Increased Sodium Reabsorption in the Proximal and Distal Tubule of Caval Dogs

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ABSTRACT The effects of water diuresis, hypotonic NaCl, and hypotonic mannitol diuresis on renal sodium and water excretion were examined in normal dogs and in dogs with chronic constriction of the thoracic inferior vena cava and ascites (caval dogs). During all three diuretic states, the capacity to excrete solute-free water relative to the supply of sodium to the water clearing segment of the nephron was significantly greater in the caval dog. This finding was most evident during hypotonic NaCl diuresis but was also striking during hypotonic mannitol diuresis despite the more unfavorable gradient for sodium reabsorption at the distal tubule produced by this agent in caval dogs. In addition, fractional distal sodium load was significantly smaller in caval dogs during water diuresis and could not be increased as readily as in normal dogs by hypotonic NaCl or mannitol infusion. The data indicate that fractional sodium reabsorption is increased at the water clearing segment and the proximal tubule in caval dogs.

The differences in the pattern of free water clearance and tubular sodium transport between normal and caval dogs could not be easily explained by alterations in renal hemodynamics or aldosterone secretion. It is suggested that in the caval dog an alteration occurs in other factors which might influence renal tubular sodium transport, such as intrarenal hemodynamics, renal interstitial volume or pressure, or a natriuretic hormone, leading to increased tubular sodium reabsorption.

INTRODUCTION

Chronic constriction of the thoracic portion of the inferior vena cava in the dog provokes marked salt and water retention by the kidneys leading to ascites formation (caval dogs) (1). Moreover, it has been demonstrated that either acute or chronic constriction of the thoracic inferior vena cava inhibits or retards the natriuresis usually seen with salt loading (2, 3). Micropuncture experiments of Cirksena, Dirks, and Berliner (4) suggest that sodium retention in the caval dog is mediated by an increased fractional sodium reabsorption along the proximal tubule. The possibility that sodium reabsorption is also increased at more distal sites of the nephron has not been explored.

In the present study the pattern of sodium and solute-free water clearance was examined during water diuresis, hypotonic NaCl, and hypotonic mannitol diuresis in normal and caval dogs. The data indicate that fractional sodium reabsorption is increased in both the proximal tubule and water clearing segment of the distal tubule in caval dogs.

METHODS

All experiments were performed on female mongrel dogs weighing 15–25 kg. Constriction of the thoracic inferior vena cava was performed according to the method of Davis and Howell (1). These animals were not studied until ascites had developed, usually 1–3 wk after surgery. All dogs were maintained on a diet containing 50–60 mEq of sodium and 20 mEq of potassium per day. On the morning of the experiment each animal received an oral water load, amounting to 5% of the body weight, via a stomach tube. 1 hr later the animal was anesthetized with sodium pentothal intravenously (1 ml/kg of a 2.5% solution) and the level of anesthesia was maintained with subsequent small doses as needed. An endotracheal tube was inserted and respiration was regulated with a respirator (Bird Corporation, Middleport, N. Y.) supplying 100% oxygen. After priming doses of inulin and *p*-aminohippurate (PAH), a sustaining solution of 0.45% sodium chloride containing sufficient inulin and PAH to maintain adequate blood levels was infused at 0.5 ml/min with a constant infusion pump (Sigmamotor, Inc., Richmond, Calif.). Urine was collected at 10-min intervals through an indwelling bladder catheter and midpoint blood samples were obtained at appropriate intervals through a

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TABLE I

*Period of Peak Free Water Clearance during Water Diuresis**

Exp. No.	V	U_{osm}	$U_{Na}V$	U_KV	P_{Na}	C_{H_2O}	C_{Na}	$C_{H_2O}+C_{Na}$	$\frac{C_{H_2O}}{C_{H_2O}+C_{Na}}\times 100$	C_{In}	C_{PAH}	FF
	ml/min	*mOsm/kg*	*μEq/min*	*μEq/min*	*mEq/liter*	*ml/min 100 ml GFR*	*ml/min 100 ml GFR*	*ml/min 100 ml GFR*	*%*	*ml/min*	*ml/min*	
Normal dogs (8)												
1	8.4	65	86	23	130	10.2	1.1	11.3	90.3	62.6	187	0.33
2	8.1	79	168	27	137	9.1	1.9	11.0	82.4	63.4	154	0.41
3	10.6	59	272	27	140	12.4	2.5	14.9	83.2	67.1	206	0.33
4	7.5	62	110	36	138	8.1	1.1	9.2	88.0	71.1	253	0.28
5	8.7	71	219	66	143	10.0	2.4	12.4	80.6	64.6	193	0.33
6	8.4	93	287	33	143	8.5	3.1	11.6	73.3	65.8	240	0.27
7	7.7	68	231	19	131	10.4	3.0	13.4	77.6	56.5	162	0.35
8	7.6	41	106	17	130	8.6	1.1	9.7	88.7	72.9	188	0.39
Mean	8.4	67	185	31	137	9.7	2.0	11.7	83.0	65.5	198	0.34
±SE	±0.35	±5.4	±28	±5.5	±2	±0.49	±0.30	±0.66	±2.1	±1.8	±12	±0.02
Caval dogs (8)												
9	4.4	83	29	74	142	7.3	0.5	7.8	93.6	42.9	91	0.47
10	5.4	42	22	29	140	9.4	0.3	9.7	96.9	49.1	108	0.45
11	5.8	82	69	35	141	7.2	0.9	8.1	88.9	57.0	131	0.44
12	7.4	72	157	15	141	9.3	1.9	11.2	83.0	59.4	229	0.26
13	9.0	42	58	19	128	11.8	0.7	12.5	94.4	64.4	192	0.34
14	4.8	50	7	10	142	8.6	0.1	8.7	98.9	45.2	107	0.42
15	7.7	57	57	23	133	8.5	0.6	9.1	93.4	72.8	256	0.28
16	6.2	65	29	24	136	5.7	0.3	6.0	95.0	82.2	172	0.48
Mean	6.3	62	54	29	138	8.5	0.7	9.1	93.0	59.1	161	0.39
±SE	±0.56	±5.9	±17	±7.0	±2	±0.65	±0.20	±0.72	±1.8	±4.8	±22	±0.03
P value	0.05	NS	0.01	NS	NS	NS	0.05	0.05	0.05	NS	NS	NS

* V, urine volume; U_{osm}, urine osmolality; $U_{Na}V$, sodium excretion; U_KV, potassium excretion; P_{Na}, plasma sodium concentration; C_{H_2O}, free water clearance; C_{Na}, sodium clearance; $C_{H_2O}+C_{Na}$, distal sodium load; $\frac{C_{H_2O}}{C_{H_2O}+C_{Na}}\times 100$, per cent sodium reabsorption in distal tubule; C_{In}, inulin clearance; C_{PAH}, *p*-aminohippurate clearance; FF, filtration fraction; SE, standard error of the mean.

Cournand needle in the femoral artery. Four groups of experiments were performed.

Group I. Water diuresis was induced in eight caval and eight normal dogs with an oral water load and maintained by infusing 0.45% NaCl at 0.5 ml/kg per min until urine flow stabilized.

Group II. Hypotonic NaCl diuresis was induced in nine caval and nine normal dogs by infusing 0.45% NaCl at progressively increasing rates until a level of 1.5 ml/kg per min was reached and then maintained at this level until urine flow stabilized. In two caval dogs the infusion rate was increased to 50 ml/min.

Group III. Hypotonic mannitol diuresis was induced in five caval and five normal dogs by infusing 2.5% mannitol at increasing rates until 1.5 ml/kg per min was reached and urine flow stabilized.

Group IV. Three normal dogs were studied as in group II (hypotonic NaCl diuresis) except that each dog received 500 μg of aldosterone intravenously 1 hr before starting the experiment followed by a sustaining infusion of 1 μg/min throughout the duration of the hypotonic NaCl diuresis.

All urine and plasma specimens were analyzed for osmolality, sodium, potassium, chloride, inulin, and PAH according to methods previously reported from this laboratory (5). Inulin clearance (C_{In}) was used as a measure of glomerular filtration rate (GFR) and PAH clearance as a measure of effective renal plasma flow (ERPF). Solute clearance (C_{osm}) was calculated as $U_{osm}V/P_{osm}$ where U_{osm} and P_{osm} represent urine and plasma osmolalities, respectively, and V represents urine flow in milliliters per minute. Solute-free water clearance (C_{H_2O}) was calculated as $V - C_{osm}$. Sodium clearance (C_{Na}) was calculated as $U_{Na}V/P_{Na}$ where U_{Na} and P_{Na} represent urinary and plasma sodium concentrations, respectively. Distal sodium load was approximated by $C_{H_2O}+C_{Na}$ and per cent distal tubule sodium reabsorption by $C_{H_2O}/(C_{H_2O}+C_{Na})\times 100$. In the text, tables, and figures, C_{H_2O}, C_{Na}, and distal sodium load are corrected for a GFR of 100 ml/min. Significance was tested by standard statistical methods.

RESULTS

The results described below are expressed as the mean for each group taken at the clearance period of peak free water clearance.

Water diuresis. Table I and Fig. 1 summarize the data in eight normal and eight caval dogs.[1] In these experiments the caval dog was able to dilute the urine to the same degree as the normal; U_{osm} averaged 62 mOsm/kg H_2O in the caval and 67 mOsm/kg H_2O in

[1] Although it is understood that the hypotonic NaCl infusion utilized for sustaining a water diuresis in these experiments might have altered tubular sodium transport, it is evident that the level of V, U_{osm}, and fractional C_{Na} or C_{H_2O} are not greatly different from the usual levels seen when water diuresis is sustained by other methods.

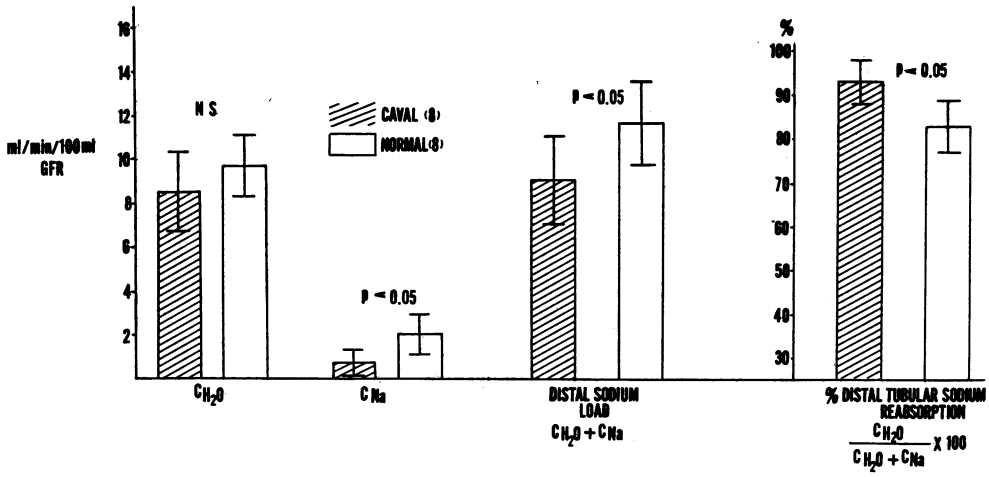

FIGURE 1 Fractional free water clearance (C_{H_2O}), sodium clearance (C_{Na}) and distal sodium load ($C_{H_2O} + C_{Na}$), and per cent sodium reabsorption in the distal tubule ($C_{H_2O}/(C_{H_2O} + C_{Na}) \times 100$) at the period of peak free water clearance during water diuresis. The hatched column represents the mean ±1 SD in eight caval dogs and the open column the mean ±1 SD in eight normal dogs.

the normal dog. In addition, the caval dog was able to excrete free water at the same rate as the normal, 8.5 ml and 9.7 ml/min per 100 ml GFR, respectively ($P > 0.3$). In contrast, sodium clearance during the same period was significantly lower in the caval dog, 0.7 ml/min per 100 ml GFR compared with 2.0 ml/min per 100 ml GFR in the normal ($P < 0.05$). It follows that fractional distal sodium load as approximated by (C_{H_2O}

TABLE II

*Period of Peak Free Water Clearance during Hypotonic Saline Diuresis**

Exp. No.	V	U_{Osm}	$U_{Na}V$	U_KV	P_{Na}	C_{H_2O}	C_{Na}	$C_{H_2O}+C_{Na}$	$\frac{C_{H_2O}}{C_{H_2O}+C_{Na}} \times 100$	C_{In}	C_{PAH}	FF
	ml/min	*mOsm/kg*	*μEq/min*	*μEq/min*	*mEq/liters*	*ml/min 100 ml GFR*	*ml/min 100 ml GFR*	*ml/min 100 ml GFR*	%	*ml/min*	*ml/min*	
Normal dogs (9)												
1	22.2	143	1332	33	139	14.5	13.1	27.6	52.5	76.6	251	0.31
2	21.4	117	1070	47	129	15.0	10.2	25.2	59.5	81.0	220	0.37
3	17.5	97	770	37	132	14.5	7.4	21.9	66.2	78.6	207	0.38
4	21.0	149	1575	48	125	15.3	19.5	34.8	44.0	64.6	164	0.39
5	23.2	140	1531	81	134	16.4	15.9	32.2	50.8	71.9	188	0.38
6	21.4	177	1712	88	120	12.4	26.8	39.2	31.6	53.3	198	0.27
7	21.3	164	1704	89	127	14.5	25.7	40.2	36.1	52.2	155	0.34
8	21.1	135	1329	89	120	13.1	13.7	26.8	48.9	80.6	205	0.39
9	24.7	122	1482	77	123	20.7	19.1	39.8	52.0	63.1	166	0.38
Mean	21.5	138	1389	65	128	15.2	16.8	32.0	49.1	69.1	195	0.36
±SE	±0.65	±8	±103	±7.9	±2	±0.79	±2.2	±2.3	±3.6	±3.8	±10	±0.01
Caval dogs (9)												
10	14.0	90	462	106	141	13.3	4.7	18.0	73.9	70.7	141	0.50
11	7.6	35	350	25	132	16.3	0.7	17.0	90.0	40.5	112	0.36
12	10.2	46	110	21	138	14.8	1.4	16.2	91.4	57.4	167	0.34
13	16.5	96	686	20	130	19.2	9.5	28.7	66.9	55.7	196	0.28
14	10.4	48	150	46	139	12.5	1.6	14.1	88.7	69.3	251	0.28
15	8.4	48	67	60	128	12.5	1.0	13.5	92.6	55.6	179	0.31
16	14.1	111	776	35	130	13.8	9.8	23.6	58.5	52.1	114	0.46
17	15.2	100	737	15	117	16.6	11.5	28.1	59.1	54.9	172	0.32
18	7.5	40	20	37	120	15.6	0.4	16.0	97.5	40.8	178	0.23
Mean	11.5	68	373	41	131	15.0	4.5	19.5	79.8	55.2	168	0.34
±SE	±1.15	±10	±101	±9.5	±3	±0.74	±1.51	±1.9	±5.1	±3.5	±14	±0.03
P value	0.01	0.01	0.01	NS	NS	NS	0.01	0.01	0.01	0.05	NS	NS

* Abbreviations are the same as in Table I.

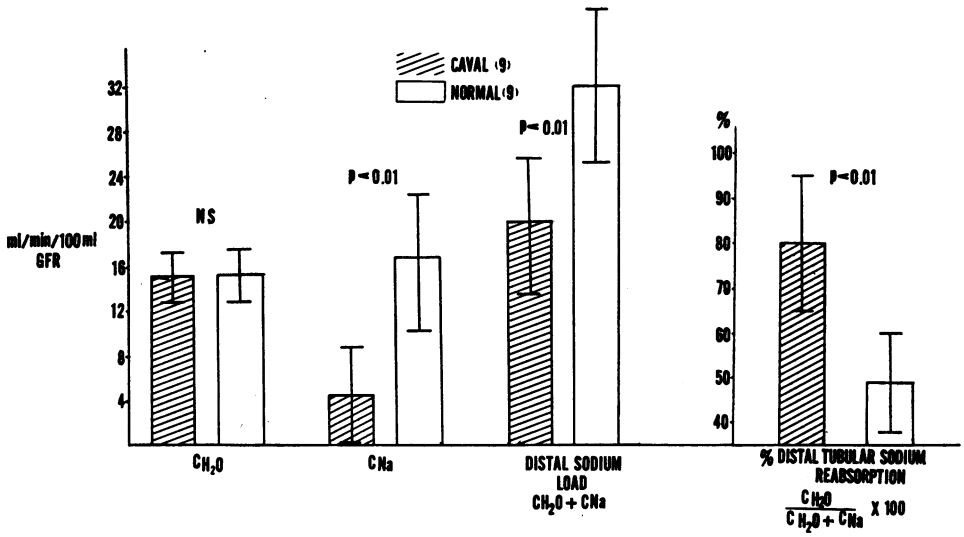

FIGURE 2 Fractional free water clearance (C_{H_2O}), sodium clearance (C_{Na}) and distal sodium load ($C_{H_2O} + C_{Na}$), and per cent sodium reabsorption in the distal tubule ($C_{H_2O}/(C_{H_2O} + C_{Na}) \times 100$) at the period of peak free water clearance during hypotonic NaCl diuresis. The hatched column represents the mean ± 1 SD in nine caval dogs and the open column the mean ±1 SD in nine normal dogs.

$+ C_{Na})/C_{In}$ was also significantly lower in the caval dog, 9.1 ml/min per 100 ml GFR compared with 11.7 ml/min per 100 ml GFR in the normal dog ($P < 0.05$). To clear free water at the same rate as the normal dog but at a lower level of distal sodium supply, the caval dog must reabsorb a larger fraction of the sodium presented to the water clearing site. The formula $C_{H_2O}/(C_{H_2O} + C_{Na})$ may be used as an index of fractional sodium reabsorption in the distal tubule. Accordingly, 93.0% of the sodium reaching the water clearing segment of the nephron was reabsorbed in the caval dog compared with 83.0% in the normal dog ($P < 0.05$).

Hypotonic NaCl diuresis. These experiments were performed to determine whether the pattern of increased

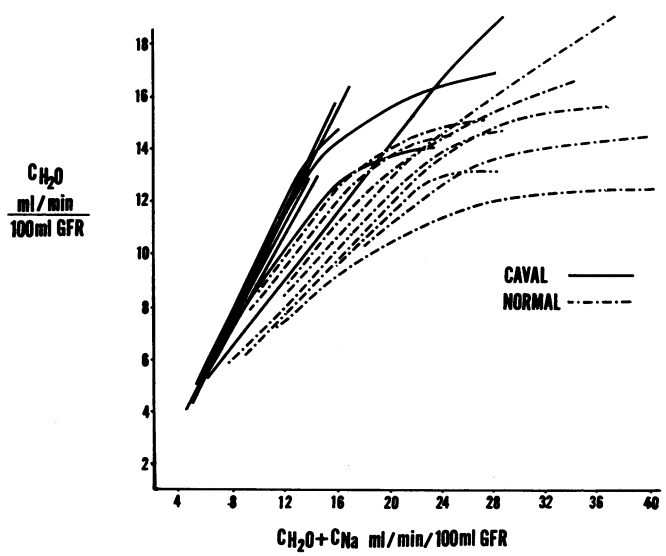

FIGURE 3 Relationship between fractional free water clearance (C_{H_2O}/100 ml GFR) and fractional distal sodium load ($C_{H_2O} + C_{Na}$/100 ml GFR) during hypotonic NaCl infusion in individual experiments. Caval dogs (n = 9) are depicted by solid lines and normal dogs (n = 9) by broken lines.

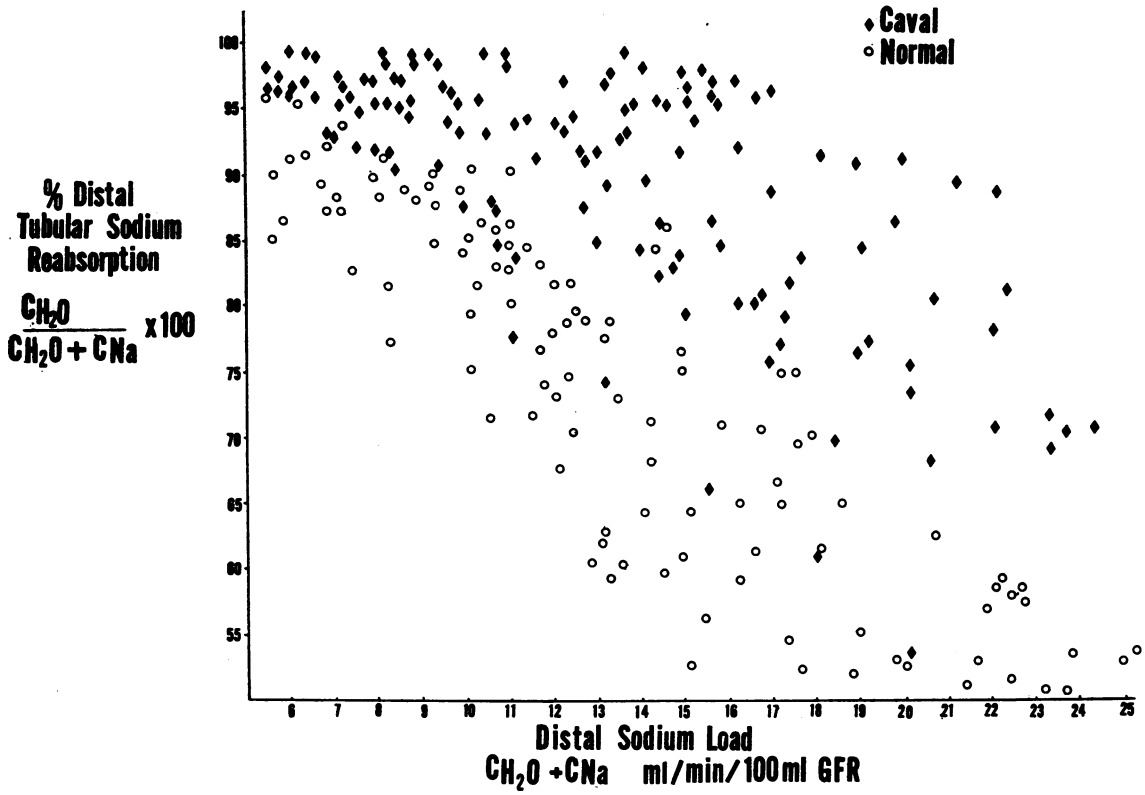

FIGURE 4 Relationship between per cent distal tubular sodium reabsorption ($C_{H_2O}/(C_{H_2O}+C_{Na}) \times 100$) and fractional distal sodium load ($C_{H_2O}+C_{Na}$/100 ml GFR) during hypotonic NaCl diuresis. The solid diamonds represent all the clearance periods from nine experiments in caval dogs and the open circles represent all the clearance periods from nine experiments in normal dogs.

distal tubular sodium reabsorption observed in the caval dog during water diuresis would be altered as more sodium was presented to the distal tubule.

The data from the experiments in nine caval and nine normal dogs are summarized in Table II and Fig. 2. Fig. 3 illustrates the pattern of free water clearance in the 18 individual experiments from both groups as distal sodium supply is increased. During hypotonic NaCl infusion caval dogs exhibited a linear rise in free water clearance as distal sodium load approached 16 ml/min per 100 ml GFR. In the three experiments in which distal sodium load could be increased further, the rise in free water clearance became curvilinear and appeared to reach a plateau in two of the three animals. Increasing the rate or duration of the infusion at this point frequently resulted in a sharp retrograde fall in free water clearance and sodium excretion. The normal dogs also exhibited a linear rise in free water clearance over the same range of distal sodium load, but the rate of increase was distinctly lower than that seen in the caval dog and is reflected by the progressive separation of the two groups with increasing distal sodium delivery. Moreover, as distal sodium load was increased beyond 16 ml/min per 100 ml GFR, the rise in free water clearance became curvilinear in all nine normal dogs and a plateau was evident in seven of the nine as distal sodium load approached 20–24 ml/min per 100 ml GFR. Although the same rate of hypotonic saline infusion effected a smaller increase in distal sodium delivery in the caval dog, it is evident from Fig. 3 that at the same rate of distal sodium supply free water clearance was consistently higher in the caval dog.

The peak free water clearance was 15.0 ml/min per 100 ml GFR in the caval and 15.2 ml/min per 100 ml GFR in the normal dog. Sodium clearance during the same period was 4.5 ml/min per 100 ml GFR in the caval compared with 16.8 ml/min per 100 ml GFR in the normal ($P < 0.01$). Thus, distal sodium load was significantly lower in the caval, 19.5 compared with 32.0 ml/min per 100 ml GFR in the normal dog ($P < 0.01$), whereas fractional sodium reabsorption in the distal tubule remained significantly higher in the caval dog, 79.8% compared with 49.1% in the normal ($P < 0.01$). The pattern of distal tubule fractional sodium reabsorp-

TABLE III

*Period of Peak Free Water Clearance during Hypotonic Mannitol Diuresis**

Exp. No.	V	U_{Osm}	$U_{Na}V$	U_KV	P_{Na}	C_{H_2O}	C_{Na}	$C_{H_2O}+C_{Na}$	$\frac{C_{H_2O}}{C_{H_2O}+C_{Na}}\times 100$	C_{In}
	ml/min	*mOsm/kg*	*μEq/min*	*μEq/min*	*mEq/liters*	*ml/min 100 ml GFR*	*ml/min 100 ml GFR*	*ml/min 100 ml GFR*	*%*	*ml/min*
Normal dogs (5)										
1	25.5	140	663	26	125	15.9	7.0	22.9	69.4	76.1
2	11.4	103	331	23	129	14.6	5.6	20.2	72.3	45.4
3	15.7	116	393	16	126	19.5	6.8	26.3	74.1	46.0
4	24.6	164	861	49	116	15.3	12.4	27.7	55.2	60.1
5	14.9	160	581	15	117	11.7	10.4	22.1	52.9	47.6
Mean	18.4	137	566	26	123	15.4	8.4	23.8	64.8	55.0
±SE	±2.81	±12	±95	±6.2	±2.6	±1.25	±1.27	±1.38	±4.5	±5.9
Caval dogs (5)										
6	12.0	133	240	12	122	16.7	5.6	22.3	74.9	35.3
7	11.7	104	187	12	120	15.4	3.3	18.7	82.4	45.8
8	20.0	130	240	60	124	13.1	2.6	15.7	83.4	74.2
9	15.0	134	60	45	127	12.1	0.7	12.8	94.5	63.3
10	12.6	150	25	50	123	8.6	0.3	8.9	96.6	62.6
Mean	14.3	130	150	36	123	13.2	2.5	15.7	86.4	56.2
±SE	±1.55	±7	±45	±10	±1.2	±1.41	±0.96	±2.32	±4.1	±6.9
P value	NS	NS	0.01	NS	NS	NS	0.01	0.01	0.01	NS

* Abbreviations are the same as in Table I.

tion in caval and normal dogs is illustrated in Fig. 4 where it is evident that at every level of distal sodium load per cent sodium reabsorption was greater in the caval dog and at the higher rates of distal sodium delivery the decrease in fractional sodium reabsorption was much less in these animals.

Since the level of distal sodium supply represents that moiety of sodium which escapes reabsorption in the proximal tubule and descending limb of Henle's loop, it provides an index of proximal tubule sodium reabsorption. Accordingly, 81.5% of the filtered sodium was reabsorbed proximal to the ascending limb of Henle's loop in the caval compared with 68% in the normal dog ($P < 0.01$). The greater per cent of proximal tubule sodium reabsorption in the caval dog was observed despite the similar degree of extracellular volume expansion as estimated by the decrease in serum sodium concentration in each group.

Finally, these experiments also provide evidence for increased exchange of potassium for sodium in caval animals. Although the absolute potassium excretion (U_KV) was lower in the caval dog, 41 μEq/min compared with 65 μEq/min in the normal, the ratio of $U_K/(U_{Na}+U_K)$, indicating the fraction of sodium exchanged for potassium in the distal tubule, was greater in the caval dog, 9.9% compared with 4.5% in the normal ($P < 0.01$).

Hypotonic mannitol diuresis. This group of experiments was performed to determine whether the pattern of increased sodium reabsorption in the distal tubule would be seen in the caval dog when the sodium supply to the distal tubule was increased by an osmotic diuretic as well as by extracellular volume expansion. Since a limiting gradient for sodium reabsorption is achieved in the proximal tubule with mannitol (6), it was also possible to test the capacity of both groups of animals to reabsorb sodium in the distal tubule against a less favorable gradient.

Table III and Fig. 5 summarize the data in five caval and five normal dogs. The peak free water clearance was 13.2 ml/min per 100 ml GFR in the caval compared with 15.4 ml/min per 100 ml GFR in the normal dog ($P > 0.2$). Sodium clearance was 2.5 ml/min per 100 ml GFR in the caval and 8.4 ml/min per 100 ml GFR in the normal ($P < 0.01$). Thus, although peak free water clearance was the same in both groups during hypotonic mannitol diuresis, distal sodium load was significantly lower in the caval dog, 15.7 compared with 23.8 ml/min per 100 ml GFR in the normal ($P < 0.01$). It follows that distal tubule sodium reabsorption was again greater in caval dogs, 86.4% compared with 64.8% in the normal ($P < 0.01$). Increased sodium reabsorption in the distal tubule was observed in caval dogs during hypotonic mannitol diuresis despite the

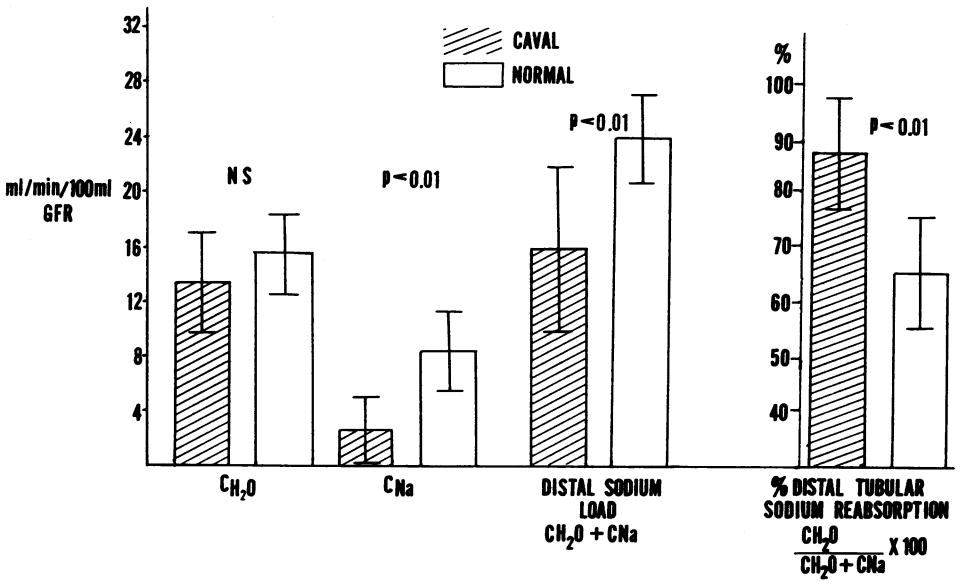

FIGURE 5 Fractional free water clearance (C_{H_2O}), sodium clearance (C_{Na}) and distal sodium load ($C_{H_2O} + C_{Na}$), and per cent sodium reabsorption in the distal tubule ($C_{H_2O}/(C_{H_2O} + C_{Na}) \times 100$) at the period of peak free water clearance during hypotonic mannitol diuresis. The hatched column represents the mean ±1 SD in five caval dogs and the open column the mean ±1 SD in five normal dogs.

lower sodium concentration in the tubular fluid reaching the water clearing site as approximated by $(C_{Na} + C_{H_2O})/V$. In the caval dog this ratio was 0.59 compared with 0.73 in the normal dog ($P < 0.05$).

Aldosterone loading–hypotonic NaCl diuresis. In the three normal dogs receiving aldosterone before and during hypotonic NaCl infusion neither peak free water clearance nor fractional distal tubule sodium reabsorption was significantly different from dogs not receiving aldosterone. A slight increase was noted in the ratio of $U_K/(U_{Na} + U_K)$ indicating an increased rate of exchange (Table IV).

DISCUSSION

In the present experiments examination of the pattern of free water clearance during water diuresis, hypotonic NaCl diuresis, and hypotonic mannitol diuresis reveals that the caval dog is able to clear free water at a rate at least as great as the normal dog but at a significantly lower level of distal sodium supply. Insofar as the clearance of free water is dependent primarily upon sodium reabsorption in the diluting segment of the nephron (7–10), it follows that fractional sodium reabsorption is increased at this site in the caval dog. Although this phenomenon was evident during water diuresis, it was particularly striking during rapid hypotonic NaCl infusion where a marked decrease in distal tubule sodium reabsorption was noted in the normal dogs compared with only a very modest decrease in caval dogs as distal sodium load increased (Fig. 4). When distal sodium supply was increased by infusing mannitol a similar pattern was observed. This is particularly significant since

TABLE IV

*Period of Peak Free Water Clearance during Hypotonic Saline Diuresis in Aldosterone Loaded Dogs**

Exp. No.	V	U_{Osm}	$U_{Na}V$	U_KV	P_{Na}	C_{H_2O}	C_{Na}	$C_{H_2O}+C_{Na}$	$\frac{C_{H_2O}}{C_{H_2O}+C_{Na}} \times 100$	C_{In}
	ml/min	*mOsm/kg*	*μEq/min*	*μEq/min*	*mEq/liters*	*ml/min 100 ml GFR*	*ml/min 100 ml GFR*	*ml/min 100 ml GFR*	%	*ml/min*
1	17.2	132	1110	52	140	12.7	11.3	24.0	52.9	70.2
2	27.8	157	2155	111	135	16.8	22.9	39.7	42.3	69.7
3	23.4	144	1708	94	137	12.7	15.1	27.8	45.7	82.8

* Abbreviations are the same as in Table I.

increased distal tubule sodium reabsorption occurred in caval animals despite a more unfavorable sodium concentration gradient.

Fractional distal tubule sodium load, $(C_{H_2O} + C_{Na})/C_{In}$, which approximates the fraction of sodium escaping reabsorption in the proximal tubule, was significantly lower in caval than normal dogs during water diuresis. Furthermore, the increased sodium reabsorption in the proximal tubule was not easily overcome by extracellular volume expansion with rapid hypotonic NaCl loading or by mannitol infusion. In general, the diuretic response to NaCl or mannitol was much slower in onset and significantly less in magnitude in caval compared with normal dogs despite the same or greater total volume infused. Thus, it may be concluded that the increase in fractional sodium reabsorption in the proximal tubule demonstrated with micropuncture techniques by Cirksena et al. (4) is not a transient phenomenon associated only with acute constriction of the vena cava but persists in the chronic caval preparation as well, as suggested by Levinsky and Lalone (2) and Friedler, Belleau, Martino, and Earley (3).

In addition to the augmented sodium transport in the proximal tubule and diluting segment of the nephron, the increased ratio of $U_K/(U_{Na} + U_K)$ indicates that the caval dog has an augmented rate of exchange of potassium for sodium in the distal nephron. Sodium retention in the caval dog, therefore, is a consequence of increased transport throughout the nephron rather than at a localized segment of the tubule.

Although many factors have been implicated as responsible for sodium retention in the caval dog, it is clear from the experiments of other investigators that the increase in tubular sodium reabsorption cannot be totally explained on the basis of alterations in renal hemodynamics, renal vein pressure, or renal innervation (2, 4, 11). In the present experiments GFR and ERPF tended to be lower in caval dogs compared with normals during water and hypotonic NaCl diuresis. Considerable overlap existed, however, so that a clear correlation between the extent of proximal or distal tubule sodium reabsorption and the GFR or ERPF could not be identified. Similarly, no consistent correlation was evident between the filtration fraction and sodium reabsorption. Nevertheless, the data do not exclude the possibility that a subtle alteration in renal hemodynamics contributes to the difference in sodium reabsorption between normal and caval dogs.

The precise role of aldosterone in caval dogs is still somewhat unclear. In addition to promoting exchange of potassium for sodium in the distal nephron, aldosterone apparently stimulates net sodium transport at another site in the nephron as well, since solute excretion is clearly diminished after aldosterone infusion (12). Sonnenblick, Cannon, and Laragh (13) reported a small but significant increase in free water clearance in normal man in response to a constant infusion of aldosterone. In the present study, however, the continuous infusion of aldosterone in three normal dogs during hypotonic NaCl diuresis did not alter the pattern of sodium excretion or free water clearance (Table IV). Although hyperaldosteronism is probably a contributing factor, it is apparent from the studies of Davis, Holman, Carpenter, Urquhart, and Higgins (11) that it is neither a sufficient nor necessary condition for sodium retention and ascites formation in the caval dog.

The role of intrarenal hemodynamics or renal interstitial pressure or volume in the control of sodium excretion has received a great deal of attention recently (14–18). It would appear that even if there is a natriuretic hormone, other factors must be operative in the regulation of tubular sodium transport and that sodium transport in the proximal tubule is under different control than that in the distal tubule (15, 16, 19).

Friedler et al. (3) have suggested that the sodium retention which accompanies acute and chronic caval constriction and the absent or blunted natriuretic response to saline loading is related to reduced renal perfusion pressure. These authors demonstrated that increasing arterial blood pressure in these animals in the presence of renal vasodilitation results in a marked natriuresis equivalent to that seen in normal dogs receiving a similar saline load. Although the present experiments do not bear directly on this problem, the lower ERPF which caval dogs tended to have may exert an effect on sodium transport by altering some aspect of intrarenal hemodynamics or interstitial volume and pressure. It is of interest that in a previous report from this laboratory a lower blood pressure was noted in a group of caval dogs examined after hypotonic NaCl loading than in another group examined during water diuresis (5), similar to the findings of Friedler et al. (3). However, it should also be noted that intrarenal artery infusion of a subpressor dose of angiotensin in caval dogs leads to a natriuresis in spite of a decrease in ERPF (5).

Whatever the mechanisms are which control renal tubule sodium transport in addition to GFR and aldosterone, it would appear that an alteration takes place in the caval dog after vena cava constriction which leads to sodium retention. It is suggested that the disturbance in volume control arises from a critical change in the distribution of extracellular fluid or the intravascular compartment in these animals.

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