THE EFFECT OF ACUTE RESPIRATORY ACIDOSIS ON THE INTERNAL EQUILIBRIUM OF POTASSIUM [1]

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There are conflicting reports on the effect of acid-base imbalance on the intracellular-extracellular distribution of potassium. The *in vitro* studies of Fenn and Cobb (1), and studies in dogs by Abrams, Lewis, and Bellet (2), Keating and his co-workers (3), and Pitts (4) suggest that metabolic acidosis results in a shift of potassium from the cells to the extracellular space, while metabolic alkalosis may lead to inward movement of potassium. In apparent contradiction, muscle analyses from Darrow's laboratory (5–8) demonstrate that muscle potassium is low in metabolic alkalosis and normal or slightly high in metabolic and respiratory acidosis. The findings of Darrow have been confirmed in metabolic alkalosis and acidosis by Cotlove, Holliday, Schwartz, and Wallace (9) and have led to the assumption that acidosis causes potassium to enter the cells and alkalosis causes potassium to leave the cells. These conflicting views may be due to a failure to separate the effect of acid-base imbalance on internal distribution of potassium from its effect on changes in total body potassium. This study attempts to separate these two effects by using inhalation of CO_2 to alter pH in dogs with ligated ureters and in dogs with intact ureters. This technique has the advantage of maintaining the total body potassium at a nearly constant level and at the same time altering the pH without inducing volume changes in the extracellular space as a result of infusions of acidifying and alkalinizing salts.

Respiratory acidosis resulted in a progressive rise over a four-hour period in the concentration of potassium in the extracellular space. This alteration in concentration ratio of potassium between the extracellular space and the cells persisted as long as the alteration in pH persisted.

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MATERIAL AND METHODS

All experiments were performed on mongrel dogs lightly anesthetized with Nembutal®. Respiratory acidosis was induced by inhalation of 30 per cent CO_2 and 70 per cent O_2 through a tight-fitting intratracheal catheter. Ventilation was well maintained and arterial oxygen unsaturation did not occur. Serial blood specimens were taken at frequent intervals with blood replacement.

Respiratory acidosis was studied in ten dogs while ten additional anesthetized dogs served as controls. Five dogs from each group underwent bilateral ureteral ligation immediately prior to the experimental period. Experiments in dogs with respiratory acidosis and in control dogs lasted ten hours when the ureters were ligated and six hours when the ureters were intact. Changes in electrolyte balances and in plasma electrolyte levels were followed for the duration of the experiments. Accurate urine collections were insured by washing the bladder with water and air.

Distribution of an intravenous potassium load was studied in ten additional dogs with intact ureters. Five control dogs and five dogs breathing 30 per cent CO_2 and 70 per cent O_2 received the potassium load. Respiratory acidosis was induced immediately prior to the beginning of the infusion, which was administered with a constant rate infusion pump using a solution which contained 400 mEq. per L. KCl and 100 mEq. per L. $KHCO_3$. This composition was selected to minimize any alteration of acid-base balance which might result from the infusion. In these experiments loading continued until the electrocardiogram demonstrated potassium intoxication as evidenced by the disappearance of P waves or widening of the QRS complex. The infusion was then slowed until a near steady state was achieved at the toxic level. This level was maintained for one hour or more. The infusion was then stopped. The final specimens were obtained about one-half hour after the infusion was stopped and the balance period terminated at this point.

In all experiments loss of water due to increased respiratory activity of the dogs breathing 30 per cent CO_2 and 70 per cent O_2 was minimized by running the gas through a porous filtercandle which was immersed in water. Differences in muscular activity due to increased respiratory effort of the acidotic dogs were minimized by keeping the control dogs so lightly an-

TABLE I

Serial changes in plasma potassium and pH in control dogs and dogs with respiratory acidosis

Dog	Time in hours	0	1/6	2	4	6	8	10
				A. Ligated Ureters				
Control								
1	K	3.9		3.8	3.5	4.8		
	pH	7.31		7.32	7.30	7.26		
2	K	4.4		4.8	5.8	7.7	6.7	5.5
	pH	7.28		7.40	7.35	7.41	7.43	7.52
3	K	4.3		4.4	4.9	4.9	4.7	4.7
	pH	7.29		7.35	7.26	7.44	7.50	7.59
4	K	3.9		3.8	4.3	4.4	4.9	4.2
	pH	7.30		7.50	7.23	7.24	7.36	7.50
5	K	4.0		4.1	4.5	5.0	4.9	4.8
	pH	7.46		7.49	7.46	7.43	7.34	7.40
Mean:	K	4.1		4.2	4.6	5.4	5.3	4.8
Mean:	pH	7.33		7.41	7.32	7.36	7.41	7.50
Acidosis								
6	K	4.4		6.0		7.8	9.4	9.5
	pH	7.41		6.92		6.91	6.91	6.92
7	K	4.6	4.0	6.7	8.2	7.7	7.3	7.8
	pH	7.50	7.17	6.86	6.83	6.78	6.78	6.72
8	K	4.2	4.5	5.8	7.5	8.1	8.8	9.1
	pH	7.37	6.88	7.04	7.05	6.87	6.96	7.05
9	K	4.0	4.0	7.0	8.6	8.3	8.1	9.2
	pH	7.36	6.95	6.95	7.13	7.20	6.98	6.96
10	K	4.0	4.4	6.1	6.3	6.6	6.0	6.8
	pH	7.37	7.10	7.16	7.18	7.22	7.23	7.18
Mean:	K	4.2	4.2	6.3	7.7	7.7	7.9	8.5
Mean:	pH	7.40	7.03	6.99	7.05	7.00	6.97	6.97
				B. Intact Ureters				
Control								
11	K	3.6			3.6	4.1		
	pH	7.40			7.42	7.40		
12	K	3.9			4.0	4.2		
	pH	7.39			7.32	7.50		
13	K	4.0			3.8	3.8		
	pH	7.34			7.41	7.45		
14	K	3.9		3.5	3.8	3.9		
	pH	7.46		7.55	7.43	7.43		
15	K	4.4		4.3	4.3	4.3		
	pH	7.35		7.47	7.44	7.50		
Mean:	K	4.0		3.9	3.9	4.1		
Mean:	pH	7.39		7.51	7.40	7.46		
Acidosis								
16	K	4.2	4.6	6.5	6.6	6.7		
	pH	7.42	6.96	6.75	6.75	6.72		
17	K	4.2	4.3	5.4	5.6	6.0		
	pH	7.35	6.88	6.90	6.90	6.84		
18*	K	3.8	3.8	4.8	5.4	4.6		
	pH	7.46	7.06	7.03	6.97	6.95		
19	K	4.3	4.0	6.2	7.0	6.9		
	pH	7.45	6.85	6.90	6.86	6.82		
20*	K	3.6	4.0	5.7	5.9	5.7		
	pH	7.43	7.00	6.91	6.94	6.94		
21†	K	4.1		7.1	9.3			
	pH	7.36	6.78	6.75	6.74			
Mean:	K	4.0	4.0	5.7	6.1	6.0		
Mean:	pH	7.42	6.95	6.90	6.88	6.85		

* Fasted 48 hours prior to acidosis.
† Not included in means because of functional oliguria.

esthetized that there were vigorous involuntary leg movements during the period of study.

Arterial blood samples were collected anaerobically from an indwelling femoral cannula. Whole blood pH was determined within one minute at 38° C. using a Coleman pH meter with a glass electrode. Heparinized plasma was analyzed for sodium and potassium using a Baird internal standard flame photometer. Plasma chloride was determined by a mercury titration (10). Plasma bicarbonate was determined by a titration method (11) modified in that the final titration was carried to the original pH of each sample instead of pH 7.4. This modification insured that the true bicarbonate value was obtained in specimens taken during 30 per cent CO_2 inhalation. Whole blood glucose was determined by the method of Benedict (12).

Changes in the internal distribution of potassium were calculated as follows:

1) Final volume of the Extracellular Space

$$E_2 = \frac{E_1Cl_1 + bCl}{Cl_2}$$

where:

E_1 = 20 per cent body weight = Initial volume extracellular space
E_2 = Final volume extracellular space
Cl_1 = Initial plasma chloride level
Cl_2 = Final plasma chloride level
bCl = Chloride balance

2) Change in the Extracellular Potassium Content

$$KE_1 = E_1 \times K_1$$
$$KE_2 = E_2 \times K_2$$
$$\Delta KE = KE_2 - KE_1$$

where:

KE_1 = Initial content of potassium in the extracellular space
KE_2 = Final content of potassium in the extracellular space
K_1 = Initial plasma potassium level
K_2 = Final plasma potassium level

3) Change in the Intracellular Potassium Content

$$\Delta KI = bK - \Delta KE$$

where:

ΔKI = Change in the intracellular potassium content
ΔKE = Change in the extracellular potassium content
bK = Potassium balance

The potassium balance was not corrected for nitrogen. Chloride space calculations were not corrected for plasma water or Donnan effect because these corrections did not significantly alter the potassium transfer calculations.

Basing calculation of potassium transfer on changes in the chloride space weights the data slightly in favor of our hypothesis because the chloride space increases in some of the acidotic animals. However, calculation of the data assuming no change in the extracellular space does not significantly alter the differences observed between control and acidotic animals.

RESULTS

Effect of respiratory acidosis on potassium transfer in dogs receiving no potassium load

Table IA records the serial changes in plasma potassium and pH in dogs with ligated ureters during respiratory acidosis and in control dogs with ligated ureters. Table IB contains similar data for animals with intact ureters. Figures 1A and 1B are graphs of the average change in the plasma potassium levels in dogs with ligated

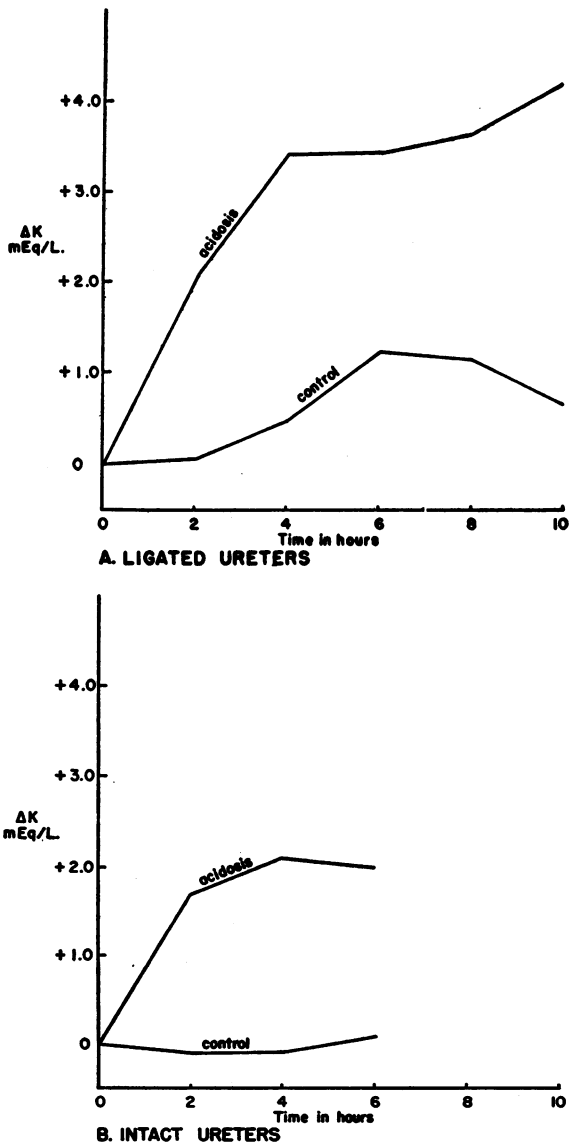

FIG. 1. AVERAGE CHANGE IN PLASMA POTASSIUM LEVELS IN CONTROL DOGS AND DOGS WITH RESPIRATORY ACIDOSIS

TABLE II

Data obtained in control dogs and dogs with respiratory acidosis

Dog	Wt. *kg.*	Exp. time *hrs.*	Blood: Hct. Init.*	Hct. 10 min.†	Hct. Final	Glucose Init.*	Glucose Max.	Glucose Time *hrs.*‡	Plasma: Bicarbonate Init.*	Bicarbonate Final	Potassium Init.*	Potassium Final	Chloride Init.*	Chloride Final	Sodium Init.*	Sodium Final	Urine: Vol. *ml.*§	Na^+ *mEq.*§	K^+ *mEq.*§	Cl^- *mEq.*§
											A. Ligated Ureters									
Control																				
1	15.0	6									3.9	4.8								
2	20.9	10	48		49	95	86	10	28.5	22.5	4.4	5.5	114	111	148	144				
3	18.6	10	49			90	75	4	24.8	24.0	4.3	4.7	110	108	147	145				
4	11.3	10	43		53				26.0	18.5	3.9	3.9	108	114	149	150				
5	14.9	10	62		58	128	210	4	25.0	18.0	4.0	4.8	110	111	149	147				
Acidosis																				
6	15.1	7									4.4	9.4								
7	10.7	10	45	66	67	99	204	¼	21.5	29.5	4.6	7.8	119	113	149	155				
8	22.7	10	51	61	67	172	210	¼	20.5	22.5	4.2	9.1	114	113	152	157				
9	21.0	10	63	55	54	141	232	4	23.8	29.5	4.0	9.2	115	111	148	150				
10	30.5	10	54	56	59	95	103	¼	17.5	24.8	4.0	6.9	107	105	148	157				
											B. Intact Ureters									
Control																				
11	13.5	6	41		41	99	89	3	21.3	22.5	3.6	4.1	110	110	150	149	38	2.2	8.6	2.8
12	15.5	6	39		40	85	104	2	17.5	22.0	3.9	4.2	109	109	146	145	54	6.8	11.9	6.7
13	11.8	6	38		41	86	66	5			4.0	3.8	112	113	147	145	30	4.4	5.6	5.9
14	21.3	6	36		39	79	87	4	27.0	23.0	3.9	3.9	112	111	146	139	295	27.4	16.2	12.8
15	18.5	6	40		50	88	63	1½	24.5	20.0	4.4	4.3	110	111	147	145	174	21.5	10.1	14.8
Acidosis																				
16	20.0	6							20.8	32.2	4.2	6.7	113	109	155	156	155	10.0	29.8	13.2
17	19.0	6	34	45	54	100	248	2	26.5	32.0	4.2	6.0	107	105	150	149	103	1.7	8.2	2.7
18‖	22.1	6	52	55	58	65	90	2	20.0	28.5	3.8	4.6	112	105	150	149	141	19.7	41.0	20.0
19	20.3	6	48	55	61	97	154	9	26.0	34.8	4.3	6.9	111	103	148	149	272	19.3	47.1	24.2
20‖	12.9	6	37	45	47	71	94	2	23.0	30.0	3.6	5.7	113	107	149	147	130	9.8	16.9	7.2
21	20.0	4	41		50				19.9	22.5	4.1	9.3	117	110	158	159	44	1.4	5.3	1.5

* Initial values obtained before induction of respiratory acidosis.
† Ten minutes after induction of respiratory acidosis.
‡ Time at which maximum glucose level was recorded.
§ Total amount excreted during experimental period.
‖ Fasted 48 hours prior to acidosis.

and intact ureters. In the acidotic dogs with ligated ureters plasma potassium levels rose an average of 4.3 mEq. per L. in ten hours as compared with 0.7 mEq. per L. rise in the controls. The plasma potassium level in acidotic dogs with intact ureters rose an average of 2.0 mEq. per L. in six hours as compared with a rise of 0.1 mEq. per L. in controls.

Tables IIA and IIB record the results of blood and urine analysis before beginning respiratory acidosis and during the experimental period. In addition to the potassium changes noted above, respiratory acidosis resulted in a rise in the plasma bicarbonate and a fall in the plasma chloride. Changes in the plasma sodium were generally small, although there was a slight rise in acidotic animals with ligated ureters. Blood glucose levels rose significantly in all but one of the non-fasted acidotic animals and tended to be maximal fifteen minutes after the onset of acidosis. Dogs No. 18 and No. 20, which were fasted for 48 hours prior to respiratory acidosis, demonstrated no elevation in blood glucose. The hematocrit rose sharply in all acidotic animals with a major portion of the rise complete within ten minutes. Urinary excretion of electrolytes varied widely and with the possible exception of dogs 18 and 19 which excreted a large amount of potassium during acidosis, there was no significant difference between control and acidotic dogs.

Calculated transfers of potassium from the cells to the extracellular space in dogs with ligated ureters are recorded in Table IIIA. The mean values in the last column of Table IIIA indicate that acidotic dogs with ligated ureters transferred approximately seven times as much potassium from the cells to the extracellular space as did the controls.

Calculated transfers in dogs with intact ureters are recorded in Table IIIB. The mean values in the last column indicate that acidotic dogs with intact ureters lost three times as much potassium from their cells as did the controls. This difference occurred despite a fairly large loss of potassium from the cells of the control dogs which resulted from basal renal excretion (daily turnover) of potassium. Even more significant was the increase of 0.41 mEq. potassium per kg. body weight in the extracellular space of acidotic dogs as compared with no change in the control dogs (column 4, Table IIIB).

In the one dog (No. 10) in which the plasma potassium level was followed after the termination of acidosis, the level fell from 6.8 mEq. per

TABLE III

Transfer of potassium in control dogs and in dogs with respiratory acidosis *

A. Ligated ureters				B. Intact ureters					
Dog	ΔCl space *liters*	ΔKe† *mEq.*	ΔKe† *mEq./kg.*	Dog	ΔCl space *liters*	ΔKe *mEq.*	ΔKe *mEq./kg.*	ΔKi *mEq.*	ΔKi *mEq./kg.*
Control				*Control*					
1	0.00	2.7	0.18	11	−0.02	1.3	0.10	− 9.9	−0.73
2	0.10	5.1	0.24	12	−0.06	0.7	0.05	−12.6	−0.81
3	0.06	1.8	0.10	13	−0.07	−0.8	−0.07	− 4.8	−0.41
4	−0.12	−0.5	−0.04	14	−0.09	−0.4	−0.02	−15.8	−0.74
5	−0.02	2.3	0.15	15	−0.17	−1.1	−0.06	− 9.0	−0.49
		Mean:	0.13			Mean:	0.00	Mean:	−0.64
Acidosis				*Acidosis*					
6	0.00	15.1	1.00	16	0.02	10.1	0.50	−39.9	−2.00
7	0.12	7.7	0.72	17	0.04	7.0	0.37	−15.3	−0.80
8	0.04	22.6	1.00	18‡	0.11	4.0	0.18	−45.0	−2.03
9	0.15	23.2	1.11	19	0.09	11.1	0.55	−58.2	−2.84
10	0.14	18.5	0.61	20‡	0.08	5.9	0.46	−22.8	−1.77
				21§	0.23	22.8	1.16	−28.1	−1.41
		Mean:	0.89			Mean:	0.41	Mean:	−1.89

* ΔKe—change in potassium in extracellular space.
ΔKi—change in potassium in intracellular space.
† ΔKe equals ΔKi because ureters are ligated.
‡ Fasted 48 hours prior to acidosis.
§ Not included in means because of functional oliguria.

TABLE IV

Effect of hypertonic potassium load on composition of blood and urine in control dogs and dogs with respiratory acidosis

Dog	Wt. kg.	Infusion Time hours	Infusion K^+ mEq.	Infusion Cl^- mEq.	Blood pH Average	Plasma Potassium Initial	Plasma Potassium Final*	Plasma Chloride Initial	Plasma Chloride Final*	Urine Vol. ml.	Urine K^+ mEq.	Urine Cl^- mEq.
Control												
22	19.0	1.6	73	58	7.45	3.4	5.8	111	115	372	43.7	24.0
23	20.0	1.5	61	49	7.47	3.7	8.5	108	114	50	5.9	3.0
24	16.2	1.6	80	64	7.30	3.0	5.8	112	119	206	25.1	23.0
25	27.0	1.8	135	108	7.33	4.4	9.7	111	117	259	34.0	32.0
26	16.3	1.9	99	79	7.36	3.8	6.8	109	115	241	31.0	41.9
Acidosis												
27	16.4	3.6	38	30	6.90	3.5	8.8	107	102	406	19.6	29.5
28	17.6	1.3	43	35	6.82	3.9	10.4	112	110	356	18.5	7.9
29	8.5	1.8	31	25	7.01	3.8	8.4	108	109	220	25.0	42.5
30	11.0	2.2	17	14	6.89	3.9	10.4	115	114	2	0.2	0.1
31	14.8	2.8	39	31	6.99	4.3	7.9	115	110	226	32.2	26.9

* Level taken one-half hour after termination of infusion.

L. to 4.8 mEq. per L. in eight hours. This fall must represent a re-entry of potassium into the cells since ureteral ligation prevented urinary loss and there were no observed gastro-intestinal losses.

Distribution of a potassium load in dogs with respiratory acidosis

The data recorded in Table IV were used to calculate the distribution of potassium infused into five acidotic and five control dogs. Table V records the calculated transfers. It is important (column 3, Table V) that despite the large amount of chloride infused, the changes in the chloride space were small, similar in both control and acidotic dogs and therefore did not contribute to the differences observed in the distribution of retained potassium. The mean values recorded in the last column of Table V indicate that on the average only 27 per cent of the potassium retained by the control dogs remained in the extracellular space. In contrast, 113 per cent of the potassium retained by the acidotic dogs remained in the extracellular space. In other words, the cells of acidotic dogs lost potassium despite an

TABLE V

Distribution of infusion of potassium in control dogs and dogs with respiratory acidosis *

Dog	Balance K^+ mEq.	Balance Cl^- mEq.	ΔChloride space liters	ΔKe mEq.	ΔKe mEq./kg.	ΔKi mEq.	ΔKi mEq./kg.	Retained K^+ remaining in extracellular space %
Control								
22	29	34	0.17	10.0	0.53	19.0	1.00	33
23	55	46	0.19	20.8	1.04	34.2	1.71	38
24	55	41	0.14	9.9	0.61	45.1	2.79	18
25	101	76	0.38	32.2	1.19	68.8	2.54	32
26	68	37	0.14	10.7	0.66	57.3	3.51	16
							Mean:	27
Acidosis								
27	18	0	0.16	18.8	1.15	−0.8	−0.05	104
28	24	27	0.31	26.0	1.48	−2.0	−0.11	108
29	7	−18	−0.17	6.4	0.75	0.6	0.07	91
30	17	14	0.15	15.8	1.43	1.2	0.11	93
31	7	4	0.16	11.9	0.80	−4.9	−0.33	170
							Mean:	113

* ΔKe—Change in potassium in extracellular space.
ΔKi—Change in potassium in intracellular space.

external potassium load which elevated the plasma potassium to toxic levels. Since the longer loading period and slightly higher serum levels in the acidotic dogs would favor movement of potassium into the cells of the acidotic dogs, the differences observed are even more significant.

DISCUSSION

The confusion regarding the effect of acid-base imbalance on the internal distribution of potassium may be due to the fact that large changes in total body potassium have in the past obscured alterations in internal distribution of potassium. The above experiments with respiratory acidosis, in which changes in total body potassium were minimized, clearly demonstrate an increase in the concentration of potassium in the extracellular space of acidotic dogs. Regardless of the source of this potassium, the concentration ratio between the extracellular space and the cells $(K)_E/(K)_I$, was increased and the increase was maintained as long as the pH remained altered. The fact that infused potassium markedly elevated the serum level of acidotic dogs without causing transfer of potassium into the cells further supports the conclusion that acidosis raises $(K)_E/(K)_I$.

That $(K)_E/(K)_I$ is elevated in acidosis was first suggested by the observations of Fenn and Cobb in 1934 (1). Studying isolated frog muscle they noted that when the external media was acid, a higher than normal potassium level was required in the media to prevent potassium loss from muscle. Abrams, Lewis, and Bellet (2), infusing ammonium chloride rapidly into dogs, noted an inverse relation between pH and serum potassium level. Keating and his co-workers (3) performed experiments similar to those of Abrams, Lewis, and Bellet but used nephrectomized dogs whose body space volumes were accurately measured. Their data demonstrate that metabolic acidosis produced by sodium chloride or ammonium chloride infusions caused hyperkalemia as a result of a transfer of potassium from the cells to the extracellular space. Pitts (4) infused HCl into nephrectomized dogs and obtained results similar to those of other workers (3).

Our studies of respiratory acidosis by demonstrating the same increase in the concentration ratio of potassium as was demonstrated in metabolic acidosis by Fenn and Cobb (1), Abrams, Lewis, and Bellet (2), Keating and his co-workers (3), and Pitts (4) permit the conclusion that the increase in $(K)_E/(K)_I$ was related to pH change rather than to alteration in bicarbonate or pCO_2.

If acidosis raises $(K)_E/(K)_I$ then alkalosis may decrease the ratio. Fenn and Cobb (1) studying isolated frog muscle noted that when pH of the external media was elevated, a lower than normal potassium concentration still prevented potassium loss from the muscle. Keating and his co-workers (3) demonstrated that when sodium bicarbonate was infused into nephrectomized dogs there was a fall of about 1 mEq. per L. in the serum potassium level. The extracellular potassium content increased about 1 mEq. due to expansion of the extracellular space. Pitts (4) reported a typical experiment involving the infusion of sodium bicarbonate into a nephrectomized dog. He noted a decrease of 1.6 mEq. per L. in serum potassium level and a decrease of about 15 per cent in the potassium content of the extracellular space despite a marked increase in the volume of this space. Studies by Stanbury and Thomson (13) of acute respiratory alkalosis in humans demonstrated both a fall in serum potassium level and an increase in urinary excretion of potassium. Although the increase in potassium excretion may have accounted for the fall in the serum level, the fact that potassium did not shift from the cells to sustain the serum level suggests that the respiratory alkalosis may have lowered $(K)_E/(K)_I$ to prevent this shift. Respiratory alkalosis (pH 7.8) was studied in this laboratory using dogs with ligated ureters. Respiratory alkalosis invariably caused a fall in the serum potassium to levels as low as 2.6 mEq. per L. The average decrease in the serum potassium level was 2.2 mEq. per L. below control levels, and was sustained as long as the pH remained elevated (14).

The data in this paper when considered in conjunction with the earlier work on metabolic acidosis and metabolic and respiratory alkalosis permit the formulation of a hypothesis: acidosis increases and alkalosis decreases the potassium concentration ratio between the extracellular space and the cells. Expressed in another way: $(K)_E/(K)_I$ varies inversely with pH of plasma. In citing the above references on alkalosis in support of this hypothesis it is important to distin-

guish changes in extracellular potassium concentration from changes in extracellular potassium content. For example, in the experiments of Keating and his co-workers (3) potassium content in the extracellular space actually increased slightly due to expansion of the space when sodium bicarbonate was infused to produce alkalosis. However, the falling serum level halved $(K)_E/(K)_I$. Acidifying infusion of NaCl, on the other hand, while causing equal expansion of the extracellular space resulted in a rise in the serum potassium level which doubled this ratio.

Muscle analyses in humans by Mudge and Vislocky (15) suggest that alterations in the potassium concentration ratio induced by acid-base disorders also exist in states of chronic potassium depletion. Tables IA and IB of Mudge and Vislocky (15) record serum potassium levels in mEq. per L. and muscle potassium levels in mEq. per L. of intracellular water. $(K)_E/(K)_I$ may be calculated for each patient. With the exception of patient R-3 who was studied *post mortem*, $(K)_E/(K)_I$ is uniformly and significantly lower in alkalotic than in acidotic patients. It is important to point out that potassium depletion alone will also decrease $(K)_E/(K)_I$. (Potassium depletion causes a greater fall in the serum level than in the intracellular level.) In spite of this, the alkalotic patients had lower ratios than the acidotic patients who were more severely depleted of potassium. For example, patient R-1 with alkalosis (venous pH 7.53) had a serum potassium level of 2.2 mEq. per L. and a muscle potassium level of 136 mEq. per L. giving a $(K)_E/(K)_I$ of 0.016. Patient P with acidosis (venous pH 7.25) had a serum potassium level of 2.9 mEq. per L. and a muscle level of 120 mEq. per L. giving a ratio of 0.024. In other words, the patient with acidosis had a higher serum level even though he was more depleted. Patient K with severe alkalosis (venous pH 7.62) is of particular interest. He had a low serum potassium level (1.8 mEq. per L.) and a nearly normal muscle level (146 mEq. per L.) giving a ratio of 0.012. If intracellular potassium levels are expressed as mEq. per kg. fat free solids the differences in the ratios are even more striking. These studies of Mudge and Vislocky therefore support the hypothesis that $(K)_E/(K)_I$ varies inversely with plasma pH and suggest that the ratio remains altered as long as the plasma pH remains altered.

When the apparently conflicting data on muscle analyses from Darrow's laboratory (5, 6, 8) are reviewed in the light of the above discussion it is apparent, as the authors point out, that their finding of a low potassium level in muscle of rats with chronic metabolic alkalosis is the result of increased renal loss of potassium. This renal response has been confirmed in dogs by Franglen, McGarry, and Spencer (16). However, these muscle analysis experiments, including the study of chronic respiratory acidosis (7) cannot be used to support the concept that raising the extracellular pH causes an internal redistribution of potassium toward the extracellular space for the following reasons: First, a large change in total body potassium must have taken place in order to have measurable changes in muscle potassium. Second, calculation of $(K)_E/(K)_I$ for these experiments cannot be evaluated because the authors point out that serum potassium levels in rats anesthetized with ether are unreliable (6). Third, the experiments were such that at the time plasma and muscle measurements were made the pH levels were near normal.

Calculation of the ratio $(K)_E/(K)_I$ can be made from the data obtained in rats studied by Cotlove, Holliday, Schwartz, and Wallace (9). Although the pH alterations in acidosis and alkalosis, group II and III, were small acidosis increased and alkalosis decreased $(K)_E/(K)_I$. Group IV with potassium deficiency alone did not have the expected lowering $(K)_E/(K)_I$. Group V with potassium deficiency and acidosis had the same serum potassium level as alkalotic group III but a much lower muscle level. The studies of Cotlove with the exception of group IV, which the author emphasized was a non-homogenous group, are consistent with our hypothesis.

Discussion of the mechanisms by which pH change alters $(K)_E/(K)_I$ must be largely speculative. Fenn and Cobb (1) originally postulated a simple buffering mechanism between the cells and the extracellular space. They likened the potassium transfers to the chloride shift that takes place in the red blood cell with variations in pH. Since anions do not freely cross membranes of tissue cells, potassium and hydrogen shift during intracellular buffering instead of chloride and bi-

carbonate. Intracellular buffering may be the chief mechanism responsible for altering $(K)_E/(K)_I$ when the pH changes because acidosis and alkalosis alter the ratio in the opposite direction.

MacKay (17) has suggested glycogen breakdown to explain the hyperkalemia of respiratory acidosis. She produced respiratory acidosis in cats with 34 per cent carbon dioxide in oxygen and demonstrated a transient marked hyperkalemia. This was maximal at five minutes and returned to near normal at thirty to sixty minutes. Since this hyperkalemic response was largely abolished by evisceration, she concluded that it represented potassium released from liver glycogen. Respiratory acidosis in dogs is accompanied by hyperglycemia (Table II). However, glycogenolysis is not the principal source of the hyperkalemia for the following reasons: 1) Hyperglycemia was not maximal at the time of maximal hyperkalemia; 2) fasted dogs No. 18 and No. 20 developed hyperkalemia without hyperglycemia; 3) judging from the distribution of potassium loads in control dogs (Table V), 70 per cent of potassium released from glycogen would enter the cells if $(K)_E/(K)_I$ were unaltered by acidosis. This would require more potassium than exists in glycogen stores.

The possibility that acidosis may produce hyperkalemia through change in the partition of sodium must also be considered. A partial interference with the metabolic reactions supplying energy to the "sodium pump" might result in a shift of sodium into the cells and an outward shift of potassium during several hours of acute respiratory acidosis. The rising plasma sodium level in the acidotic dogs with ligated ureters suggests that, if anything, sodium entered the extracellular space. However, careful measurements of changes in the volume of the extracellular space are needed to determine the direction of the sodium transfer.

The rise in hematocrit values of acidotic dogs was largely complete within ten minutes and appears to be significant. It can be explained only in small part by the swelling of cells known to occur as part of the chloride shift. The other factors involved in this change in hematocrit await further investigation.

Even in the presence of intact kidneys (Figure IB) respiratory acidosis increased $(K)_E/(K)_I$. The data of Mudge and Vislocky (15) and of Cotlove, Holliday, Schwartz, and Wallace (9) demonstrate that in both alkalosis and acidosis the alterations in $(K)_E/(K)_I$ persist as long as the pH remains altered. These observations suggest that acidosis decreases and alkalosis increases renal potassium clearance. This is certainly true in alkalosis where concomitant increase in potassium excretion occurs.

The increase in the renal clearance of potassium in alkalosis may be explained by applying our hypothesis to the postulates of Berliner concerning potassium excretion. If, as Berliner, Kennedy, and Orloff propose (18), potassium excretion is a function of the concentration of potassium in the renal tubular cell, then alkalosis would be expected to increase renal potassium clearance by moving potassium into the renal tubule cell just as it may move it into all other cells.

The increased renal clearance of potassium in alkalosis explains the apparent paradox between our hypothesis and Darrow's observations. The fact that the muscle potassium becomes low in chronic alkalosis seems to conflict with the hypothesis that $(K)_E/(K)_I$ is lowered in alkalosis. However, the hypothesis defines a concentration ratio and does not preclude a concomitant decrease in total body potassium as a function of increased renal excretion. Hence, alkalosis leads to a decrease in the ratio $(K)_E/(K)_I$ as a result of movement of potassium into the cells, and a further small decrease in serum potassium induced by the kidneys in order that potassium be transported via the extracellular space from muscle to urine.

The fact that acid-base imbalance changes the serum potassium level by altering $(K)_E/(K)_I$ may prove to be of clinical importance. It has been pointed out that often the correlation is not good between the serum level and the total body potassium (19). This lack of correlation might be obviated in part if consideration were given to the increased $(K)_E/(K)_I$ in acidosis and the decreased $(K)_E/(K)_I$ in alkalosis. Thus hypokalemia in a patient with acidosis might indicate more severe potassium depletion than a similar degree of hypokalemia in a patient with alkalosis. This seems to be true in our limited experience and would be inferred from the studies of Mudge and Vislocky discussed above. That acute re-

spiratory acidosis may lead to fatal hyperkalemia under certain circumstances is a question of clinical importance. Observations on this subject have been reported (20, 21).

SUMMARY AND CONCLUSION

1. Acute respiratory acidosis in dogs causes hyperkalemia as a result of movement of potassium out of the cells.

2. When potassium is infused into dogs with respiratory acidosis virtually none of the administered potassium enters the cells. Similar infusions in normal dogs cause large transfers of potassium into the cells.

3. Accumulated evidence permits the formulation of the hypothesis that the internal equilibrium of potassium is in part a function of pH. Acidosis increases and alkalosis decreases the extracellular-intracellular concentration ratio of potassium. The altered ratio persists as long as the pH remains altered.

4. This hypothesis may be useful clinically in permitting better interpretation of the serum potassium level so that it more accurately reflects the potassium needs of the patient.

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