs, inferior vena caval pressure was monitored by means of polyethylene catheter. The ureters were cannulated via bilateral flank incisions and the left kidney was mobilized for micropuncture. The peritoneum was separated as completely as possible from the renal capsule. To avoid entrance into the peritoneal cavity, the adherent portion of the peritoneum at the upper pole of the kidney was ligated before releasing the peritoneal reflection. This avoided any loss of ascitic fluid in chronic caval dogs. The kidney was immobilized on a plastic holder and a 1 cm section of renal capsule was removed. The exposed area was illuminated with a flexible fiber-optic rod and bathed with warm mineral oil.

The kidney surface was visualized using a stereoscopic microscope, and middle or late segments of proximal convoluted tubules were located by the injection of 10% lissamine green. The located segments were then punctured using oil-filled glass micropipetes 8–11 μ I.D. Timed collections were obtained after the rapid introduction of light-mineral oil colored with Sudan black in a volume large enough to extend at least several tubule diameters distal to the puncture site. Gentle to moderate aspiration was then usually required to keep this oil block stationary. After sample collection, the puncture site was marked by staining adjacent tubules with nigrosine and drawing a map. Six to ten control samples were collected. The same site was repunctured in an identical manner, after one of the maneuvers to be described. During micropuncture, urine collections were obtained at 20–30 min intervals with accompanying midpoint plasma sample. Plasma inulin concentration was maintained at approximately 80 mg per 100 ml by the constant infusion of 100 mg/ml inulin, after the appropriate loading dose. Plasma PAH concentration was maintained at approximately 2 mg per 100 ml in a similar manner.

[1] *Abbreviations used in this paper:* C_{In} and C_{PAH}, inulin and PAH clearance; DOCA, desoxycorticosterone acetate; GFR, glomerular filtration rate; IVC pressure, inferior vena cava pressure; P_{prot} and PNa, plasma protein and sodium concentrations. RPF, renal plasma flow; TF/P_{In}, tubular fluid to plasma concentration ratio of inulin; $U_{Na}V$, urinary sodium excretion; V_o, nephron GFR.

Four types of experiments were performed. (*a*) Hydropenic normal dogs: initial samples were obtained and after 1 hr without experimental intervention, repuncture collections were begun. (*b*) Isotonic saline infusion in normal dogs: collections were obtained before and during the infusion of saline. In this and all other types of experiments, except the first, saline was infused at 30 ml/min for 15 min, then at 10–12 ml/min throughout the remainder of the experiment. Recollections were begun 60 min after the start of saline infusion. In six dogs, repunctures were collected alternately with fluid from tubules not entered previously. (*c*) Acute thoracic vena cava (TVC) obstruction: observations were made before and after caval obstruction alone and again during continued obstruction and simultaneous isotonic saline infusion. After control clearance and micropuncture collections, the balloon in the thoracic inferior vena cava was inflated until venous pressure below the obstruction increased by more than 10 cm. 30 min after venous pressure became steady, first repuncture and clearance collections were obtained. Isotonic saline was then infused while balloon inflation was maintained. 1 hr after initiating saline infusion, the second repuncture samples and clearance periods were collected. (*d*) Chronic TVC obstruction: the thoracic vena cava was partially occluded with umbilical tape 3–8 days before an experiment. Only dogs having clearly demonstrable ascites and caval pressures greater than 10 cm saline were studied during acute saline infusion. Tubular punctures were performed and clearance periods collected before and after saline infusion. If sodium excretion after saline exceeded 150 μEq/min, the experiment was discarded. In four chronic caval dogs, after saline loading, repuncture collections were alternated with collections from previously unpunctured tubules.

Sodium in plasma and urine was measured using the IL flame photometer (Instrumentation Laboratory Inc., Lexington, Mass.). Plasma and urine inulin determinations were performed by the method of Davidson and Sackner (8) on the AutoAnalyzer (Technicon Instruments Corporation, Ardsley, N. Y.). Plasma protein was estimated using a Hitachi refractometer (Hitachi America Ltd., Electric Motor Div., Indianapolis, Ind.). The volume of timed tubular fluid samples was obtained by direct transfer to a 100 μ diameter constant bore glass capillary tube. The sample was placed into a drop of 30% silicone–70% chloroform solution to prevent evaporation. Tubular fluid inulin concentration was measured by the fluorometric method of Vurek and Pegram (9). Sample analysis was performed in triplicate. Standard statistical methods were used: means ± 1 SE are reported and based on the average results for each animal unless otherwise stated. The *t* test was used to determine statistical significance.

RESULTS

Normal dogs: hydropenic. 51 tubules were repunctured during hydropenia in eight dogs. The tubular fluid to plasma inulin concentration $(TF/P)_{In}$ repuncture ratio, experimental/control, was 1.02 ± 0.03. The repuncture ratio for nephron filtration rate in the same tubules was 1.08 ± 0.03 ($P < 0.05$). (Values represent mean ± 1 SE of tubular samples.)

Normal dogs. The results obtained before and after saline loading in 13 normal hydropenic dogs are found in Table I and Fig. 1. Volume expansion resulted in a brisk natriuresis. Glomerular filtration rate (GFR) and

TABLE I

Summary of Data in Normal and Chronic TVC Dogs before and after Saline Loading

	Normal (n = 13)		Chronic TVC (n = 12)	
	Hydropenia	Saline	Hydropenia	Saline
$(TF/P)_{In}$	1.45 ±0.05	1.22 ±0.04	1.55 ±0.07	1.35 ±0.06
Fractional reabsorption, %	29.5 ±2.5	17.6 ±2.3	34.6 ±3.3	24.1 ±2.9
C_{In}, *ml/min*	35.4 ±2.9	38.9 ±3.7	35.5 ±2.9	31.9 ±2.0
C_{PAH}, *ml/min*	93.3 ±9.4	91.0 ±10.5	86.0 ±10.1	71 ±7.0
BP, *mm Hg*	131 ±4.8	142 ±7.2	122 ±4.9	116 ±4.8
P_{prot}, *g/100 ml*	5.9 ±0.12	4.3 ±0.17	4.8 ±0.17	3.0 ±0.16
IVC pressure, *cm* H_2O	—	—	15 ±1.0	20 ±1.3
PNa, *mEq/liter*	144 ±2.3	145 ±2.3	138 ±2.3	138 ±2.1
$U_{Na}V$, *μEq/min*	28 ±6.3	584 ±65	3 ±0.6	41 ±9.5

Values are means ±SE; Abbreviations: C_{In}, C_{PAH}, inulin and PAH clearance of micropunctured kidney; P_{prot} and PNa, plasma protein and sodium concentrations; ICV pressure, inferior vena cava pressure; $U_{Na}V$, urinary sodium excretion.

filtration fraction tended to rise slightly ($P > 0.1$) while renal plasma flow (RPF) did not change. Mean blood pressure tended to increase ($P > 0.05$), while plasma protein fell from 5.9 to 4.3 g per 100 ml. In 13 dogs, (67 repunctured nephrons), proximal TF/P inulin fell from 1.45 ±0.05 to 1.22 ±0.04 ($P < 0.01$), a 39% fall in fractional sodium reabsorption. These results are similar to data from other laboratories (2, 10).

Chronic thoracic vena caval constriction. The results obtained in 12 dogs studied after previous TVC ligation are found in Table I and Figs. 1 and 2. In the experimental kidney, GFR decreased slightly ($P > 0.1$) while RPF fell an average of 16 ml/min ($P < 0.05$). Filtration fraction rose slightly. Mean sodium excretion was only 41 μEq/min after volume expansion. Plasma protein concentration fell from 4.8 g per 100 ml to 3.0 g per 100 ml after saline. Mean systemic blood pressure tended to decrease slightly from 122 to 116 mm Hg ($P > 0.1$) while inferior vena caval pressure rose from 15 to 20 cm H_2O. In 12 dogs (53 repunctured proximal tubules), TF/P inulin fell from 1.55 ±0.07 to 1.35 ±0.06 ($P < 0.01$), representing a 31% depression in fractional reabsorption (Figs. 1 and 2). A representative experiment is shown in Table II.

Acute thoracic vena caval obstruction. The data from the acute TVC studies are summarized in Table III, and Figs. 1 and 3. In five dogs after acute TVC obstruction, caval pressure was elevated to a mean of 11 cm above

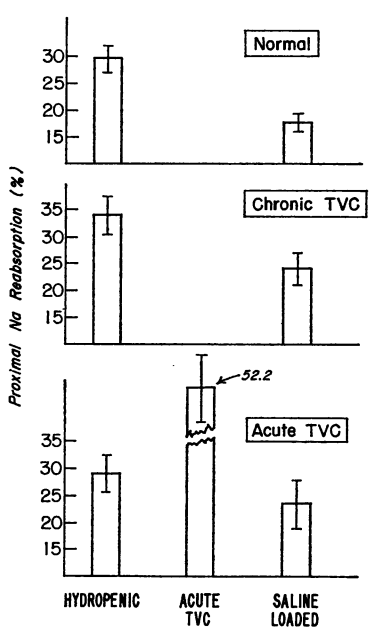

FIGURE 1 Fractional reabsorption of sodium in the proximal tubule. The data in each panel represent repunctures.

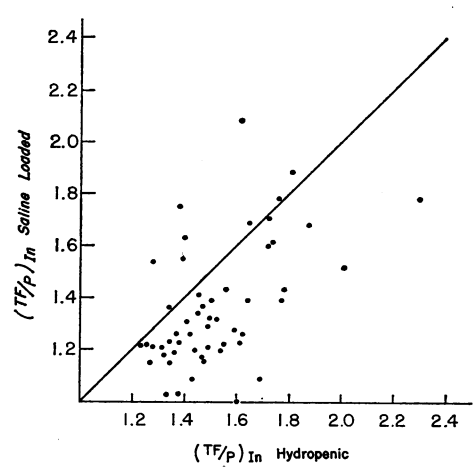

FIGURE 2 Comparison of proximal TF/P inulin in chronic caval dogs before and after saline loading. Each point represents one repuncture. Points below the identity line indicate a decrease in TF/P inulin.

TABLE II

A Representative Experiment in a Chronic TVC Dog

Time	Sample No.	C_{In}	C_{PAH}	$U_{Na}V$	P_{prot}	$(TF/P)_{In}$	V_0
min		*ml/min*	*ml/min*	*μEq/min*	*g/100 ml*		*nl/min*
−8 days	TVC constriction weight 14.5 kg						
−60	Inferior vena cava pressure, 15.5 cm H_2O, weight 20 kg						
0	Infusion I: inulin, 100 mg/ml; and PAH, 5 mg/ml at 0.7 ml/min						
232	T_{1A}					1.28	67
240	T_{2A}					1.49	75
263		22	43	3	3.8		
266	T_{3A}					1.38	63
277	T_{4A}					1.23	59
284	T_{5A}					1.37	66
298	T_{6A}					1.42	87
303		27	47	3	3.7		
306	0.9% Na Cl infused at 30 ml/min for 15 min, continued at 12 ml/min						
372	IVC pressure 22.5 cm H_2O						
376	T_7					1.40	53
381	T_{4B}					1.13	74
386	T_8					1.27	124
394	T_{3B}					1.23	105
398	T_9					1.31	59
400		23	39	56	2.7		
413	T_{5B}					1.26	126
420	T_{6B}					1.26	103
432	T_{1B}					1.21	119
434		21	36	49	2.6		
441	T_{10}					1.21	53
451	T_{2B}					1.21	104
456	T_{11}					1.24	52
458	T_{12}					1.40	58
460	IVC pressure, 22.5 cm H_2O						
462		21	35	42	2.5		

Abbreviations: $(TF/P)_{In}$, tubular fluid to plasma concentration ratio of inulin; V_0, nephron GFR. Tubular samples designated A and B are obtained by repuncture of a single nephron. Other abbreviations as in Table I.

TABLE III

Summary of Data in Dogs during Hydropenia, after Acute Thoracic Vena Cava Obstruction, and Saline Loading with TVC Obstruction Maintained

	Hydropenia (n = 5)	Acute TVC (n = 5)	TVC + saline (n = 4)
$(TF/P)_{In}$	1.44 ±0.07	2.39 ±0.47	1.34 ±0.08
Fractional reabsorption, %	29.4 ±3.4	52.2 ±6.3	23.2 ±4.7
V_0, *nl/min*	106 ±15	63 ±14	—
C_{In}, *ml/min*	40 ±3.3	26 ±4.4	32 ±6.5
C_{PAH}, *ml/min*	110 ±16.2	55 ±13.9	63 ±15
BP, *mm Hg*	116 ±3	106 ±3	114 ±7
P_{prot}, *g/100 ml*	5.8 ±0.1	5.5 ±0.2	3.6 ±0.2
IVC pressure, *cmH_2O*	3.0 ±0.8	11 ±0.5	16 ±1
PNa, *mEq/liter*	144 ±2	145 ±2	144 ±1
$U_{Na}V$, *μEq/min*	23 ±3	8 ±3	49 ±10

Abbreviations as in Table I.

control. By inspection, total kidney volume appeared to be strikingly reduced. GFR fell from 40 to 26 ml/min and RPF decreased from 110 to 55 ml/min (Table III). Fractional sodium reabsorption rose from 29 to 52%, an increase of 74% ($P < 0.02$). Single nephron filtration rate (Vo) in repunctured tubules decreased from 106 nl/min to 63 nl/min after caval obstruction.

In four of these five animals, observations were made after saline infusion during continued TVC obstruction. Sodium excretion increased only slightly. GFR and RPF rose somewhat, toward control levels. In the four dogs in which 19 nephrons were punctured three times, fractional reabsorption increased from 29% during hydropenia to 53% after TVC obstruction alone, and fell to 23% after saline loading with TVC obstruction. Thus, in these four dogs, fractional sodium reabsorption fell by 56% after saline infusion ($P < 0.01$). The latter value was not significantly different from the original control fractional reabsorption in these dogs. A representative study is shown in Table IV.

Nephron filtration rate. In our early experiments, we found a striking increase in nephron filtration rate in normal and chronic TVC dogs after saline loading (11). Subsequently, Mandin, Israelit, Rector, and Seldin (12) suggested that the repuncture technique in dogs produced an artifactual increment in nephron filtration rate during saline infusion. Therefore, in later studies in six normal and four chronic TVC dogs, we measured nephron filtration rate in previously unpunctured nephrons after saline loading, as well as by the usual repuncture technique. The data from these 10 dogs are presented in Table V. In normal dogs, Vo was 64 nl/min during hydropenia, 66 nl/min after saline loading in fresh tubules, and 97 nl/min in repunctured nephrons ($P < 0.01$). Vo, during hydropenia in caval dogs, was 79 nl/min. After saline loading, Vo was unchanged in fresh tubules while in repunctured tubules it increased to 127 nl/min ($P < 0.01$). The ratio of nephron filtration rate to whole kidney GFR (Vo/GFR) was not statistically different in hydropenic normal and caval dogs. This ratio did not change after saline loading in either group, when data from fresh tubules are used, while the value rose strik-

TABLE IV

Acute Thoracic Vena Cava Constriction, Representative Experiment

Time	Sample No.	C_{In}	C_{PAH}	$U_{Na}V$	P_{prot}	$(TF/P)_{In}$	Vo
min		*ml/min*	*ml/min*	*μEq/min*	*g/100 ml*		*nl/min*
−14 hr	10 *mg* DOCA 10 U vasopressin in oil intramuscularly						
−60	10 *mg* DOCA, 10 U vasopressin in oil intramuscularly						
0	Infusion of inulin, 100 mg/ml and PAH, 5 mg/ml at 0.65 ml/min IVC pressure 2 cm H_2O						
91	T_{1A}			13		1.27	107
93		38	133	19	6.0		
110	T_{2A}					1.45	132
117		51	156	42	6.1		
141		46	157	37	6.2		
159	T_{3A}					1.30	146
166	T_{4A}					1.35	131
172		40			6.2		
178	IVC balloon inflated, IVC pressure 14.5 cm H_2O						
290	IVC pressure 14.0 cm H_2O						
291	T_{3B}					2.67	115
300	T_{4B}					2.28	50
314	T_{2B}					2.03	77
316		19			5.9		
325	T_{1B}					1.65	—
343		32	79	13	6.0		
356		34	75	26	6.0		
358	0.9% Na Cl infused at 25 ml/min for 28 min; continued at 11 ml/min						
404	IVC pressure, 14.5 cm H_2O						
405	T_{4C}					1.24	105
417		31	74	61	4.0		
439	T_{1C}					1.15	100
445		28	82	68	3.9		
454	IVC pressure, 15.5 cm H_2O						
455		37	83	76	3.4		

Abbreviations as in Tables I and II.

TABLE V

Kidney and Nephron Filtration Rate in Normal and Chronic TVC Dogs

	GFR		V_0			V_0/GFR × 10^6		
				Saline-infused			Saline-infused	
	Hydropenia	Saline-infused	Hydropenia	Repuncture	Fresh	Hydropenia	Repuncture	Fresh
Normal	29 ±4 (n = 6)	31 ±5	64 ±3	97 ±8 (n = 25)	66 ±6 (n = 30)	2.3 ±0.2	3.5 ±0.3	2.3 ±0.2
Chronic TVC	29 ±2 (n = 4)	29 ±2	79 ±4	127 ±16 (n = 16)	79 ±4 (n = 25)	2.9 ±0.3	5.1 ±0.9	2.8 ±0.2

Abbreviations: GFR, inulin clearance of micropunctured kidney.

ingly if repunctured nephrons are considered. It should be noted that the discrepancy in nephron GFR between fresh and repunctured tubules is attributable to differences in flow rates. $(TF/P)_{In}$ after saline was actually slightly higher in fresh tubules (1.24 ±0.02 vs. 1.17 ± 0.03) but still reflected a marked decrease in fractional reabsorption. There is no significance in small differences in $(TF/P)_{In}$ from nephrons punctured at only approximately comparable locations.

DISCUSSION

TVC dogs have been widely used as a model for the study of renal sodium retention in edema-forming states. Dirks, Cirksena, and Berliner (2, 3), found that saline infusion induced natriuresis and depressed proximal tubular sodium reabsorption in normal dogs, while neither response occurred in acute TVC dogs. They suggested, therefore, that renal sodium retention in TVC dogs could be due to the failure of proximal reabsorption to fall with volume expansion. However, acute obstruction of the vena cava produces important systemic and renal hemodynamic abnormalities. Blood pressure falls and renal blood flow and GFR are often markedly reduced (1, 3, 13). These hemodynamic changes presumably are due to acute sequestration of a part of the circulating blood volume below the caval obstruction and are comparable to those which occur during hemorrhage. Early studies (2) had shown no change in proximal fractional reabsorption when GFR was reduced acutely by renal artery clamping. Hence, Cirksena, and associates (3) discounted the influence of acutely reduced GFR on proximal reabsorption in their acute caval obstruction experiments. However, recent work both in dogs (4, 5) and in rats (6, 7) demonstrates that proximal fractional reabsorption is in fact enhanced when GFR is acutely reduced. Thus, it seemed likely that acute caval obstruction and saline loading had opposing effects on proximal reabsorption. Since Cirksena, Dirks, and Berliner (3) studied only the combination of acute caval obstruction and saline infusion, it seemed probable that they would have been unable to detect an independent effect of saline. The present studies indicate that this is indeed the case. Acute caval constriction produced marked increases in proximal fractional reabsorption, presumably related to major reductions in renal hemodynamics (Table III, Figs. 1 and 3).[2] Saline infusion subsequently increased renal hemodynamics toward normal, while proximal reabsorption de-

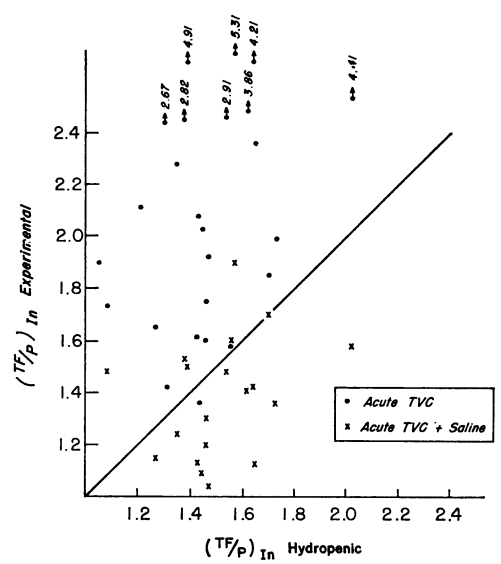

FIGURE 3 Comparison of proximal TF/P inulin in normal hydropenic dogs before and after acute obstruction of the vena cava and subsequent saline loading. Each (●) represents a repuncture after acute caval obstruction and (×) a third puncture in most of the same tubules while caval obstruction was continued, and after saline was infused.

[2] The magnitude of the increase in proximal fractional reabsorption is greater than that which occurred in other studies in which comparable reductions in renal hemodynamics were induced by arterial clamping (4–7). This implies an additional effect of caval obstruction on proximal reabsorption, beyond that attributable to changes in renal hemodynamics. A direct tubular effect of volume depletion has been postulated in the rat (14). However, it will require additional studies to determine definitively whether caval obstruction has a direct tubular effect in the dog.

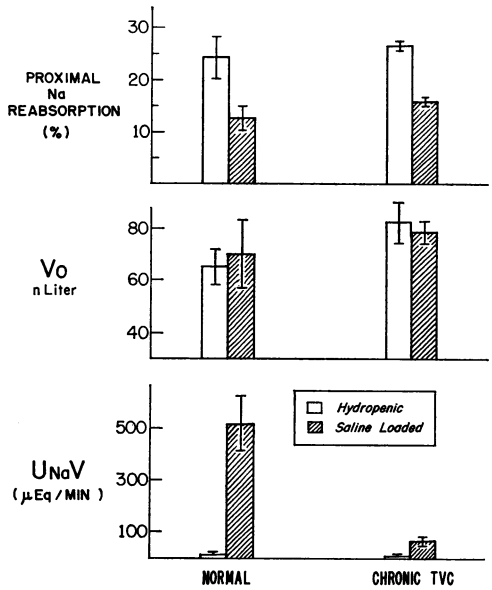

FIGURE 4 Proximal fractional sodium reabsorption, nephron filtration rate, and sodium excretion in normal and chronic caval dogs. These data are from the six normal and four chronic caval dogs in which nephron filtration rate was measured in fresh and repunctured tubules (see text). The values for sodium reabsorption are from repunctured tubules and the nephron filtration rates from freshly punctured tubules.

creased more than in normal dogs (Fig. 1). Thus, there is no evidence for any defect in the normal proximal tubular response to extracellular volume expansion in acute TVC dogs; it merely begins from an enhanced level of reabsorption. In the studies of Cirksena et al., proximal reabsorption was still increased above control during the combination of saline infusion and caval obstruction. In our experiments, proximal reabsorption was reduced slightly but not significantly below control under similar conditions. We cannot account definitively for this difference. It is possible that the hemodynamic effects of TVC obstruction were greater in the experiments of Cirksena et al., despite comparable elevations in vena caval pressure.

Our data indicated that sodium excretion in acute TVC dogs is influenced by factors of doubtful relevance to chronic states of sodium retention. Acute TVC dogs may be a suitable model only for the earliest stages in the development of edematous states. We proceeded, therefore, to study chronic caval dogs, a sodium retaining model in which renal hemodynamics are normal (1). In chronic caval dogs, proximal sodium reabsorption during hydropenia was not significantly different than in normal dogs. However, valid comparisons of $(TF/P)_{In}$ cannot be made between different dogs in our studies, since nephrons were punctured at only approximately comparable locations in the proximal tubule. Our data, therefore, do not permit any conclusions about basal proximal sodium reabsorption. From clearance experiments in water-loaded dogs, Kaloyanides, Cacciaguida, Pablo, and Porush (15) have suggested that reabsorption is increased in chronic caval dogs. Our data do demonstrate clearly that volume expansion in chronic caval dogs markedly depresses proximal fractional sodium reabsorption (Table I, Figs. 1 and 2). The decrease in reabsorption in normal dogs, 39 ±7%, was slightly larger than in caval dogs, 31 ±6%, but these values were not significantly different ($P > 0.2$). In addition, there is ample evidence that a difference in the magnitude of depression of proximal reabsorption does not, by itself, account for the difference in sodium excretion. This is illustrated in Fig. 4, in which data from selected normal and caval dogs are shown. These six normal and four caval dogs are all those in which nephron GFR measurements were made in previously unpunctured tubules after saline infusion. The depression of fractional reabsorption after saline loading is virtually identical in these two groups of dogs, yet sodium excretion was 519 μEq/min in the normal dogs and 65 μEq/min in the caval dogs. Moreover, differences in the magnitude of the increment in distal delivery after saline loading do not explain this difference in sodium excretion. Nephron GFR did not change after saline either in normal or in caval dogs, nor did plasma sodium concentration. Accounting for all these factors, the increment in distal delivery after saline in the two groups was wholly comparable.

Certain technical considerations about nephron filtration rate measurements bear comment. Mandin et al. (12) have reported that repuncture collections after saline loading in the dog artifactually raise nephron filtration rate. We originally reported (11) striking but comparable increases in nephron GFR after saline infusion in normal and caval dogs. However, our data (Table V) confirm Mandin et al.,[8] therefore we have used only collections from fresh tubules in estimating changes in distal load. Since the apparent increment in nephron GFR in our repuncture data was comparable in normal and chronic TVC dogs, the conclusion from these calculations would be qualitatively the same if repuncture data were used. The accuracy of measurements of nephron GFR has also been questioned on other technical grounds. It has been suggested that intratubular pressure changes produced by the micropuncture collection method alter nephron GFR (16). Even if the absolute values for nephron GFR prove to be incorrect, collections

[8] As noted in the first section of the Results, we also found a small (8%) but probably significant increase in nephron GFR in repunctured tubules even during hydropenia.

in normal and caval dogs were performed identically. Since our conclusions depend on comparative, not absolute values, nephron filtration rates and distal sodium delivery calculated from our data should be at least qualitatively correct. It seems clear that differences in the increment in distal load cannot account for the difference in sodium excretion after saline loading in normal and caval dogs.

A disproportionate increase in superficial nephron filtration rate has been suggested (17) as a possble factor in the natriuresis of saline loading. Our data (Table V) from fresh tubules show no evidence for redistribution of filtrate to superficial nephrons, nor is there any significant difference between normal and caval dogs in Vo/GFR, either in hydropenia or during saline infusion. Thus, there is no evidence that the large difference in sodium excretion is due to differences in the distribution of nephron filtration.

In light of the above-mentioned considerations, we conclude that distal reabsorptive mechanisms play a major role in limiting the natriuretic response to acute saline loads in dogs with chronic caval constriction. Kaloyanides et al. (15), reached a similar conclusion on the basis of clearance experiments during hypotonic diuresis in which they demonstrated that chronic caval dogs had enhanced distal sodium reabsorption. It should also be noted that their data (Tables I and II) suggest a depression of proximal reabsorption in caval dogs after saline loading. Our experiments directly demonstrate this point.

The overriding importance of distal tubular adjustments in natriuresis has also recently been stressed by others. Howards, Davis, Knox, Wright, and Berliner (10) found that proximal reabsorption in normal dogs could be depressed equally by hyperoncotic albumin or saline loading but sodium excretion increased markedly only in saline infused animals. Knox, Schneider, Dresser, and Lynch (18) found comparable increments in distal delivery, but large differences in sodium excretion, after hyperoncotic albumin in dogs with and without salt retention subsequent to mineralocorticoid treatment. In a preliminary report, Levy (19) has confirmed that proximal reabsorption in chronic caval dogs is depressed by saline infusion. Moreover, his data indicate that sodium reabsorption in the loop of Henle is enhanced in chronic caval dogs. The cause of the difference between normal and chronic caval dogs in distal sodium reabsorption is not apparent. It is possible that a natriuretic hormone which depresses distal sodium transport is released during volume expansion in normal but not caval dogs. However, microperfusion studies in the rat (20) failed to demonstrate depression of sodium reabsorptive capacity in the loop of Henle during saline infusion. If this applies to the dog, it would argue against a natriuretic hormone as the cause of lower sodium reabsorption in the loop of Henle in normal than in caval dogs as reported by Levy (19). An anti-natriuretic hormone other than aldosterone can be invoked, but there is no definite evidence for such a hormone. Alternatively, physical factors may be the principal determinants of distal sodium reabsorption and these may differ in normal and caval dogs. Friedler, Belleau, Martino, and Earley (13) have shown that saline loaded caval dogs are able to achieve a normal natriuresis during infusion of a vasodilator into the renal artery and elevation of arterial blood pressure. In view of our findings that proximal reabsorption is depressed by saline, it seems likely that this effect is exerted at a distal site. This would imply that capillary pressure may be an important physical determinant of distal reabsorption, as has been postulated for the proximal tubule (21, 22).

Finally, the data from acute and chronic TVC dogs suggest a possible sequence of renal responses to caval obstruction. Initially, "effective intravascular volume" falls. GFR and hence filtered sodium are reduced. Proximal fractional sodium reabsorption increases; physical factors such as decreased peritubular capillary pressure and increased oncotic pressure are possible mechanisms. Moreover, at some uncertain point in time, distal reabsorption is enhanced, both by increased aldosterone and by additional unknown factors. These mechanisms increase sodium reabsorption in the loop of Henle and possibly at other distal sites. As dietary sodium is retained, "effective circulating volume" is partially restored. Systemic and renal hemodynamics improve and proximal fractional reabsorption returns towards normal. Indeed, during acute expansion of extracellular volume by intravenous or dietary salt, proximal reabsorption may decrease below the control level and distal sodium load may increase correspondingly. However, enhanced distal reabsorption causes renal sodium retention even under these circumstances. This sequence implies a differential sensitivity of the mechanisms controlling proximal and distal sodium reabsorption to partial restoration of "effective circulating volume." Such a possibility is reasonable but wholly speculative. Even more speculative is the role of a similar sequence of events in the renal sodium retention of clinical edematous states.

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