The Influence of Extracellular Volume Expansion on Renal Phosphate Reabsorption in the Dog

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ABSTRACT Extracellular volume expansion (ECVE) was produced, by normal saline infusion, in five normal and six thyroparathyroidectomized anesthetized dogs while glomerular filtration rate was reduced by the inflation of an intra-aortic balloon located above the renal arteries. The effect of ECVE on the maximum renal tubular reabsorptive capacity of phosphate (phosphate Tm) was also evaluated in five additional dogs. During ECVE, phosphate excretion increased both in normal and thyroparathyroidectomized dogs, and a direct and significant correlation was found between the fractional excretion of phosphate and sodium. Despite a substantial decrease in filtered phosphate which is produced by the acute reduction in glomerular filtration rate, phosphate excretion, during ECVE, exceeded control values. ECVE was associated with a reduction in phosphate Tm. The results demonstrate that ECVE increases phosphate excretion independent of changes in glomerular filtration rate and parathyroid gland activity. The data indicate that ECVE produced by saline infusion decreases the renal tubular reabsorption of phosphate.

INTRODUCTION

Evidence exists that extracellular volume expansion (ECVE), which is produced by saline infusion, causes a definite decrease in the renal tubular reabsorption of several actively transported substances, such as sodium (1–3), calcium (4–6), magnesium (5, 7), and glucose (8). The reabsorption of the last two is limited by a maximum capacity (Tm) (9, 10), and it has been shown that during ECVE both glucose Tm and magnesium Tm are lowered (8, 10).

Phosphate is actively reabsorbed by the nephron and its reabsorption exhibits a maximum capacity or Tm (11). Although ECVE may also decrease the tubular reabsorption of phosphate, data on the effect of saline infusion and ECVE on phosphate excretion are limited. In some of the experiments carried out in the dog by Foulks and Perry (12), ECVE was associated with phosphaturia which they attributed, at least in part, to the increase in filtered phosphate. Blythe, Gitelman, and Welt (6), while evaluating the effect of ECVE on calcium excretion in dogs, found that phosphate excretion during ECVE and acute reduction in filtered phosphate was either less than, or not statistically significantly different from, the control levels. However, in most of their experiments the fraction of filtered phosphate excreted was higher than the control values, a finding suggesting a decrease in tubular reabsorption of phosphate.

During ECVE, glomerular filtration rate and filtered phosphate may increase, resulting in phosphaturia. Also, hemodilution, which follows ECVE, may lower serum calcium, which in turn may stimulate the release of parathyroid hormone. The latter may, in itself, cause phosphaturia (13). The present study was designed to evaluate whether ECVE may effect renal handling of phosphate independent of both filtered load and a possible change in activity of the parathyroid glands.

METHODS

20 experiments were carried out during pentobarbital anesthesia on 11 normal and 6 thyroparathyroidectomized (T-PTX) female mongrel dogs. Thyroparathyroidectomy was performed under pentobarbital anesthesia, 2 days before the study. The complete removal of the parathyroid

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glands was confirmed by the appearance of hypocalcemia. Respiration was controlled by a Harvard respirator pump which was adjusted initially with a stroke volume of 10 ml/kg body weight and a rate of 30 strokes/min. Arterial pH was measured throughout the experiment by Radiometer pH meter (London Co., Westlake, Ohio), and the stroke volume was adjusted, thereafter, to maintain blood pH within 7.39–7.43. Usually little adjustment was necessary. Glomerular filtration rate (GFR) was measured by exogenous creatinine clearance. Urine was collected from a retention catheter, and the bladder was washed with air at the end of each period from an indwelling needle in the left femoral artery.

In 11 dogs (five intact and six T-PTX), a triple-lumen catheter (U. S. Catheter & Instrument Corp., Glens Falls, N. Y.), with a balloon attached to its distal end, was inserted via the right femoral artery into the aorta to a level above the renal arteries. Abrupt inflation of the balloon invariably led to cessation of urine flow and confirmed its location above the renal arteries. Intra-aortic pressure was monitored, both proximal and distal to the balloon, by mercury manometers. After collection of three control clearance periods of 20 min duration, between 9 and 10 a.m., 0.9% NaCl was infused to both the normal and T-PTX dogs at a rate of 20 ml/min for 90 min; the rate of saline infusion was then reduced to equal urine flow. After 30 min, another three clearance periods, each of 10 min, were obtained. Acute reduction in GFR was then produced by inflation of the intra-aortic balloon; 5 min were allowed for the distal intra-aortic pressure to stabilize at 60–70% of its control levels. Each inflation period lasted 20–40 min, and urine was collected for three to five clearance periods, each of 5–7 min duration. In some instances the distal intra-aortic pressure was further reduced to 45–55% of its initial level for two to three additional clearance periods.

In six additional normal dogs, the phosphate Tm was measured during the infusion of 0.9% NaCl. Saline was infused in a manner similar to that described above. After 120 min of saline infusion, and while the latter is continued at a rate equal to urine flow, a buffered solution of sodium phosphate was added to the infusion to deliver 30 mg of elemental phosphorus per kg per hr. The phosphate infusion was given for 3 hr during which clearance periods, each of 20 min, were collected. In three of these dogs phosphate Tm was also measured in a similar way but in the absence of saline infusion; several days separated the studies carried out in the same dog.

Blood samples were analyzed for creatinine, calcium, and sodium, and urine samples for creatinine and sodium by methods previously reported from this laboratory (5). Phosphate was determined by the method of Fiske and Subbarow (14).

RESULTS

A detailed protocol of a representative experiment with saline infusion and acute reduction in GFR in a normal dog is shown in Table I, and that in thyroparathyroidectomized (T-PTX) animal is given in Table II. A summary of all experiments is presented in Table III; each data point represents a mean of three to five clearance periods. In every experiment, both in normal

TABLE I

*Detailed Protocol of Experiment with Saline Infusion and Acute Reduction in GFR in a Normal Dog**

Time	V	C_{Cr}	S_{Ca}	S_{Na}	F_{Na}	$U_{Na}V$	S_P	U_PV	F_P	C_P	$\frac{C_P}{C_{Cr}} \times 100$	TRP	TRP
min	*ml/min*	*ml/min*	*mg/100 ml*	*mEq/liter*	*mEq/min*	*μEq/min*	*mg/100 ml*	*μg/min*	*mg/min*	*ml/min*		*mg/min*	*%*
−20	Balloon inserted into the aorta												
0	Priming dose of creatinine, 500 mg												
	Infusion I started: 8 mg/min creatinine delivered in 0.45% NaCl at 1 ml/min												
60–90	0.42	74.9	10.63	143	10.71	28	4.3	245	3.22	5.7	7.6	2.98	92.4
90–120	0.47	71.6	10.63	143	10.24	42	4.3	183	3.21	4.3	5.9	2.89	94.1
120–150	0.49	74.7	10.50	146	10.91	49	4.3	154	3.21	3.6	4.8	3.05	95.2
151	Infusion II started: 0.9% NaCl at 20 ml/min												
211	Rate of infusion II adjusted to equal urine flow												
270–280	12.80	86.2	9.03	151	13.02	909	3.9	864	3.36	22.2	25.7	2.50	74.3
280–290	14.50	83.9	9.03	151	12.67	986	4.0	906	3.36	22.6	27.0	2.45	73.0
290–300	14.00	81.1	9.03	151	12.25	938	4.0	1050	3.24	26.3	32.4	2.19	67.6
305	Balloon inflated												
310–315	5.20	62.4	8.47	150	9.36	364	4.1	520	2.55	12.9	20.3	2.03	79.7
315–320	3.80	65.6	8.56	150	9.48	258	4.1	580	2.69	14.1	21.7	2.11	78.3
320–325	4.30	64.5	8.43	150	9.68	310	4.1	559	2.64	13.6	21.1	2.09	78.9
327	Balloon further inflated												
330–335	5.20	59.8	8.43	150	8.97	348	4.1	364	2.45	8.9	14.8	2.09	85.2
335–340	3.25	57.7	8.42	150	8.66	228	4.1	260	2.37	6.3	11.0	2.11	89.0

* Dog No. 5, 20 kg.

GFR = glomerular filtration rate, V = urine volume, C_{Cr} = creatinine clearance, S_{Ca} = serum calcium, S_{Na} = serum sodium, $U_{Na}V$ = sodium excretion, S_P = serum inorganic phosphorus, F_P = filtered phosphate, C_P = phosphate clearance, and, TRP = tubular reabsorption of phosphate, F_{Na} = filtered sodium.

TABLE II

*Detailed Protocol of Experiment with Saline Infusion and Acute Reduction in GFR in a Thyroparathyroidectomized Dog**

Time	V	C_{Cr}	S_{Ca}	S_{Na}	F_{Na}	$U_{Na}V$	S_P	F_P	U_PV	C_P	$\frac{C_P}{C_{Cr}} \times 100$	TRP	TRP
min	*ml/min*	*ml/min*	*mg/ 100 ml*	*mEq/ liter*	*mEq/min*	*μEq/min*	*mg/ 100 ml*	*mg/min*	*μg/min*	*ml/ min*		*mg/ min*	*%*
−20	Balloon inserted into the aorta												
	Priming dose of creatinine, 500 mg												
	Infusion I started: 8 mg/min creatinine delivered in 0.45% NaCl at 1 ml/min												
70–100	0.37	66.6	7.47	146	9.72	45	3.9	2.60	75	1.9	2.9	2.52	97.1
100–130	0.43	64.5	7.47	146	9.42	76	3.7	2.39	53	1.4	2.2	2.34	97.8
130–160	1.07	64.2	7.47	146	9.37	64	3.5	2.24	85	2.4	3.8	2.16	96.2
161	Infusion II started: 0.9% NaCl at 20 ml/min												
221	Rate of infusion II adjusted to equal urine flow												
280–290	14.70	75.8	6.39	149	11.29	1381	3.3	2.50	257	7.8	10.3	2.24	89.7
290–300	13.50	71.0	6.39	149	10.58	1229	3.3	2.34	223	6.8	9.5	2.12	90.5
300–310	14.20	70.0	6.39	150	10.50	1263	3.3	2.31	227	6.9	9.8	2.08	90.2
315	Balloon inflated												
320–325	5.80	58.0	6.16	151	8.76	342	3.3	1.91	136	4.1	7.1	1.77	92.9
325–330	5.30	54.4	6.11	151	8.21	254	3.2	1.74	114	3.6	6.5	1.63	93.5
330–335	6.20	54.0	6.00	151	8.15	297	3.4	1.84	127	3.7	6.9	1.71	93.1
337	Balloon further inflated												
340–345	2.40	43.2	5.87	152	6.57	134	3.5	1.51	97	2.8	6.4	1.41	93.6
345–350	3.10	43.4	5.84	151	6.55	192	3.6	1.56	125	3.5	8.0	1.44	92.0
350–355	2.40	49.5	5.65	149	7.38	204	3.6	1.78	126	3.5	7.1	1.65	92.9

* Dog No. 6, 19.5 kg.

GFR = glomerular filtration rate, V = urine volume, C_{Cr} = creatinine clearance, S_{Ca} = serum calcium, S_{Na} = serum sodium, $U_{Na}V$ = sodium excretion S_P = serum inorganic phosphorus, F_P = filtered phosphate, C_P = phosphate clearance, and TRP = tubular reabsorption of phosphate, F_{Na} = filtered sodium.

and T-PTX dogs, saline infusion was accompanied by a fall in serum calcium of 1.5–3.0 mg/100 ml and a marked increase in phosphate excretion.

The fraction of filtered phosphate excreted increased during saline infusion and was directly related to fractional sodium excretion both in the normal and T-PTX dogs (Figs. 1 and 2). However, at any given level of fractional sodium excretion, the per cent of filtered phosphate excreted by the normal dogs exceeded that observed in the T-PTX animals. As fractional sodium excretion increased from 10 to 20% in both the normal and T-PTX dogs, the per cent of filtered phosphate excreted was 10–45% in the former and only 5–15% in the latter.

GFR was reduced by 13–52% (mean ±SE, −22 ±5%) in normal dogs and by 15–36% (−24 ±3%) in T-PTX dogs by the inflation of the intra-aortic balloon. Subsequently, filtered loads of phosphate fell by 25 ±5% in normal dogs and by 29 ±2% in T-PTX dogs. Despite the reduced filtered loads of phosphate, its excretion exceeded the control levels in all experiments.

In Table IV data from six dogs are presented which show the Tm values for phosphate during saline infusion and ECVE. The mean Tm rates for these six dogs were 121, 126, 59, 115, 69, and 108 μg/min per kg body weight, values lower than those observed by others (11, 12). The values for phosphate Tm for two dogs calculated from data of Pitts and Alexander (11) were 168 and 200 μg/min per kg body weight, and those for another two dogs form the work of Foulks and Perry (12) were 167 and 206 μg/min per kg body weight. In the present study, when phosphate Tm was measured both with and without ECVE in the same dogs (Nos. 15, 16, and 17), the values were 214, 175, and 232 μg/min per kg body weight before and 115, 69, and 108 μg/min per kg body weight after ECVE, respectively (Fig. 3).

DISCUSSION

The results of the present study demonstrate that phosphate excretion is increased during ECVE. The factors which may be responsible for this phosphaturia include: (*a*) a rise in GFR and filtered phosphate; (*b*) an increase in parathyroid activity consequent to the fall in serum calcium; (*c*) phosphate secretion; and (*d*) a decrease in tubular reabsorption of phosphate.

Saline infusion and ECVE were usually associated with a rise in both GFR and filtered load of phosphate. However, this cannot solely explain the observed phosphaturia, since the excretory rates of phosphate noted during ECVE exceeded control levels even when GFR

TABLE III

Summary of All Experiments with Saline

Dog No.	Dog weight	Period	C_{Cr}	S_{Ca}	S_{Na}	F_{Na}	$U_{Na}V$
	kg		*ml/min*	*mg/100 ml*	*mEq/liter*	*mEq/min*	*μEq/min*
Normal dogs							
1	15.0	Control	45.0	10.56	146	6.57	9
		Inflation	37.4	8.26	149	5.58	473
		Δ %	−17			−14	
		Inflation	21.4	8.10	148	3.17	163
		Δ %	−52			−52	+1711
2	16.0	Control	76.5	10.18	151	11.55	18
		Inflation	62.0	7.06	150	9.30	164
		Δ %	−19			−19	+1950
3	18.0	Control	84.8	11.53	151	12.80	40
		Inflation	69.4	9.33	146	10.13	185
		Δ %	−18			−20	+361
4	22.0	Control	133.7	10.62	149	19.92	95
		Inflation	112.2	9.06	150	16.83	504
		Δ %	−16			−16	+431
5	20.0	Control	73.7	10.59	144	10.61	40
		Inflation	64.2	8.49	151	9.69	311
		Δ %	−13			− 9	+677
		Inflation	58.8	8.43	150	8.82	288
		Δ %	−20			−17	+620
Thyroparathyroidectomized dogs							
6	19.5	Control	65.1	7.47	146	9.50	62
		Inflation	55.5	6.09	151	8.38	298
		Δ %	−15			−12	+380
		Inflation	45.4	5.79	150	6.81	177
		Δ %	−30			−28	+184
7	18.0	Control	56.7	7.34	146	8.28	10
		Inflation	43.6	4.81	147	6.41	127
		Δ %	−23			−23	+1170
8	14.0	Control	48.5	6.55	138	6.69	30
		Inflation	40.9	4.22	139	5.69	353
		Δ %	−17			−15	+1077
9	15.0	Control	77.6	7.47	144	11.17	32
		Inflation	49.6	5.65	143	7.09	374
		Δ %	−36			−37	+1067
10	15.0	Control	66.7	7.4	145	9.67	39
		Inflation	50.6	6.1	145	7.34	455
		Δ %	−24			−24	+1066
11	16.0	Control	64.0	6.9	140	8.96	39
		Inflation	49.0	5.8	143	7.00	620
		Δ %	−23			−22	+1490

GFR = glomerular filtration rate, C_{Cr} = creatinine clearance, S_{Ca} = serum calcium, S_{Na} = serum sodium, F_{Na} = filtered sodium, $U_{Na}V$ = sodium excretion, S_P = inorganic serum phosphorus, F_P = filtered phosphate, U_PV = phosphate excretion, C_P = phosphate clearance, TRP = tubular reabsorption of phosphate, $\Delta\ \% = \frac{\text{Mean inflation} - \text{mean control} \times 100}{\text{Mean control}}$.

Each data point represents the mean of three to five clearance periods.

S_P	F_P	U_PV	C_P	$\frac{C_P}{C_{Cr}} \times 100$	TRP	TRP
mg/100 ml	*mg/min*	*µg/min*	*ml/min*		*mg/min*	%
3.7	1.67	35	0.9	2.1	1.64	97.9
3.9	1.46	359	9.2	24.6	1.10	75.4
	−13	+923				
4.1	0.88	140	3.4	16.0	0.74	84.0
	−47	+300				
2.8	2.14	8	0.3	0.4	2.13	99.6
3.0	1.86	198	6.6	10.6	1.66	89.4
	−13	+2375				
6.6	5.57	93	1.4	1.7	5.48	98.3
5.0	3.47	273	5.5	8.6	3.20	92.6
	−38	+193				
4.8	6.41	7	0.2	0.1	6.40	99.9
5.0	5.61	556	11.1	10.0	5.05	90.0
	−12	+7843				
4.3	3.17	194	4.5	6.1	2.98	93.9
4.1	2.63	553	13.4	20.9	2.08	79.1
	−17	+185				
4.1	2.41	312	7.6	12.9	2.10	87.1
	−24	+61				
3.7	2.40	71	1.9	2.9	2.33	97.1
3.3	1.83	126	3.8	6.8	1.70	93.2
	−24	+76				
3.6	1.73	116	3.3	7.2	1.51	92.8
	−32	+63				
5.2	2.95	4	0.1	0.2	2.95	99.8
5.4	2.35	35	0.6	1.5	2.31	98.5
	−20	+775				
2.8	1.36	4	0.2	0.3	1.36	99.7
2.5	1.02	18	0.7	1.8	1.00	98.2
	−25	+350				
3.9	3.03	32	0.8	1.1	3.00	98.9
4.0	1.98	108	2.7	5.4	1.87	94.6
	−35	+237				
4.2	2.80	45	1.1	1.6	2.75	98.4
3.6	1.82	93	2.5	5.1	1.73	94.9
	−35	+106				
3.8	2.43	57	1.5	2.3	2.37	97.7
3.4	1.67	116	3.4	6.9	1.55	93.1
	−31					

TABLE IV

Data from Six Normal Dogs in Which Phosphate Tm Was Measured during Saline Infusion

C_{Cr}	S_P	F_P	U_PV	TRP
ml/min	*mg/100 ml*	*μg/min per kg body weight*		
Dog No. 12, 20 kg				
67.5	6.8	228	98	130
66.6	9.3	307	165	143
66.6	10.0	331	226	104
67.5	11.5	387	257	128
61.6	12.4	379	256	123
61.5	13.0	397	278	118
64.2	13.2	421	311	108
61.4	14.0	427	294	133
61.9	14.0	430	325	105
Dog No. 13, 16 kg				
64.8	3.9	158	30	128
63.6	5.8	231	104	126
68.3	7.7	329	187	142
66.1	8.4	347	224	123
65.9	9.1	374	254	121
69.8	9.7	423	297	126
61.3	11.0	421	317	105
73.4	10.8	495	352	143
Dog No. 14, 15 kg				
51.4	6.0	206	124	81
51.0	7.7	262	194	68
56.3	9.4	352	296	56
54.1	10.2	367	321	46
53.1	10.8	382	334	48
56.0	11.6	433	378	55
Dog No. 15, 16 kg				
46.7	6.7	195	77	118
40.8	8.4	214	115	99
43.7	10.1	276	147	129
40.3	11.0	277	155	122
Dog No. 15, 16 kg				
50.1	11.4	357	250	107
43.5	12.0	326	216	110
47.5	12.3	365	248	118
43.0	12.8	344	234	110
46.5	13.4	389	269	121
53.6	13.6	454	332	122
57.6	14.6	526	413	113
Dog No. 16, 14 kg				
43.5	6.1	189	110	79
39.1	7.2	201	125	76
37.8	8.7	235	150	85
39.4	9.9	278	201	77
39.9	11.0	313	248	66
39.9	12.4	353	289	64
39.8	12.4	352	200	52
36.7	13.4	351	274	77
39.9	13.6	387	326	61
38.5	14.2	390	337	53
Dog No. 17, 18 kg				
65.0	5.8	205	88	121
68.1	6.0	226	116	110
68.9	7.2	255	122	133
69.9	9.0	350	255	95
75.2	9.5	396	300	96
75.1	10.5	437	317	120
76.1	11.5	485	394	91
79.8	12.0	533	408	125
75.1	12.0	500	399	101
72.0	11.5	460	375	85
78.0	11.4	494	379	115

Phosphate Tm = maximum renal tubular reabsorptive capacity of phosphate, C_{Cr} = creatinine clearance, S_P = serum inorganic phosphorus, F_P = filtered phosphate, U_PV = phosphate excretion, TRP = tubular reabsorption of phosphate.
The data represent sequential individual clearance periods in each dog.

and filtered loads were acutely reduced below control values by the inflation of the intra-aortic balloon.

The fall in serum calcium observed during saline infusion may stimulate the parathyroid glands, and an increased release of parathormone could underly the phosphaturia seen in the normal dogs. However, the augmentation of phosphate excretion during ECVE in the T-PTX animals indicates that phosphaturia did occur even in the absence of parathyroid glands. The difference in the magnitude of fractional phosphate excretion between the normal and T-PTX dogs indicates that the presence of intact parathyroid glands and a probable increase in circulating parahormone may contribute significantly to the greater degree of phosphaturia noted during ECVE in the normal animals.

The possibility that phosphate secretion may account for the results cannot be excluded, but such an event seems remote. Efforts to demonstrate phosphate secretion in the dog (15) or the rat (16) have been unsuccessful. Furthermore, if such a secretory process does exist it must be of a very small magnitude, which could not account for the marked changes in fractional phosphate excretion.

Since the increase in phosphate excretion during ECVE occurred in the face of a marked reduction in filtered load, a decrease in the tubular reabsorption of

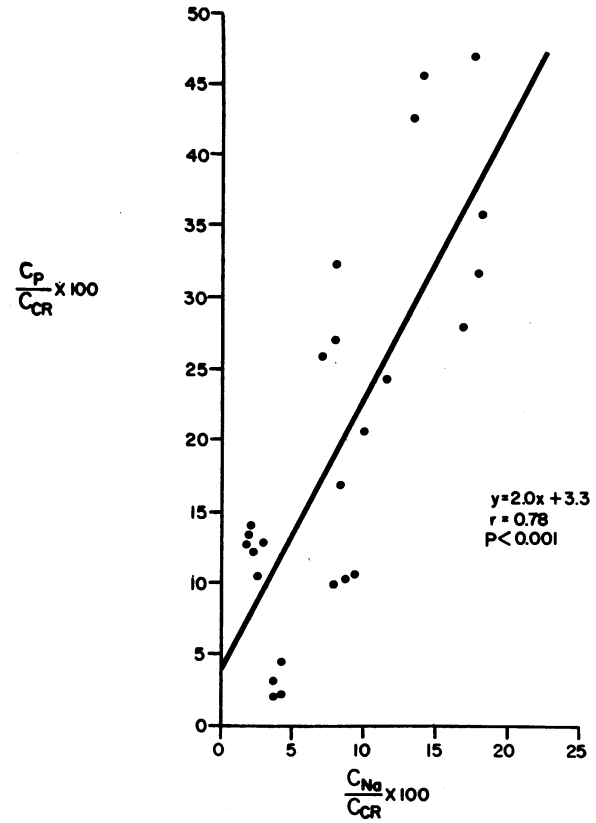

FIGURE 1 Relation between fractional phosphate excretion and fractional sodium excretion during saline infusion and normal glomerular filtration rate in intact dogs. C_P = phosphate clearance, C_{Cr} = creatinine clearance, C_{Na} = sodium clearance.

phosphate seems most likely. In addition, measurements of phosphate Tm show that ECVE is associated with a fall in Tm rate. These results suggest that the kinetics of phosphate reabsorption may be altered during ECVE.

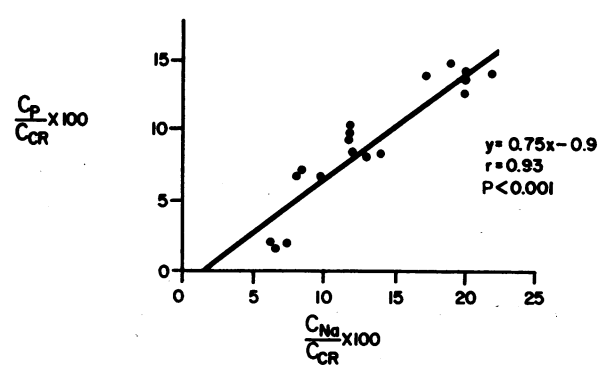

FIGURE 2 Relation between fractional phosphate excretion and fractional sodium excretion during saline infusion and normal glomerular filtration rate in thyroparathyroidectomized dogs. C_P = phosphate clearance, C_{Cr} = creatinine clearance, C_{Na} = sodium clearance.

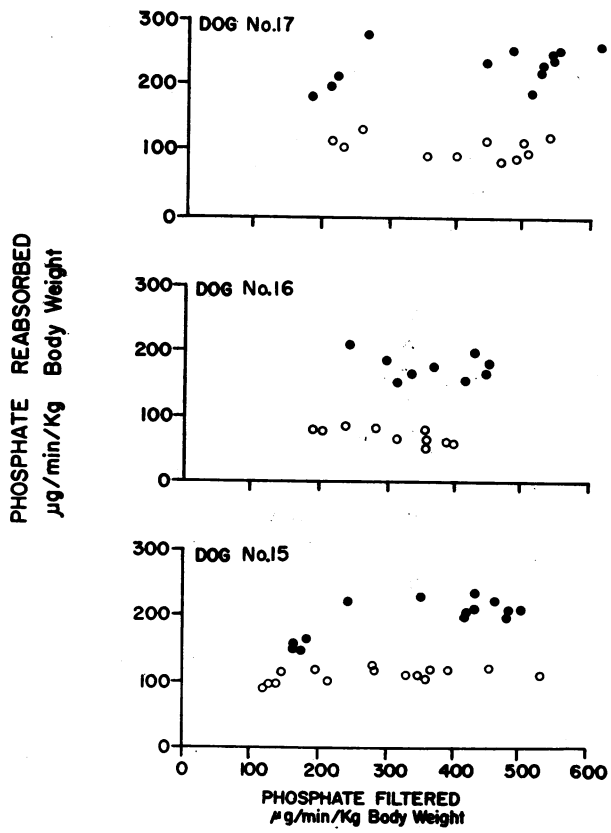

FIGURE 3 Effect of saline infusion on maximum renal tubular reabsorptive capacity of phosphate (phosphate Tm). The closed circles represent data obtained in the absence of saline infusion. The open circles represents data obtained in the same dog during saline infusion. Several days separated the two studies. The dog numbers refer to those in Table IV.

The factor(s) involved in this phenomenon cannot be delineated from the present study, but several possibilities may be considered.

It is possible that during ECVE the decrease in tubular reabsorption of various actively transported substances is secondary to a fall in their concentration in tubular fluid subsequent to a decrease in the fractional reabsorption of sodium and water in the proximal tubule. In studies carried out for the measurement of phosphate Tm, the concentration of phosphate in blood and, hence, in tubular fluid was raised at least two to three times above normal. Therefore, a fall of 10–20% in the fractional reabsorption of water cannot reduce the tubular fluid concentration of phosphate enough to explain the decrease in its tubular reabsorption. However, it is theoretically possible that in conditions other than phosphate loading the tubular transport of phosphate might diminish in response to a fall in the concentration of phosphate in tubular fluid.

The decrease in tubular phosphate reabsorption may not be explained on the basis of increased velocity of tubular fluid flow, since osmotic diuresis with a comparable degree of salt and water excretion (17) has no effect on phosphate reabsorption.

ECVE may affect a key rate-limiting step in the transport process of phosphate. Such a mechanism was suggested to explain the reduction in tubular glucose transport observed during ECVE (8). Evidence exists to suggest that some step in the reabsorptive mechanisms for glucose is common to that for phosphate (18). It is possible that events which occur as a consequence of ECVE (19) may affect such a common step in the renal transport of both glucose and phosphate.

Early, Martino, and Friedler (20) showed that a change in the interstitial fluid volume in relation to tubular fluid may underly the decrease in the tubular reabsorption of sodium during ECVE. A similar mechanism may also be responsible for the change in phosphate reabsorption. The close relationship between the fractional excretion of sodium and phosphate strongly suggests some factor(s) which is operative during ECVE decreases the tubular reabsorption of both phosphate and sodium.

In humans with chronic renal disease, there is reduced fractional reabsorption of sodium (21), calcium (22), and magnesium (22) in a pattern analogous to that observed in experimental animals undergoing ECVE (23). Furthermore, the same fraction from plasma of both uremic patients and animals with ECVE has been shown to impair *p*-aminohippurate transport by slices of renal cortex (19). The latter observation suggests the existence of a possible humoral factor which might be responsible, at least in part, for the reduced reabsorption of sodium and other substances in both uremia and ECVE. It has been shown that the reduced fractional reabsorption of phosphate observed in uremia is primarily caused by the increased activity of the parathyroid glands (24, 25). In patients with advanced renal failure (GFR $<$ 10 ml/min), the circulating levels of parathyroid hormone are greatly elevated (26), possibly to a degree that there may be maximum reduction of phosphate reabsorption; indeed, the administration of exogenous hormone to such uremic patients did not increase fractional phosphate excretion (25, 27). In spite of the possibility that there may be a maximal effect of parathyroid hormone on the renal tubules, fractional phosphate excretion varies widely in patients with advanced renal failure (22, 25, 27). The demonstration, by the present study, that ECVE reduces tubular reabsorption of phosphate permits the suggestion that factor(s) common to both ECVE and uremia could decrease the fraction reabsorption of phosphate independent of parathormone activity. Theoretically, changes in this factor(s) could contribute to variations in the magnitude of fractional phosphate excretion in uremia.

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