Regulation of Renal Bicarbonate Reabsorption by Extracellular Volume

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ABSTRACT The ability of the kidney to reabsorb bicarbonate is held to be a function of plasma CO_2 tension, carbonic anhydrase activity, and potassium stores. The effects of alterations of extracellular volume on bicarbonate reabsorption were studied in dogs whose arterial PCO_2 was kept constant at 40 mm Hg (range 35–45 mm Hg).

The effect of extracellular volume expansion was studied in dogs receiving hypertonic bicarbonate and isotonic saline, isotonic saline alone (two of the animals in this group received HCl to lower the plasma bicarbonate concentration), and isotonic bicarbonate. The results were similar in each group. Extracellular volume expansion depressed bicarbonate reabsorption. This depression was related not to changes in glomerular filtration rate (GFR) or bicarbonate concentration, but to the increase of fractional sodium excretion. In addition, volume expansion with bicarbonate increased chloride excretion.

Bicarbonate loading was performed in two groups of dogs in which effective expansion of extracellular volume was minimized by hemorrhage or acute constriction of the thoracic vena cava. Both groups demonstrated enhanced bicarbonate reabsorption relative to that seen in the volume-expanded groups. Release of the caval ligature promptly decreased bicarbonate reabsorption.

Plasma potassium decreased in all animals studied, but the changes in bicarbonate reabsorption noted could not be related to the decrease.

This study demonstrates that the state of effective extracellular volume is a major determinant of bicarbonate reabsorption by the kidney.

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INTRODUCTION

It is generally agreed that under normal conditions all of the bicarbonate filtered by the kidney is reabsorbed until the plasma concentration reaches 24–26 mEq/liter (in the dog), the so-called “renal bicarbonate threshold.” When the plasma concentration rises above 26 mEq/liter a limited amount of bicarbonate (T_m), 2.6 mEq/100 ml, of GFR is reabsorbed. All of the filtered bicarbonate in excess of this quantity is excreted into the urine. The variables controlling the level of renal bicarbonate reabsorption are held to be the plasma CO_2 tension, carbonic anhydrase activity, and body potassium stores (1).

Schwartz and coworkers (2–5) have demonstrated that most types of metabolic alkalosis can be corrected by administration of sodium chloride without the correction of any accompanying hypokalemia. Since correction of metabolic acidosis is synonymous with decreasing renal bicarbonate reabsorption, this decrease in bicarbonate reabsorption is effected by a maneuver that seems not to involve the plasma PCO_2 , carbonic anhydrase activity, or body potassium stores. It is apparent that there must be at least one additional mechanism regulating bicarbonate reabsorption.

Saline administration might decrease bicarbonate reabsorption by raising the chloride concentration and/or by expanding extracellular volume (ECV) and thereby depressing NaHCO_3 reabsorption as well as NaCl reabsorption.

This study was designed to determine if NaCl infusion would lower bicarbonate reabsorption in normal animals as it has been shown to in dogs and human subjects with metabolic alkalosis and, if such were the case, to examine the mechanism for this phenomenon.

METHODS

Experiments were performed on normal, healthy, mongrel dogs which were anesthetized with pentobarbital. An endotracheal tube fitted with an inflatable cuff was inserted into

TABLE I
The Effect of Infusion of Hypertonic NaHCO₃ and Isotonic NaCl on Bicarbonate Reabsorption

Time	Plasma					Urine			$\frac{C_{Na}}{GFR} \times 100$	Bicarbonate		
	HCO ₃ ⁻	pH	Pco ₂	Na ⁺	K ⁺	GFR	Flow	pH	Na ⁺	Filtered	Excreted	Reabsorbed
<i>min</i>	<i>mEq/liter</i>		<i>mm Hg</i>	<i>mEq/liter</i>		<i>ml/min</i>	<i>ml/min</i>		<i>μEq/min</i>		<i>μEq/min</i>	<i>mEq/100 ml GFR</i>
Dog 4; wt 13.1 kg												
0-45	Infuse 5% dextrose in H ₂ O at 1 ml/min											
45-60	21.0	7.40	35	149	3.4	17.3	0.21	5.80	3	0.1	365	0
60-75	21.0	7.40	35	147	3.5	17.8	0.21	6.14	7	0.3	370	0
75-90	20.5	7.39	35	144	3.3	21.4	0.29	6.03	6	0.2	439	0
90-105	18.5	7.31	39	146	3.1	20.5	0.23	6.10	8	0.3	379	0
105-120	Infuse 0.7 M NaHCO ₃ at 1 ml/min; stop infusion of 5% dextrose in H ₂ O											
120-135	20.4	7.33	40	148	3.0	24.3	0.20	6.32	2	0.1	496	0
135-150	23.0	7.35	43	150	3.0	20.2	0.25	6.66	8	0.3	465	1
150-165	24.6	7.37	44	153	2.9	22.6	0.46	7.09	22	0.6	556	6
165-180	23.5	7.45	35	155	3.4	21.9	1.13	7.57	54	1.6	515	37
180-195	25.8	7.49	35	156	3.0	22.1	1.47	7.76	97	2.8	570	79
195-210	26.1	7.46	38	155	2.8	18.8	1.49	7.95	127	4.4	491	113
210-225	26.2	7.45	39	156	2.9	20.5	1.73	7.88	179	5.6	537	148
225-240	28.2	7.45	41	155	3.1	20.4	2.31	7.91	264	8.4	575	197
240-255	Infuse 0.15 M NaCl at 15 ml/min											
255-270	28.8	7.46	42	161	2.7	24.4	4.95	7.73	569	14.5	703	308
270-285	27.5	7.44	42	157	2.7	19.8	5.40	7.74	628	20.2	545	287
285-300	26.3	7.43	41	156	2.6	22.0	8.33	7.67	979	28.5	579	365
300-315	25.7	7.42	41	155	2.6	25.7	9.60	7.68	1166	29.3	660	417

the trachea and connected to a Bird respirator.¹ The arterial plasma CO₂ tension was monitored throughout each experiment and kept as close to 40 mm Hg as possible by appropriate manipulation of the respirator. No clearance period was included in the study if the plasma Pco₂ was outside the range of 35-45 mm Hg. All collection periods were 10-15 min in duration.

Bicarbonate reabsorption was studied in five groups of dogs. In the first group of seven dogs, after four control periods had been obtained, 0.7 M NaHCO₃ was infused at 1 ml/min. After eight experimental periods, an infusion of 0.15 M NaCl at 10-15 ml/min was superimposed on the NaHCO₃ infusion; four more experimental periods were then obtained.

In the second group of four dogs studied, 0.15 M NaCl was infused at 10-15 ml/min; two of the dogs received 40 and 60 ml of 1 N HCl in the first liter of NaCl to lower the plasma bicarbonate concentration; 12-16 experimental periods were obtained.

In the third group of five dogs studied, 0.15 M NaHCO₃ was infused at 10-15 ml/min after three to four initial control periods were obtained; eight experimental periods were obtained.

In the fourth group of seven dogs studied, 100-200 ml of blood was collected during the two control periods, 0.7 M NaHCO₃ was then infused at 1 ml/min; 100-200 ml of blood was collected at 30-min intervals thereafter; six to eight experimental periods were obtained. While the blood was being collected, 1-2 g of NaHCO₃ were injected to raise the plasma bicarbonate concentration. After each injection an equilibration period of 15-20 min was permitted before beginning a collection period.

In the fifth group of four dogs studied, two control periods were obtained; the thoracic inferior vena cava was

then partially ligated so as to raise the venous pressure below the ligature 100 mm of H₂O above the control value. Two additional control periods were then obtained; 0.7 M NaHCO₃ was then infused at 1 ml/min. The plasma bicarbonate was raised in stepwise fashion by injections of 1-2 g of NaHCO₃. After each injection, an equilibration period of 15-20 min was permitted before beginning a collection period; four to six experimental periods were then run. Each experiment was concluded by obtaining two to three additional periods after the caval ligature had been removed.

Arterial blood samples were obtained anaerobically via an arterial catheter. CO₂ tension and pH were measured on urine aspirated from the bladder by a glass syringe at the midpoint of each collection period. In order to insure complete urine collection, the bladder was washed with air at the end of each collection period. The CO₂ tension and pH of all specimens were measured immediately after collection.

The concentration of sodium and potassium in blood and urine were measured with an Instrumentation Laboratory flame photometer.² Chloride in blood and urine was measured with a Buchler-Cotlove chloridometer.³ The pH and CO₂ tension of blood and urine were measured at 37°C with an Instrumentation Laboratory pH-gas analyzer. The concentration of CO₂ used to calibrate the CO₂ curve on this machine was checked for accuracy by both gas chromatography and Scholander determinations. The glomerular filtration rate was determined from the clearance of iothalamate-125. Iothalamate-125 was counted in blood and urine by a Packard well counter attached to a Packard automatic scaler.⁴ The validity of this technique as a measure of glomerular filtration rate was checked by running simul-

² Instrumentation Laboratory, Inc., Lexington, Mass.

³ Buchler Instruments, Fort Lee, N. J.

⁴ Packard Instrument Co., Downers Grove, Ill.

¹ Phipps and Bird, Inc., Richmond, Va.

TABLE II
The Effect of Isotonic Saline on the Renal Bicarbonate Threshold

Time	Plasma					GFR	Urine			$\frac{C_{Na}}{GFR} \times 100$	Bicarbonate		
	HCO ₃ ⁻	pH	Pco ₂	Na ⁺	K ⁺		Flow	pH	Na ⁺		Filtered	Excreted	Reabsorbed
<i>min</i>	<i>mEq/liter</i>		<i>mm Hg</i>	<i>mEq/liter</i>		<i>ml/min</i>	<i>ml/min</i>		<i>μEq/min</i>	<i>%</i>	<i>μEq/min</i>		<i>mEq/100 ml GFR</i>
Dog 23, wt 17.7 kg													
0-60	Infuse 5% dextrose in H ₂ O at 1 ml/min, 0.15 M NaCl at 10 ml/min, 40 ml 1 N HCl added to first liter of NaCl												
60-75	14.1	7.15	42	146	3.8	55.5	4.3	6.36	426	5.3	783	7	1.40
75-90	13.3	7.18	37	146	3.9	54.8	5.2	6.38	551	6.9	729	11	1.31
90-105	14.4	7.18	40	147	4.0	57.4	6.7	6.47	757	9.0	827	16	1.41
105-115	14.5	7.13	45	147	4.2	51.7	6.0	6.50	738	9.7	750	18	1.42
115-125	15.2	7.16	44	148	4.2	57.7	6.4	6.50	826	9.7	877	20	1.49
125-135	14.5	7.17	41	148	4.0	55.1	6.3	6.51	781	9.6	799	18	1.42
135-145	14.9	7.16	43	152	4.2	58.7	7.4	6.59	932	10.4	875	26	1.45
145-155	14.8	7.18	41	147	3.8	54.5	7.6	6.56	996	12.4	807	24	1.44
155-165	15.1	7.21	39	146	4.0	57.3	8.0	6.60	1088	13.0	865	28	1.46
165-175	14.7	7.21	38	147	3.9	60.3	8.0	6.68	1104	12.5	886	32	1.42
175-185	14.4	7.18	40	149	3.8	60.8	8.7	6.62	1157	12.8	876	30	1.41
185-195	14.5	7.17	41	148	3.9	57.1	8.6	6.60	1092	12.9	828	27	1.40
195-205	15.5	7.18	43	147	3.8	55.0	9.3	6.62	1135	14.0	853	32	1.51
205-215	15.5	7.18	43	148	3.7	58.4	9.9	6.71	1218	14.1	905	34	1.49
215-225	15.1	7.19	41	149	3.5	55.0	9.6	6.68	1200	14.6	831	41	1.44

taneous iohalamate-125 and exogenous creatinine clearances. 50 clearance periods were obtained from five dogs. The mean ratio of iohalamate-125 clearance for creatinine clearance was 1.01. The individual pairs of clearances were compared using the Student's *t* test for paired comparison. No significant difference was identified (*t* = 0.25, *P* = 0.4).

The bicarbonate concentration in blood and urine was calculated from the Henderson-Hasselbalch equation. A *pK'* of 6.1 was used for blood. The *pK'* used for urine was 6.33 - 0.5V/B, where B represents the total cation concentration estimated as the sum of sodium plus potassium expressed in equivalents per liter. The solubility coefficients used to convert CO₂ tension to H₂CO₃ were 0.0301 and 0.0309 for blood and urine, respectively. No correction for a Donnan factor was made in any of the calculations.

RESULTS

Volume expansion

Group 1, hypertonic NaHCO₃ and isotonic NaCl. In this group of seven dogs, hypertonic bicarbonate was slowly infused. After measurements of bicarbonate reabsorption were made, volume was expanded with isotonic NaCl. Bicarbonate reabsorption fell markedly in each animal. A representative study is presented in Table I.

In this study bicarbonate reabsorption was complete during the control period. The infusion of hypertonic bicarbonate raised the plasma bicarbonate concentration from 18.5 to 28.2 mEq/liter. At this point bicarbonate reabsorption was 1.84 mEq/100 ml GFR. With saline infusion, the plasma bicarbonate fell slightly from 28.8 to 25.7 mEq/liter. Bicarbonate reabsorption, however, halved, reaching a low level of 0.95 mEq/100 ml GFR. This decrease in bicarbonate reabsorption was associated with a marked increase in fractional sodium excretion,

the highest value noted being 29.3%. The plasma potassium was 3.4 mEq/liter at the start of this experiment; it was 2.6 mEq/liter at its conclusion. Since hypokalemia has been associated with increased bicarbonate reabsorption, it is apparent that change in the plasma potassium concentration played no role in the decrease in bicarbonate reabsorption seen in this experiment.

Group II, isotonic NaCl. This group of four dogs received isotonic saline alone in order to judge the effect of volume expansion on the bicarbonate threshold. While no clearance periods were run before the administration of saline, the urine bicarbonate concentration was measured before the saline was infused and was zero in all four animals. A representative experiment is shown in Table II.

In this experiment, where 40 ml of 1 N HCl were given with the first liter of saline, saline diuresis was already established by the time the first collection period began. Despite the fact that the plasma bicarbonate concentration was only 14.1 mEq/liter, there was a small amount of bicarbonate present in the urine (7 μEq/min). As the magnitude of the saline diuresis increased, bicarbonate excretion increased to a high of 41 μEq/min despite little change in the plasma bicarbonate concentration or in the GFR. This experiment is not remarkable for the magnitude of the bicarbonate diuresis noted, but rather for the fact that any bicarbonate at all was present in the urine at such a low plasma concentration. It clearly demonstrates that volume expansion with isotonic saline lowers the bicarbonate threshold. In this experiment the bicarbonate threshold is about 14-15 mEq/liter instead of the ac-

TABLE III
The Effect of Infusion of Isotonic NaHCO_3 on Bicarbonate Reabsorption

Time	Plasma						GFR	Urine				$\frac{\text{C}_{\text{Na}}}{\text{GFR}} \times 100$	Bicarbonate		
	HCO_3^-	pH	P_{CO_2}	Na^+	K^+	Cl^-		Flow	pH	Na^+	Cl^-		Filtered	Excreted	Reabsorbed
min	mEq/liter		mm Hg	mEq/liter			ml/min	ml/min		$\mu\text{Eq/min}$		%	$\mu\text{Eq/min}$	mEq/100 ml GFR	
Dog 18, wt 15.6 kg															
0	Infuse 5% dextrose in H_2O at 1 ml/min														
60-75	19.4	7.32	40	136	3.7	112	42.2	0.33	6.15	2	3	0.0	819	0	1.94
75-90	17.8	7.26	41	131	3.6	109	42.8	0.46	6.33	4	3	0.1	762	0	1.78
90-105	16.9	7.25	40	132	3.4	110	39.8	0.47	5.95	1	0	0.0	673	0	1.69
105-120	Infuse 0.15 M NaHCO_3 at 15 ml/min														
105-120	20.4	7.28	45	136	3.7	108	36.5	0.39	5.73	1	1	0.0	745	0	2.04
120-135	22.8	7.40	38	136	3.4	103	43.2	1.07	7.25	17	3	0.3	985	11	2.25
135-150	30.1	7.51	38	135	3.3	98	39.1	4.87	7.35	321	15	6.1	1177	291	2.27
150-165	27.5	7.46	40	139	3.1	100	43.4	6.00	7.85	318	6	5.3	1194	354	1.94
165-180	28.8	7.48	40	140	2.9	97	36.5	6.80	7.78	408	7	8.0	1051	515	1.47
180-195	34.8	7.52	44	140	2.8	95	45.7	8.33	7.90	675	8	8.0	1590	668	2.01
195-210	39.8	7.57	45	142	2.8	93	37.0	10.1	7.95	879	30	16.7	1473	929	1.47
210-225	38.9	7.59	42	145	2.7	92	41.2	11.7	7.89	1006	59	16.8	1603	1003	1.46

cepted value for dogs of 24-26 mEq/liter. Similar results were obtained in the other three dogs similarly studied.

Group III, isotonic NaHCO_3 . Five dogs were volume expanded with isotonic NaHCO_3 to determine if volume expansion alone would depress bicarbonate reabsorption independent of chloride administration. As shown in the experiment presented in Table III. ECV expansion with isotonic NaHCO_3 depressed bicarbonate reabsorption in a fashion similar to that observed when the ECV was expanded with isotonic saline. As the fractional excretion of sodium rose from less than 1 to over 16%, bicarbonate reabsorption fell despite a rising plasma bicarbonate concentration. When the plasma bicarbonate was 38.9 mEq/liter and the fractional sodium excretion 16.8%, the bicarbonate reabsorption was only 1.46 mEq/100 ml GFR. Chloride excretion which had been zero, also rose reaching a high level of 59 $\mu\text{Eq/min}$.

Table IV presents the maximum inhibition of bicarbonate reabsorption noted in all the dogs subjected to volume expansion. A standard plot of bicarbonate reabsorption per 100 ml of GFR vs. the plasma bicarbonate concentration is shown in Fig. 1. This plot includes all the points from each experiment in groups I through III. Thus, there are points obtained from each animal both before and during volume expansion. There is no discernible relationship apparent on this graph between bicarbonate reabsorption and plasma concentration. A similar plot is presented in Fig. 2. In this plot, however, only those points associated with a fractional sodium excretion of 10% or more are presented. A fractional sodium excretion of 10% or more was arbitrarily chosen so that only those points associated with

massive sodium diuresis, and inferentially massive expansion of the effective ECV, were plotted. In this graph, the bicarbonate threshold is about 13 mEq/liter; bicarbonate reabsorption plateaus at about 1.7-1.8 mEq/100 ml GFR. These values are in sharp contrast to the

TABLE IV
Maximum Inhibition of Bicarbonate Reabsorption during Volume Expansion

Dog No.	Blood		$\frac{\text{C}_{\text{Na}}}{\text{GFR}} \times 100$	Reabsorbed HCO_3^-
	HCO_3^-	P_{CO_2}		
	mEq/liter	mm Hg	%	mEq/liter 100 ml GFR
Group I				
1	21.9	35	9.0	1.42
2	19.8	45	4.7	1.75
3	33.2	36	29.6	0.50
4	25.7	41	29.3	0.95
5	25.9	35	18.2	1.41
6	22.9	35	6.7	1.57
7	27.4	35	14.2	1.78
Group II				
20	17.9	36	16.8	1.51
21	17.7	44	18.8	1.67
22	13.5	42	10.9	1.34
23	15.1	41	14.6	1.44
Group III				
15	32.3	45	11.8	1.82
16	31.7	38	6.4	1.96
17	31.3	41	6.7	2.08
18	38.9	42	16.8	1.46
19	37.4	38	21.9	1.09

FIGURE 1 Bicarbonate reabsorption vs. plasma bicarbonate concentration. All the points from each animal in groups I-III are plotted.

"normal" values for bicarbonate threshold and T_m which are 24-26 mEq/liter and 2.6 mEq/100 ml GFR, respectively.

Fig. 3 demonstrates the relationship of bicarbonate reabsorption to fractional sodium excretion. Only those points associated with a plasma bicarbonate concentra-

tion of 20 mEq/liter or more are plotted. Under "normal" conditions, all points would be expected to fall above the horizontal line were there no relationship between the two variables plotted. As is apparent, the greater the fractional sodium excretion, the lower the rate of bicarbonate reabsorption.

FIGURE 2 Bicarbonate reabsorption vs. plasma bicarbonate concentration. Only those points associated with a fractional sodium excretion of 10% or more are plotted.

Blunted volume expansion

Group IV. Seven dogs were subjected to hemorrhage and bicarbonate loading in an effort to blunt the volume expansion seen in the first three groups of dogs. The pattern of bicarbonate reabsorption seen in these

animals differed markedly from that seen in the volume-expanded dogs. Here bicarbonate reabsorption increased as the plasma bicarbonate concentration increased. A sample experiment is shown in Table V. In this experiment, the plasma bicarbonate was elevated to 37.2

FIGURE 3 The relationship between bicarbonate reabsorption and fractional sodium excretion. Only those points associated with a plasma bicarbonate concentration of 20 mEq/liter or more are plotted.

TABLE V
The Effect of Hemorrhage on Bicarbonate Reabsorption

Time	Plasma					GFR	Urine				$\frac{C_{Na}}{GFR} \times 100$	Bicarbonate		
	HCO ₃ ⁻	pH	Pco ₂	Na ⁺	K ⁺		Flow	pH	Na ⁺			Filtered	Excreted	Reabsorbed
<i>min</i>	<i>mEq/liter</i>		<i>mm Hg</i>	<i>mEq/liter</i>		<i>ml/min</i>	<i>ml/min</i>		<i>μEq/min</i>		<i>%</i>	<i>μEq/min</i>		<i>mEq/100 ml GFR</i>
Dog 10, wt 16.2 kg														
0- 60	Infuse 5% dextrose in H ₂ O at 1 ml/min													
60- 75	19.3	7.34	37	141	3.0	39.0	0.37	5.98	6		0.1	753	0	1.93
80- 95	Collect 200 ml blood													
	19.6	7.36	36	140	2.9	28.3	0.23	6.11	6		0.2	628	0	1.96
95-110	Infuse 0.7 M NaHCO ₃ at 1 ml/min; stop infusion of 5% dextrose in H ₂ O													
	19.6	7.36	36	137	3.0	30.9	0.35	6.09	9		0.2	606	0	1.96
130-145	Collect 100 ml blood; inject 1 g NaHCO ₃													
	22.7	7.41	37	139	2.7	28.2	0.42	6.13	8		0.2	640	0	2.27
165-180	Collect 100 ml blood; inject 2 g NaHCO ₃													
	27.3	7.50	36	142	2.8	38.2	0.63	6.75	20		0.4	1043	7	2.71
200-215	Collect 100 ml blood; inject 2 g NaHCO ₃													
	33.7	7.53	42	148	2.6	32.4	0.55	7.58	35		0.7	1092	44	3.23
235-250	Collect 100 ml blood; inject 2 g NaHCO ₃													
	37.2	7.55	44	152	2.5	37.3	1.01	7.95	100		1.8	1388	137	3.35

mEq/liter in a stepwise fashion by injection of sodium bicarbonate. Bicarbonate reabsorption also rose in a stepwise fashion to 3.35 mEq/100 ml GFR. The GFR at this point was almost identical with the control value. Fractional sodium excretion was only 1.8%. The ob-

served bicarbonate reabsorption is in excess of that expected for a "normal" dog with a plasma Pco₂ of 44 mm Hg. The major drawback of this technique of blunting volume expansion was that the GFR was unstable falling by as much as 50% in some animals.

TABLE VI
The Effect of Constriction of the Thoracic Inferior Vena Cava on Bicarbonate Reabsorption

Time	Plasma						GFR	Urine				$\frac{C_{Na}}{GFR} \times 100$	Bicarbonate		
	HCO ₃ ⁻	pH	Pco ₂	Na ⁺	K ⁺	Cl ⁻		Flow	pH	Na ⁺	Cl ⁻		Filtered	Excreted	Reabsorbed
<i>min</i>	<i>mEq/liter</i>		<i>mm Hg</i>	<i>mEq/liter</i>			<i>ml/min</i>	<i>ml/min</i>		<i>μEq/min</i>		<i>%</i>	<i>μEq/min</i>		<i>mEq/100 ml GFR</i>
Dog 24; wt 21.7 kg															
0- 60	Infuse 5% dextrose in H ₂ O at 1 ml/min														
60- 75	20.0	7.29	43	140	3.2	111	44.0	0.48	6.32	1	1	0.0	880	1	2.00
75- 90	20.0	7.30	42	136	3.1	111	38.5	0.51	6.02	2	2	0.0	770	0	2.00
95-100	Constrict thoracic inferior vena cava														
110-125	18.4	7.32	37	133	3.1	108	41.4	0.48	5.61	3	1	0.1	762	0	1.84
	18.5	7.31	38	135	3.1	107	35.7	0.49	5.71	2	0	0.0	660	0	1.85
140-155	Infuse 0.7 M NaHCO ₃ at 1 ml/min; stop infusion of 5% dextrose in H ₂ O; inject 1 g NaHCO ₃														
	26.9	7.45	40	145	3.0	105	38.5	0.55	7.69	29	3	0.5	1036	36	2.60
175-190	Inject 2 g NaHCO ₃														
	31.6	7.49	43	146	2.7	104	40.6	0.72	7.97	102	3	1.7	1283	121	2.86
205-220	Inject 2 g NaHCO ₃														
	34.8	7.52	44	151	2.7	103	38.5	0.69	8.10	131	2	2.3	1340	185	3.00
235-250	Inject 2 g NaHCO ₃														
	40.8	7.60	43	155	2.7	102	47.6	1.27	8.23	253	3	3.4	1942	409	3.22
255-270	Release caval constriction														
	37.1	7.54	45	158	2.7	102	43.4	3.20	8.13	707	90	10.3	1610	835	1.78
270-285	38.0	7.55	45	155	2.6	102	39.6	2.87	8.17	640	46	10.4	1505	718	1.99

Group V. Bicarbonate reabsorption was studied in four dogs subjected to acute ligation of the thoracic inferior vena cava, a maneuver known to prevent effective expansion of the ECV (6, 7). Fluctuation of the GFR was not a problem in these animals. The results obtained in this group were almost identical with those obtained in Group IV. Bicarbonate reabsorption rose as the plasma bicarbonate rose. A sample experiment is shown in Table VI. In this experiment, bicarbonate reabsorption was 3.22 mEq/liter when the plasma bicarbonate was 40.8 mEq/liter. At this point, fractional sodium excretion was 3.4% and chloride excretion 3 μ Eq/min. When the caval ligature was released, the association between plasma bicarbonate concentration and bicarbonate reabsorption was broken. There was only a slight fall in plasma bicarbonate to 37.1 mEq/liter; bicarbonate reabsorption, however, fell to 1.78 mEq/100 ml GFR; fractional sodium excretion rose to 10.3%; and chloride excretion rose to 90 μ Eq/min.

Table VII presents the highest rate of bicarbonate reabsorption noted in each animal in the two groups in which volume expansion was blunted. All the points obtained in these two groups are plotted in Fig. 4. The direct relationship between bicarbonate reabsorption and plasma bicarbonate concentration is apparent.

ECV expansion with bicarbonate was found to depress chloride reabsorption as well as bicarbonate. Fig. 5 shows the change in chloride excretion before and after ECV expansion with isotonic bicarbonate in the left panel. The right panel presents chloride excretion before and after release of the caval ligature. Chloride excretion rose significantly in every dog despite the fact

TABLE VII
Maximal Rate of Bicarbonate Reabsorption with
Blunted Volume Expansion

Dog No.	HCO ₃ ⁻	Pco ₂	$\frac{C_{Na}}{GFR} \times 100$	Reabsorbed HCO ₃ ⁻
	mEq/liter	mm Hg	%	mEq/100 ml GFR
Group IV				
8	30.9	37	1.3	3.05
9	39.2	44	0.7	2.86
10	37.2	44	1.8	3.35
11	40.5	45	2.6	3.74
12	35.2	44	3.4	3.14
13	30.3	42	0.6	2.95
14	42.3	45	2.1	3.74
Group V				
24	40.8	43	3.4	3.22
25	35.1	39	3.3	3.02
26	32.4	45	1.9	2.98
27	37.0	44	2.1	3.35

that filtered load of chloride always fell and despite the fact that no chloride whatsoever had been given during any of these experiments.

The plasma potassium concentration tended to fall in all groups of dogs studied, except group II. Table VIII shows the mean plasma potassium concentration $\pm$ the standard deviation from the mean for each experimental group. Ka and Kb represent the initial and final potassium concentration respectively. It seems unlikely that the changes in bicarbonate reabsorption noted in this

FIGURE 4 Bicarbonate reabsorption vs. plasma bicarbonate is plotted in those animals in which volume expansion was prevented by hemorrhage (closed circles) or acute constriction of the thoracic inferior vena cava (TIVC), x.

study are related to changes in plasma potassium concentration as bicarbonate reabsorption both fell and rose on the background of a falling plasma potassium concentration depending on the manipulation of ECV performed.

DISCUSSION

Renal bicarbonate reabsorption has heretofore been considered to be under the control of plasma CO_2 tension, the level of body potassium stores, and carbonic anhydrase activity (1). It has been apparent for some time that at least one other mechanism controlling bicarbonate reabsorption exists. The infusion of hypertonic NaCl has lowered bicarbonate reabsorption in normal dogs (8) and animals subjected to acute respiratory acidosis (9). This effect has been attributed to an increase in the plasma chloride concentration.

NaCl also depresses bicarbonate reabsorption in subjects with virtually all forms of metabolic alkalosis save that seen in primary aldosteronism (2-5). Since these types of metabolic alkalosis are almost all associated

TABLE VIII
Mean Plasma Potassium Values for Each
Experimental Group

Group	Ka*	Kb†
	mEq/liter $\pm$ SD	mEq/liter $\pm$ SD
I	3.4 $\pm$ 0.3	2.7 $\pm$ 0.3
II	3.6 $\pm$ 0.2	3.5 $\pm$ 0.2
III	3.4 $\pm$ 0.2	2.6 $\pm$ 0.2
IV	3.1 $\pm$ 0.2	2.5 $\pm$ 0.3
V	3.1 $\pm$ 0.2	2.4 $\pm$ 0.2

* Ka, potassium at start of experiment.

† Kb, potassium at end of experiment.

with contraction of the effective ECV, the mechanism by which NaCl depresses renal bicarbonate reabsorption might be related to changes in ECV, as well as to increased availability of chloride. The study of Cohen (10) supports this view. He corrected metabolic alkalosis in dogs, induced by ethacrynic acid and a low electrolyte diet, by expanding the ECV of his animals with an electrolyte solution isometric to their plasma, i.e., with a solution high in bicarbonate and low in chloride.

The present study demonstrates that expansion of the effective ECV with either isotonic NaCl or isotonic NaHCO_3 depresses renal bicarbonate reabsorption. Thus, chloride administration is not necessary during volume loading to depress bicarbonate reabsorption. Expansion of the effective ECV per se will depress bicarbonate reabsorption.

Volume expansion is known to depress sodium reabsorption (11-14). Fig. 3 demonstrates that as sodium reabsorption is inhibited so is that of bicarbonate. Fig. 5 shows that when volume is expanded with isotonic NaHCO_3 chloride reabsorption is also inhibited. These observations lend further weight to the thesis that acute expansion of effective ECV, by whatever means, results in decreased chloride and bicarbonate reabsorption, most likely as a consequence of depressed sodium reabsorption.

Volume expansion with NaHCO_3 alone has not previously been shown to depress bicarbonate reabsorption. Pitts and Lotspeich (8) infused bicarbonate at rates equivalent to those used in this study. However, they used hypertonic NaHCO_3 raising the plasma bicarbonate concentration to almost 60 mEq/liter. Such a procedure results in marked metabolic alkalosis and hypernatremia which by itself might change the rate of bicarbonate transport. In this study, when volume was expanded with isotonic NaHCO_3 , the pH was always less than 7.60 and the plasma sodium concentration was less than 150 mEq/liter. Some of Pitts and Lotspeich's dogs were made acidotic with NH_4Cl before being studied. These animals may have been volume depleted because of this

FIGURE 5 Chloride excretion before (open circles) and after (closed circles) volume expansion with isotonic NaHCO_3 is presented in the left panel. The right panel presents chloride excretion before (open circles) and after (closed circles) release of thoracic vena caval ligature in dogs subjected to bicarbonate loading.

maneuver and thus relatively resistant to volume expansion. In addition, the plasma P_{CO_2} was not controlled and their animals were unanesthetized. A recent study (15) has suggested that dogs are more easily volume expanded when anesthetized. While the infusion rates in Pitts and Lotspeich's study were equivalent to those used in this study, the rate of infusion relative to GFR was much less. The GFR's of their animals ranged from 50 to 100 ml/min, while the range of GFR of the animals in group III of this study was 20–50 ml/min. Since $NaHCO_3$ is so much more readily excreted than $NaCl$, more of it, relative to GFR, must be given to cause effective expansion of ECV.

The finding that ECV expansion inhibits bicarbonate reabsorption in the dog is in accord with studies in the rat that have demonstrated that volume expansion depresses bicarbonate reabsorption in the proximal tubule (16) and that over-all bicarbonate reabsorption is depressed by volume expansion (17).

This study also demonstrates that when volume expansion during bicarbonate loading is prevented or minimized, no T_m is reached. Bicarbonate reabsorption rises as the plasma bicarbonate concentration rises, albeit with a marked splay. This observation is in agreement with studies in humans (18) and rats (17) which show no bicarbonate T_m when volume is not expanded.

The present study demonstrates that the state of effective ECV is of critical importance in setting the level of renal bicarbonate reabsorption. It would, therefore, seem unwarranted to use the term T_m since bicarbonate reabsorption varies so markedly depending on the state of effective ECV and since three separate studies have failed to demonstrate a maximal rate of bicarbonate reabsorption when volume is not expanded.

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