INTERRELATIONS OF PLASMA POTASSIUM CONCENTRATION, PLASMA SODIUM CONCENTRATION, ARTERIAL pH AND TOTAL EXCHANGEABLE POTASSIUM *

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Accurate and quantitative definition of the factors that determine plasma potassium concentration has not yet been attained. However, important relationships have been noted between plasma potassium concentration and acid-base disturbances (1–11), acute and chronic losses of body potassium (2, 12) and changes in plasma sodium concentration (13, 14). Conversely, frequent exceptions to these individual relationships are seen. The intimate association between plasma sodium concentration and body sodium, potassium, and water suggests that an analogous multifactored control might obtain for plasma potassium concentration (15). When body potassium content is constant, changes in the plasma potassium level may reasonably be attributed to osmotic and electrochemical influences which alter the concentration gradient of potassium across the cell membrane. The status of intracellular metabolism has a major effect on this gradient, since the anoxic, damaged or glucose-depleted cell leaks potassium at an accelerated rate (16–18).

An analysis of the various determinants of plasma potassium concentration and a consideration of their possible interrelationships are of some importance. Clarification of the nature and degree of any such interrelationships may modify or verify concepts of the physiological mechanisms affecting changes in electrolyte distribution and in addition may facilitate more precise clinical interpretations.

Simultaneous measurements of total exchangeable potassium, total body water, arterial and venous blood pH and arterial and venous plasma electrolyte concentrations were made in a heterogeneous group of chronically ill patients who had been in a steady state [1] for at least two or three days before study. The correlations of plasma potassium concentration with plasma sodium concentration, arterial pH, pCO_2, total exchangeable potassium and various combinations of these measurements were analyzed statistically.

METHODS

Definitions. The symbols and abbreviations used in this paper are defined as follows: K_p, potassium concentration in milliequivalents per liter of arterial plasma water; Na_p, sodium concentration in milliequivalents per liter of arterial plasma water; Cl_p, chloride concentration in millequivalents per liter of arterial plasma; $(CO_2)_p$ total CO_2 content in millimoles per liter of arterial plasma; pCO_2, partial pressure of CO_2 in millimeters Hg in arterial plasma; H_a, hydrogen ion concentration in Moles $\times 10^{-8}$ per liter of arterial blood (to simplify calculation, the factor of 10^{-8} is omitted); K_e, total exchangeable potassium in milliequivalents; TBW, total body water in liters; DBW, dry body weight in kilograms calculated as body weight minus total body water; D_2O, deuterium oxide; THO, tritiated water.

Seventy-four patients were studied. The age, sex, state of hydration, and clinical diagnosis are summarized in Table I. The patients were selected to provide a wide range of plasma potassium concentrations and pH values; the group was also limited to lean or malnourished subjects to eliminate as far as possible the distorting effect of body fat in interindividual comparisons of K_e. In 23 subjects who were seriously ill the investigation was confined to measurements of blood pH and electrolyte concentrations. The group as a whole consisted of 7 patients with various types of heart disease, 15 with cirrhosis of the liver, 14 with renal disease, 21 with pulmonary disease, 3 with gastrointestinal disease, 8 with neurological disease, and 6 with other disorders, including carcinomatosis, barbiturate intoxication, and senility. Thirty-eight of these patients were edematous.

The patients were classified as far as possible accord-

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[1] No significant changes in clinical status, renal or respiratory function or plasma electrolyte concentrations.

ing to the four major categories of acid-base disturbance. Normal pH in this laboratory for arterial blood is 7.43 ± 0.02; the normal $(CO_2)_p$ is 25.6 ± 2.4 mMoles per L. Acidotic patients, *i.e.*, those with arterial pH less than 7.41, were designated under respiratory acidosis if $(CO_2)_p$ was greater than 28.0 mMoles per L., and under metabolic acidosis if $(CO_2)_p$ was less than 23 mMoles per L. Alkalotic patients, *i.e.*, those with arterial pH greater than 7.45, were listed under respiratory alkalosis if $(CO_2)_p$ was less than 23 mMoles per L. and under metabolic alkalosis if $(CO_2)_p$ was greater than 28 mMoles per L. In seven cases in which normal arterial pH was associated with abnormal $(CO_2)_p$ the findings were interpreted in the light of the clinical status. Four patients with unidentifiable acid-base disturbance, together with 16 cases in which data were insufficient and five patients in whom both arterial pH and $(CO_2)_p$ were normal were listed in the unclassified category. No attempt has been made to separate compensated from uncompensated cases. None of the experimental subjects was treated with carbonic anhydrase inhibitors during the period of study.

All subjects were given an analyzed diet containing 10 mEq. sodium and 21 mEq. potassium daily during the period of study. Food and fluid were withheld for the period of D_2O or THO equilibration.

TABLE I

Summary of clinical data

Disease		Male	Female	Age range	Weight range	Transudates
	(*No. of cases*)			*yr.*	*Kg.*	
Heart	(*7*)	6	1	40–74	33–80	7
Kidney	(*14*)	11	3	17–75	39–80	7
Gastrointestinal	(*3*)	2	1	35–40	40–56	0
Liver	(*15*)	7	8	35–86	39–72	13
Lung	(*21*)	19	2	25–82	39–68	5
Neurological	(*8*)	6	2	25–80	42–67	4
Miscellaneous	(*6*)	4	2	40–72	46–50	2

TABLE II

Summary of laboratory data: plasma values

Patient	K_p*	Na_p*	Cl_p*	$(CO_2)_p$*	pH		pCO_2*
					Arterial	Venous	
No.	*mEq./L. plasma water*	*mEq./L. plasma water*	*mEq./L. plasma*	*mMoles/L. plasma*			*mm. Hg*
Metabolic acidosis							
14	4.65	172.5	121.3	20.9	7.37		36.0
17	5.72	140.2	115.8	11.6	7.36		21.5
19	5.32	153.1	118.6	9.8	7.32		20.0
20	4.70	150.1	109.9	16.8	7.40		28.0
25	5.84	143.9	116.5	8.1	7.15		25.0
31	5.12	141.0		10.2	7.28	7.24	23.5
35	6.53	114.7		14.4	7.40	7.36	24.0
37	2.98	154.2		6.9	7.29	7.24	15.0
39	4.76	142.9	105.7	17.6	7.34	7.35	35.5
40	6.16	127.1		18.4	7.35	7.26	35.0
42	4.74	157.2	116.8	6.6	7.15	7.11	19.5
55	3.51	131.6	99.2	15.2	7.40		25.0
56	5.34	146.0	109.0	22.3	7.36	7.33	40.0
61	4.08	148.6	115.0	18.9	7.37	7.36	32.5
66	5.60	135.4	88.8	20.4	7.39	7.33	35.2
69	5.15	143.9	116.6	10.3	7.23		24.5
71	5.48	127.5	98.5	19.7	7.35		36.0
74	4.35	132.8		18.3	7.28	7.30	39.5
Metabolic alkalosis							
5	4.58	141.2	94.8	34.4	7.44		51.0
6	3.55	139.8		29.6	7.55		35.5
9	3.74	161.6	96.7	34.5	7.46		49.0
10	3.08	140.8	92.1	35.8	7.50		46.0
13	5.12	143.2	91.4	30.4	7.47		42.2
15	2.89	139.0	95.2	29.3	7.54		35.5
44	3.11	146.6	101.5	28.1	7.52	7.45	36.0
46	2.34	142.8		33.2	7.56	7.51	38.0
47	2.54	144.0	100.0	30.8	7.49	7.49	41.0
49	2.78	150.7		31.7	7.54	7.50	38.0
54	3.46	135.5	89.4	29.4	7.53	7.47	37.5
62	4.26	146.8	103.0	29.8	7.46	7.42	42.5
63	3.57	158.3	100.0	34.9	7.49	7.44	46.5
72	2.56	134.0	91.8	30.5	7.53	7.49	37.5

* K_p = potassium concentration; Na_p = sodium concentration; Cl_p = chloride concentration; $(CO_2)_p$ = total CO_2 content; pCO_2 = partial pressure of CO_2.

TABLE II—*Continued*

Patient	K_p*	Na_p*	Cl_p*	$(CO_2)_p$*	pH		pCO_2*
					Arterial	Venous	
No.	*mEq./L. plasma water*	*mEq./L. plasma water*	*mEq./L. plasma*	*mMoles/L. plasma*			*mm. Hg*
Respiratory alkalosis							
4	3.95	131.0	96.6	22.6	7.48		30.5
11	4.18	139.5		18.8	7.59		20.0
38	6.15	125.7		15.8	7.48	7.45	23.0
51	5.01	148.5	115.8	17.5	7.54	7.51	21.0
53	1.93	143.9	109.3	14.3	7.51	7.42	19.0
57	2.87	145.6	95.7	22.6	7.48	7.44	33.5
59	4.93	142.1	106.1	20.8	7.47	7.41	29.0
Respiratory acidosis							
1	4.57	144.7		26.3	7.25		59.0
2	4.82	141.9	92.3	32.0	7.37		54.5
3	4.25	146.9	98.3	32.0	7.29		66.0
7	4.37	144.3	99.3	28.5	7.41		47.5
16	4.41	146.2	98.2	33.3	7.43		50.0
41	5.42	140.8	85.1	45.2	7.39	7.37	74.5
52	4.85	143.9	100.0	35.8	7.42	7.37	55.0
58	4.28	141.8	100.0	28.8	7.40	7.29	47.0
70	4.31	142.8	103.5	30.9	7.37		53.0
73	5.58	139.2	101.6	28.6	7.42	7.41	44.5
Unclassified							
8	4.97	140.1	104.2	24.5	7.45		35.0
12	3.58	140.3	106.8	24.2	7.45		35.5
18	4.02	142.5		26.6	7.52		33.5
21	4.52	141.1			7.44		
22	4.50	148.5			7.39		
23	3.78	142.5	98.5		7.48		
24	2.75	134.9			7.49		
26	4.43	141.4			7.44		
27	3.38	132.6	91.8		7.56		
28	4.67	146.6	106.2		7.47		
29	4.28	151.9			7.45	7.42	
30	6.68				7.27	7.25	
32	5.11	137.5			7.44	7.35	
33	4.62	142.9			7.46	7.39	
34	4.42	136.0			7.56	7.52	
36	4.80	139.0		26.4	7.44	7.38	41.0
43	5.00	148.8	105.3	25.3	7.44	7.42	42.0
45	4.12	139.5	101.0	22.2	7.44	7.43	33.0
48	5.20	144.2	100.2	29.1	7.45	7.39	41.5
50	4.87	141.9	97.5		7.39	7.33	
60	3.11	142.5	102.7	25.7	7.48	7.44	35.0
64	2.60	138.6	87.5		7.51	7.46	
65	5.17	141.3	101.0	24.3	7.45	7.42	36.0
67	3.81	136.3	97.7		7.50	7.42	
68	4.62	141.0	104.1		7.38		
Mean	4.34	141.8	101.8	23.8	7.43	7.39	37.1
Range	1.93–6.68	114.7–172.5	85.1–121.3	6.9–45.2	7.15–7.59	7.11–7.52	15.0–74.5

The sequence and technique of isotope administration and collection of urine and blood for isotope assay have been described previously (19, 20). Three hundred to 350 μc. K^{42}, and to a few subjects 1 to 2 mc. tritium, were the maximum doses of administered radioactivity. The periods of isotope equilibration were 40 hours for K^{42} and six hours for D_2O or THO. Blood was drawn almost simultaneously from the femoral artery and antecubital vein at the end of the K^{42} equilibration period and immediately before the deuterium or tritium injection. Glycolysis and clotting in these samples were inhibited by icing and heparin.

The analytical methods for isotope assay have been described previously (19, 21, 22). Sodium and potassium were measured in dilutions of urine and plasma with a lithium internal-standard flame photometer. Plasma water was determined gravimetrically by drying 1 ml. aliquots, delivered from calibrated pipettes, at 104° C. for 72 hours. Plasma chloride was estimated by electrometric titration (23), and total CO_2 content of

TABLE III

Summary of laboratory data: body composition and derived values

Patient	K_e*	K_e/Kg. body wt.	TBW*	TBW/Kg. body wt.	K_e/DBW*	K_e/DBW × H_a	$\frac{K_e/DBW \times H_a}{Na_p}$*
No.	*mEq.*	*mEq./Kg.*	*L.*	*%*	*mEq./Kg.*		
Metabolic acidosis							
17	2,508	36.8	45.9	67.3	112.5	490.5	3.50
19	2,164	38.5	39.9	71.1	133.6	639.9	4.18
20	1,251	34.6	18.7	51.9	71.9	286.1	1.90
25	2,234	34.6	33.2	51.4	71.4	505.5	3.51
31	2,295	48.8	30.7	65.2	140.8	739.2	5.24
35	2,012	32.2	47.6	76.4	136.9	532.5	4.64
39	1,176	23.6	28.2	55.8	53.5	244.4	1.71
40	2,887	35.9	55.5	69.0	115.9	518.1	4.08
42	1,357	29.8	29.0	63.7	82.2	582.0	3.70
56	2,975	43.1	49.9	72.2	154.9	676.9	4.64
61	1,422	24.6	44.3	76.8	106.1	453.0	3.05
66	1,572	34.2	28.1	61.1	88.1	358.6	2.65
69	1,929	36.1	27.8	52.1	75.5	444.7	3.29
71	1,707	31.8	38.0	70.8	109.2	488.1	3.83
74	2,265	32.1	40.9	57.9	76.4	401.1	3.02
Metabolic alkalosis							
5	2,165	35.8	38.6	63.7	98.4	375.2	2.66
6	1,529	30.7	30.9	62.1	80.9	228.1	1.63
13	1,893	35.9	28.6	54.1	78.1	264.8	1.85
15	1,381	24.0	36.0	62.5	64.2	184.9	1.33
44	1,973	39.6	32.5	65.3	114.2	344.9	2.38
47	1,751	29.9	31.6	53.9	64.9	210.3	1.46
49	1,213	23.0	26.7	50.6	46.7	134.5	0.89
54	2,817	39.3	49.4	69.0	126.9	399.7	2.95
62	1,318	30.9	24.7	57.7	73.0	253.3	1.73
63	2,549	45.2	33.9	60.1	113.2	366.8	2.32
72	1,492	28.7	26.5	51.0	58.5	172.6	1.28
Respiratory alkalosis							
4	1,934	41.7	28.9	62.2	110.3	365.1	2.79
51	869	27.7	20.3	64.8	78.3	225.5	1.52
53	1,623	33.7	28.3	58.7	81.6	252.1	1.75
57	1,725	34.5	29.4	58.7	83.6	276.7	1.90
59	2,261	28.5	49.6	62.4	75.7	256.6	1.81
Respiratory acidosis							
1	1,859	34.4	27.7	51.1	70.3	395.1	2.73
2	2,201	42.1	33.7	64.5	118.3	505.1	3.56
16	1,860	38.8	28.7	59.7	96.4	358.6	2.45
58	2,036	32.7	34.9	55.9	74.2	295.3	2.08
70	1,914	49.0	25.3	64.7	138.7	592.2	4.15
73	1,102	33.2	21.2	63.9	91.8	348.8	2.51
Unclassified							
8	1,092	27.9	28.0	71.7	97.5	346.1	2.47
12	1,887	39.9	27.7	58.6	96.3	341.9	2.44
23	1,054	23.2	25.3	55.5	52.2	172.8	1.21
27	1,469	25.7	28.2	49.3	50.7	139.4	1.05
28	2,214	49.6	30.0	67.5	151.6	513.9	3.51
43	1,306	33.2	26.7	68.0	104.0	377.5	2.53
45	1,338	21.2	39.6	62.7	56.7	205.9	1.49
48	1,894	38.7	26.4	54.0	84.2	292.2	2.03
50	1,203	24.4	28.7	58.1	58.3	237.3	1.67
60	1,545	29.9	32.4	62.7	80.3	265.8	1.87
64	1,162	29.7	20.5	52.4	62.4	192.8	1.39
65	1,518	32.4	27.7	59.1	79.3	281.5	1.99
67	1,607	34.0	26.3	55.5	76.5	241.7	1.77
68	2,049	30.9	33.0	49.7	61.3	255.6	1.81
Mean	1,776	33.7	32.3	60.9	89.8	353.6	2.51
Range	869–2,975	21.2–49.6	18.7–55.5	49.3–76.8	46.7–154.9	134.5–739.2	0.89–5.24

* K_e = total exchangeable potassium; TBW = total body water; DBW = dry body weight; H_a = hydrogen ion concentration; Na_p = sodium concentration.

arterial plasma was determined by Van Slyke's manometric method (24). The pCO_2 was estimated from the Singer-Hastings nomogram (25). Arterial and venous blood pH were measured at 37° C. with a Beckman model GS pH meter, calibrated with buffer standards prepared from high purity salts provided by the National Bureau of Standards. The latter measurements were made within 30 minutes of sampling; previous experiments in this laboratory had indicated that iced specimens showed no change in pH for at least 60 minutes after sampling. All chemical determinations were done in duplicate or triplicate.

Calculations, statistics, and analytical error. . Standard formulas were used in calculating specific activities, K_e and TBW, including corrections for isotope excretion in the urine (21, 26). Whenever a 24 hour interval elapsed between K_e and TBW determinations, the K_e was corrected to the time of TBW measurement by metabolic balance for potassium by using measured intake and urinary losses. The plasma potassium and sodium concentrations, expressed in milliequivalents per liter of plasma water, were derived from the measured plasma sodium and potassium concentrations and plasma water content.

Conventional statistical equations were used to calculate standard deviations (S.D.) and correlation coefficients (r). The probability (p) of a correlation coefficient being obtained by chance was evaluated by the "t" test (27).

RESULTS

The data obtained in this study are listed in Tables II and III. There were 18 subjects with metabolic acidosis, 14 with metabolic alkalosis, 7 with respiratory alkalosis, 10 with respiratory acidosis, and 25 with normal acid-base status or without readily identifiable acid-base disturbance. The K_p varied from 1.93 to 6.68 mEq. per L. of plasma water, Na_p from 114.7 to 172.5 mEq. per L. of plasma water, Cl_p from 85.1 to 121.3 mEq. per L. of plasma, arterial blood pH from 7.15 to 7.59 units, venous blood pH from 7.11 to 7.51 and pCO_2 from 15.0 to 74.5 mm. Hg. The range of body composition values was also quite wide: TBW varied from 49.3 to 76.8 per cent of body weight; K_e ranged from 21.2 to 49.6 mEq. per Kg. of body weight and from 46.7 to 154.9 mEq. per Kg. of dry body weight.

TABLE IV

Relationship between plasma potassium concentration and arterial pH

pH range	Plasma potassium concentration mEq./L. plasma water	
	Mean	S.D.
7.14–7.36	5.10	±0.89
7.37–7.46	4.66	±0.50
7.47–7.60	3.58	±1.04

Plasma sodium concentration and plasma potassium concentration

The lowered intracellular potassium content frequently noted in such states as congestive heart failure is almost invariably associated with increased intracellular sodium concentration; this has been demonstrated in muscle (28–30) and in erythrocytes (31, 32). Hyponatremic and sodium retentive states have been reported to be associated with diminished renal excretion of potassium and titratable acid; this has been attributed to excessive proximal resorption of sodium, with consequent diminution in the amount of potassium secreted by exchange with sodium in the distal tubule (33). In dogs, however, the tendency to develop hyperkalemia in association with hyponatremia and sodium depletion could not be explained by renal retention of potassium (13). Conversely, administration of potassium to hyponatremic subjects has resulted in elevation of serum sodium levels (34), perhaps as a result of extrusion of sodium from potassium-depleted cells. The multiple determinants of the plasma sodium concentration and its apparent independence of extracellular pH, however, render unlikely any significant direct correlation between K_p and Na_p (15). The correlation between K_p and Na_p ($r = -0.22$) indicates that K_p tends to vary independently of Na_p or plasma osmolality. No significant difference in this correlation was found in the individual subgroups with either metabolic or respiratory acid-base disturbances (see Table V).

Plasma potassium concentration and extracellular pH

Numerous observations have confirmed the inverse relationship between the plasma potassium level and extracellular pH. The *in vitro* demonstration that acidification of the nutrient medium with mineral acid induced extracellular migration of potassium (35) led to experiments in nephrectomized animals subjected to acid and alkaline loads (36–39), artificial induction of respiratory acidosis and alkalosis (3–11) and infusion of acid and alkaline loads into humans (1). A direct re-

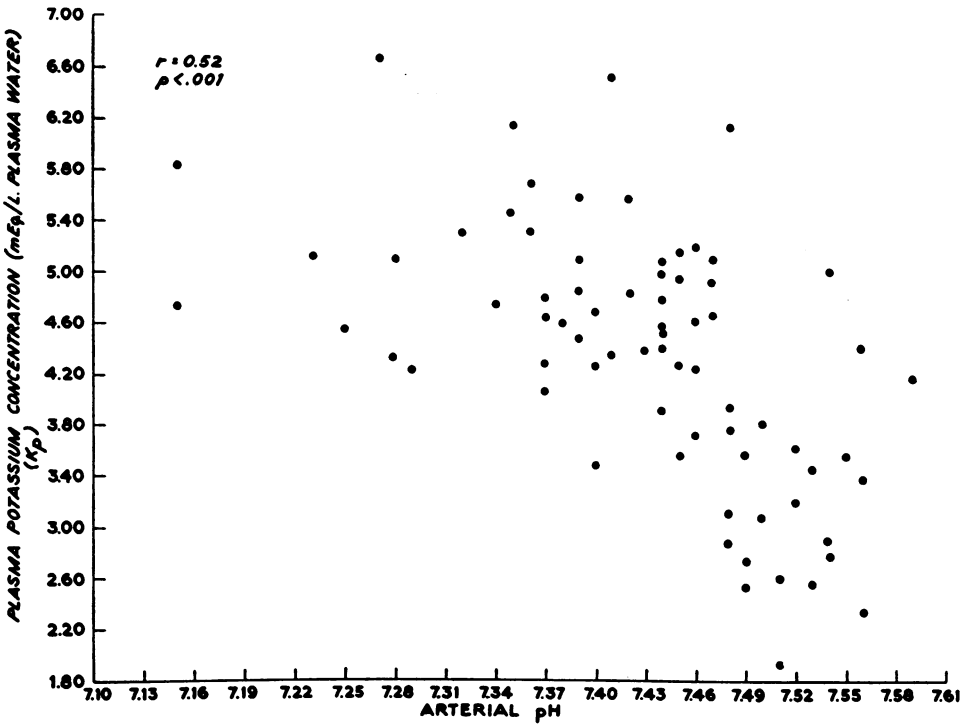

FIG. 1. RELATION BETWEEN PLASMA POTASSIUM CONCENTRATION AND ARTERIAL pH

lationship between hyperkalemia and acidosis and between hypokalemia and alkalosis without accompanying changes in body potassium content seems well established. The mean values for K_p according to pH_a subgroups, as summarized in Table IV, verify this trend. However, these are by no means invariable associations. Early respiratory alkalosis and the period immediately following respiratory acidosis have been reported to be associated with initial or further elevations of K_p, ascribed either to splanchnic release of potassium or to epinephrine effect (9, 10, 40, 41). Respiratory alterations of acid-base balance probably involve different buffering mechanisms than metabolic disturbances, *i.e.*, the buffer capacity of the extracellular fluids is usually increased with respiratory acidosis and decreased with metabolic acidosis, whereas the converse obtains in respiratory alkalosis and metabolic alkalosis. Furthermore, the nature of the metabolic disturbance seems to influence differentially the accompanying ionic redistributions (42, 43). Clinically, both alkalosis and acidosis often are not associated with significant deviations of plasma potassium level from the normal. These exceptions to the correspondence between K_p and extracellular pH attest to the importance of other regulatory factors. In this study the correlation between K_p and pH of extracellular fluid as represented by arterial blood was significant, $r = -0.52$ ($p < 0.001$) (see Figure 1 and Table V). If the cases are limited to those with $pH > 7.30$, then $r = -0.60$. A still higher correlation, $r = -0.64$, was found within the category of metabolic acid-base disturbances, while, surprisingly, in the respiratory subgroup, $r = -0.16$. No significant difference in correlation was found with venous blood pH. The influence of changes in pCO_2 on K_p proved to be negligible; for the entire group, there was no correlation at all, $r = -0.03$. In the metabolic disturbance subgroup a minor negative correlation was noted between K_p and pCO_2, $r = -0.36$; the respiratory subgroup demonstrated a similar degree of correlation in the opposite direction, $r = 0.30$.

Plasma potassium concentration and body content of potassium

Without doubt hypokalemia can be induced by loss of body potassium, if the loss is prolonged,

TABLE V

Correlation of plasma potassium concentration (K_p) with plasma sodium concentration (Na_p), plasma pCO_2 and total exchangeable potassium (K_e)*

	All cases N† = 51–74	Metabolic acid-base disturbances N = 26–32	Respiratory acid-base disturbances N = 11–17
K_p vs. Na_p	− 0.22	− 0.24	− 0.20
K_p vs. pCO_2‡	− 0.03	− 0.36	0.30
K_p vs. pH_a (pH > 7.30)	− 0.60		
K_p vs. H_a‡	0.52	0.64	0.16
K_p vs. pH_a	− 0.52 ($p < 0.001$)	− 0.64	− 0.16
K_p vs. K_e/body weight	0.22		
K_p vs. K_e/DBW‡	0.39 ($p < 0.005$)	0.45	− 0.28
K_p vs. $H_a \times K_e$/DBW	0.58 ($p < 0.001$)	0.70	0.20
K_p vs. $\frac{H_a \times K_e/DBW}{Na_p}$	0.62 ($p < 0.001$)	0.74 ($p < 0.001$)	0.24

* Correlation coefficient, $r = \frac{\Sigma [(X - \bar{X})(Y - \bar{Y})]}{\sqrt{\Sigma (X - \bar{X})^2 \Sigma (Y - \bar{Y})^2}}$.

† N = number of cases.

‡ pCO_2 = partial pressure of CO_2; H_a = hydrogen ion concentration; DBW = dry body weight.

acute or associated with stress or alkalosis (12). An attempt has been made to quantitate such an isolated relationship (2). No consistent correspondence between K_p and body potassium content as reflected by K_e determinations, however, has been demonstrated (44). As expected, the correlation

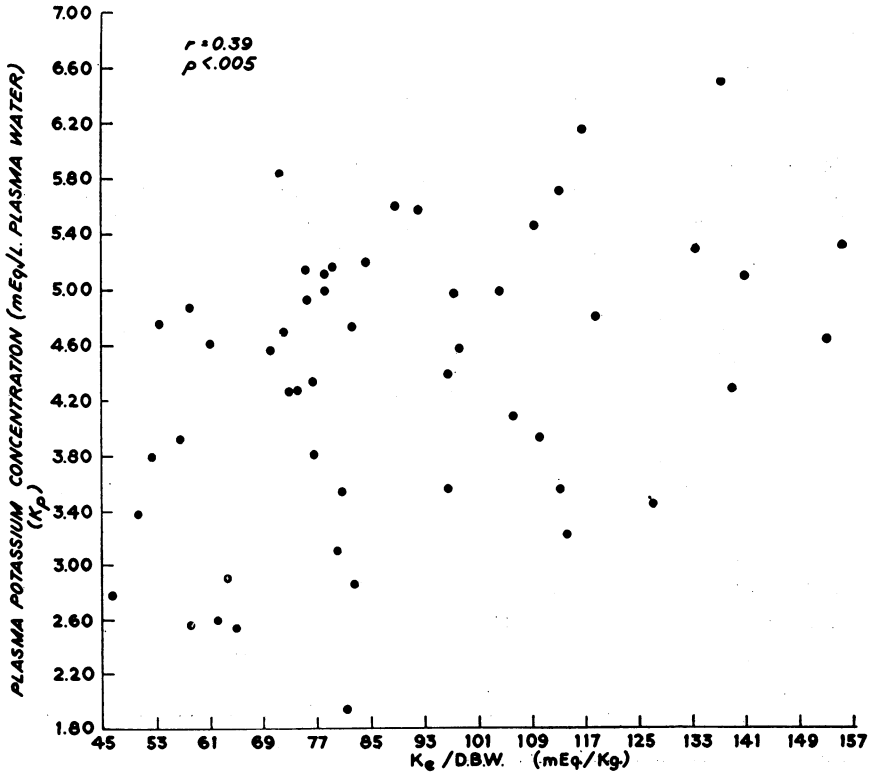

FIG. 2. RELATION BETWEEN PLASMA POTASSIUM CONCENTRATION (K_p) AND RATIO OF EXCHANGEABLE POTASSIUM TO DRY BODY WEIGHT (K_e/DBW)

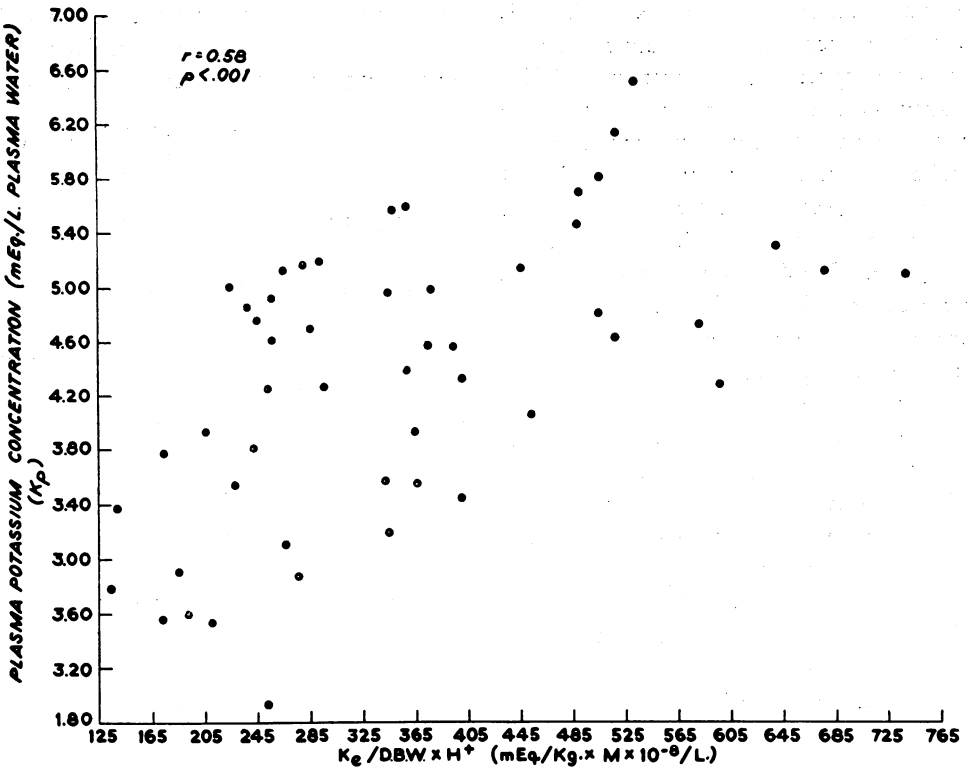

FIG. 3. RELATION BETWEEN PLASMA POTASSIUM CONCENTRATION (K_p) AND PRODUCT OF EXCHANGEABLE POTASSIUM PER KG. DRY BODY WEIGHT (K_e/DBW) AND ARTERIAL HYDROGEN ION CONCENTRATION (H^+)

found in this study between K_p and K_e/body weight was insignificant, $r = 0.22$ (Table V). One possible reason for this lack of correlation may be the difficulty in quantitating body potassium in the presence of the variable amounts of body fat and water in disease states. An attempt to circumvent this problem was made, first by deliberate selection of lean subjects only for study, and second by measurement of TBW, thus allowing calculation of the artificial parameter "dry" body weight (DBW). In fact, K_p did correlate significantly better with K_e/DBW ($r = 0.39$, $p < 0.005$) than with K_e/body weight (see Figure 2). In the subgroup with respiratory acid-base disturbances, $r = -0.28$ (see Table V). These imperfect correlations, while confirming the significant effect of alterations of body potassium content on K_p, attest to the need for a more comprehensive analysis of the factors affecting K_p, and again suggest that selective influences operate on K_p in metabolic and respiratory acid-base disturbances.

Plasma potassium concentration, body content of potassium, and extracellular pH

The almost invariable association of acid-base disturbances with those conditions which result in significant changes of body potassium content and K_p implies the existence of some overall quantitative relationship between K_p, body potassium content, and extracellular pH. Burnell, Scribner and co-workers (1, 2) have derived semiquantitative formulations which purport to define the relationships between changes in K_p and body potassium content and changes in K_p and extracellular pH. These formulations are of some value clinically, but provide no integrated account of the determinants of K_p at any one time. It seemed reasonable, therefore, to examine the proposition that the extracellular fluid pH, or H_a, quantitatively controls the gradient of potassium concentration across the cell membrane in the steady state, *i.e.*, in the absence of acute distorting factors such as changes in potassium balance. The simplest repre-

sentation of this relationship is: $K_p/K_{ic} = k \times H_a$ where K_{ic} is the intracellular potassium concentration and k is a proportionality constant. If K_e/DBW is taken as a measure of the intracellular potassium concentration (since extracellular potassium probably comprises no more than 3 to 4 per cent of exchangeable potassium) (45), then one may test experimentally the relationship: $K_p = k \times H_a \times K_e/DBW$. The correlation coefficient, r, for this relationship is 0.58 ($p < 0.001$) (see Figure 3), a modest improvement over the correlation between K_p and pH alone. In the metabolic subgroup, the correlation coefficient for the relationship between K_p and $H_a \times K_e/DBW$ is 0.70, an increase which parallels a similar increase in the correlation between K_p and pH in this subgroup. However, the respiratory subgroup again demonstrates a poor correlation, r = 0.20. The empirical observation that in some cases which did not correlate well the plasma sodium concentrations were abnormal, and the experimental observations cited previously, suggested the possibility that the ratio $H_a : Na_p$ might be more decisive in determining K_p than H_a alone. Accordingly we tested the expression:

$$K_p = \frac{k \times K_e/DBW \times H_a}{Na_p}$$

(see Figure 4). This maneuver resulted in still higher degrees of correlation, r = 0.62 for the entire group, r = 0.74 for the metabolic subgroup (see Figure 5) and r = 0.24 for the respiratory subgroup. Logarithmic and semilogarithmic formulations did not materially modify any of the described statistical relationships.

DISCUSSION

Previous observations have indicated that changes in extracellular pH, body potassium content, and plasma sodium concentration individually are associated with acute and chronic aberrations of plasma potassium concentration. The data obtained in this study show that plasma potassium

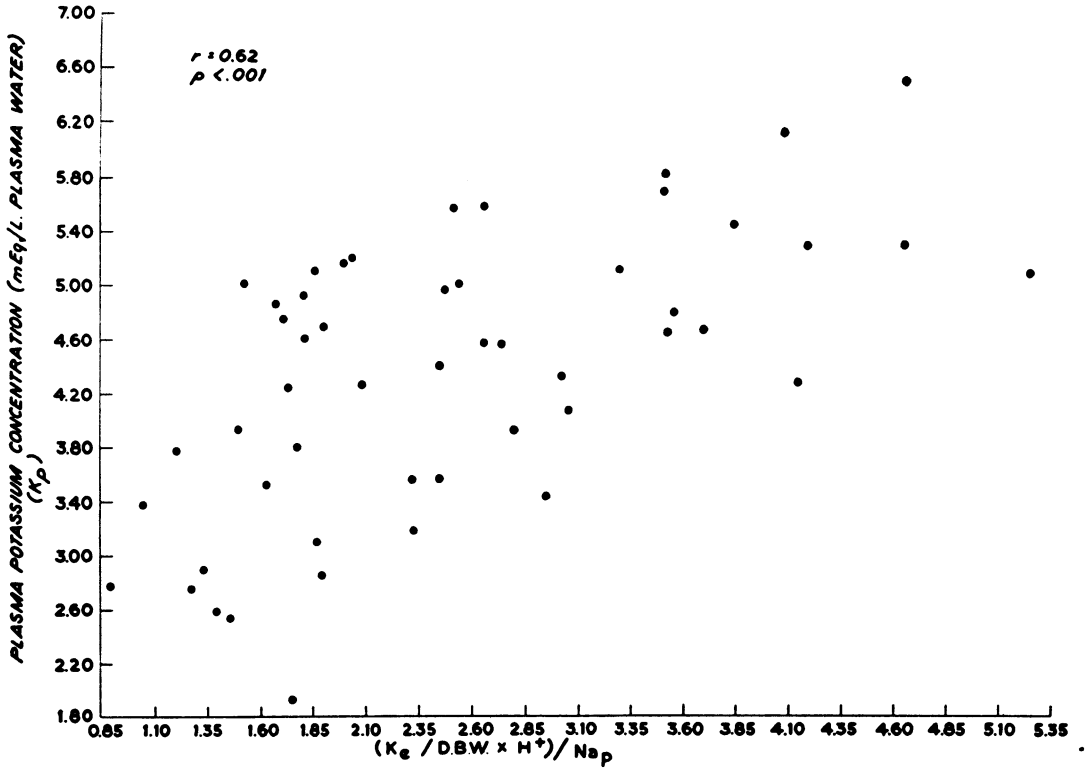

FIG. 4. RELATION BETWEEN PLASMA POTASSIUM CONCENTRATION (K_p) AND RATIO OF EXCHANGEABLE POTASSIUM PER KG. DRY BODY WEIGHT (K_e/DBW) × ARTERIAL HYDROGEN ION CONCENTRATION (H^+) TO PLASMA SODIUM CONCENTRATION (Na_p)

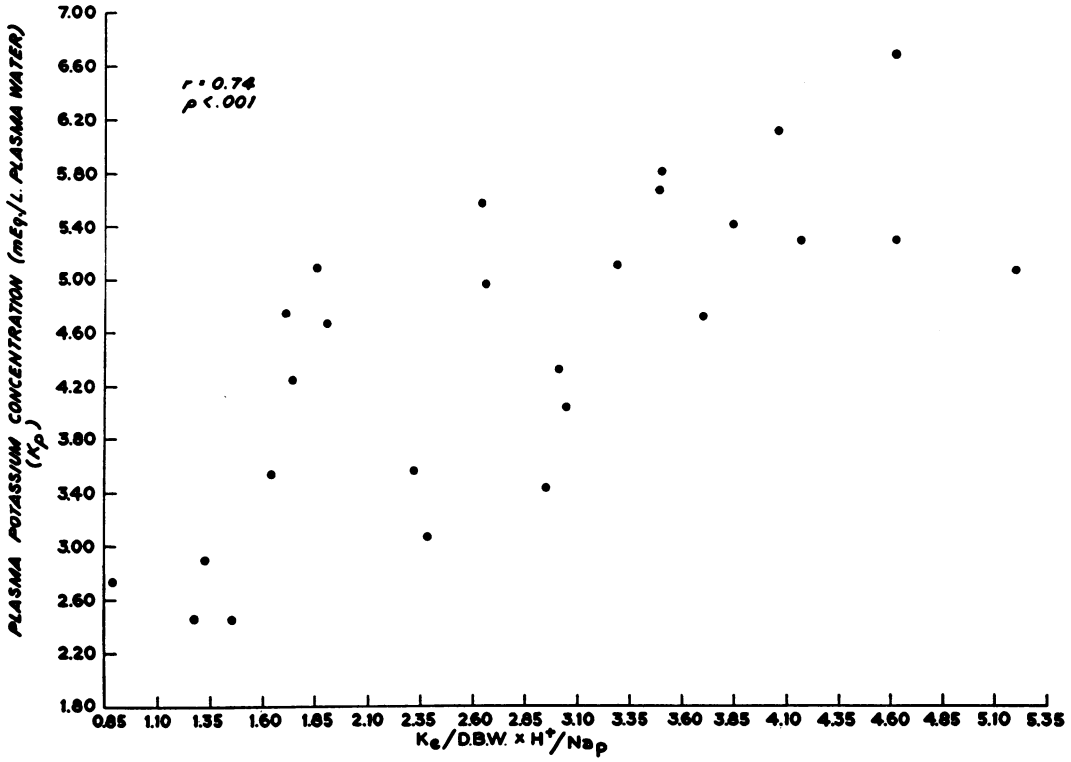

FIG. 5. RELATION BETWEEN PLASMA POTASSIUM CONCENTRATION (K_p) AND RATIO OF EXCHANGEABLE POTASSIUM PER KG. DRY BODY WEIGHT (K_e/DBW) × ARTERIAL HYDROGEN ION CONCENTRATION (H^+) TO PLASMA SODIUM CONCENTRATION (Na_p) IN PATIENTS WITH METABOLIC ACID-BASE DISTURBANCES

concentration is related to these three factors in decreasing order of importance. A summary of statistical correlations is presented in Table V. Striking differences are apparent between metabolic and respiratory acid-base disturbances, in that K_p seems much less dependent on these variables in the latter category (see Table V). A very close relationship ($r = 0.74$) has been found between K_p and the ratio $\frac{H_a \times K_e/DBW}{Na_p}$ in patients with metabolic acid-base disturbances.[2] It may be inferred from these observations that additional factors or different mechanisms affect K_p in patients with respiratory acid-base disturbances. This interesting finding suggests that H_a does not directly effect changes in K_p, but exerts its influence by its effects on intracellular buffering processes, and ultimately on intracellular hydrogen ion concentration. These effects probably depend on whether the primary disturbance is metabolic or respiratory in nature. Such a possibility is supported by Tobin's demonstration (43) that different degrees of acidosis and K_p change could be induced by equal loads of mineral and organic acids and by Fenn and Cobb's experiment showing that under certain conditions raising the extracellular concentration of dissolved CO_2 resulted in movement of potassium into cells (35). A possibly related factor may be the inherent lability of respiratory disturbances; the rapid diffusibility of CO_2 into and out of cells in response to changes in ventilation may preclude the establishment of the steady state envisioned in this study.

The proposal that K_p is proportional to the ratio $\frac{H_a \times K_e/DBW}{Na_p}$ may be interpreted as having fundamental physiological significance, provided that simplifying assumptions are valid. This relationship may indicate the passive distribution of potassium and hydrogen ions in proportion to resting transmembrane potential differences, prob-

[2] The consistently improved correlation coefficient resulting from the inclusion of Na_p in the denominator (although not statistically conclusive) strongly suggests that this observation is valid.

ably modified by a Gibbs-Donnan equilibrium. Such a relationship may be represented by the expression: $K_p/K_{ic} = H_a/H_{ic}$, where "ic" denotes concentrations inside the cell. The experimental verification of this simple construct is hampered by the lack of accurate measures of K_{ic} and H_{ic}. However, if the equation is rearranged, *viz.*, $K_p = \frac{K_{ic} \times H_a}{H_{ic}}$, then a resemblance emerges to the formulation presented in this study, except that the factor H_{ic} is replaced by Na_p and K_{ic} is approximated by K_e/DBW.

If potassium and hydrogen ions are passively transported across cell membranes, then the magnitude and direction of their movements, as conditioned by both the Donnan equilibrium and the transmembrane potential, would be similar. If, however, potassium is actively transported into the cell, it is conceivable that hydrogen ion competes for transport sites in the membrane in a fashion analogous to the apparent competition of potassium and hydrogen for secretion into the distal tubular segment of the kidney (46). Such a process would also reveal a dependence of K_p on H_a. A mechanism of this kind, however, would not in itself account for the differences noted in the correlations of K_p with pH_a between the group of patients with metabolic acid-base disturbances and the group with respiratory acid-base disturbances. The possible correspondence between Na_p and H_{ic} suggested above may arise from a dependency of intracellular osmolality on H_{ic} analogous to the dependency of extracellular osmolality on Na_p, which has been verified experimentally (15).

The expression K_e/DBW provides only a gross estimate of intracellular potassium content based on separate measurements of K_e, body weight, and total body water. Despite selection of lean subjects only, variable quantities of body fat were unquestionably present. Considering the close correlation between K_e and lean body mass it is probable that a measurably greater dependence of K_p on the product of H_a and body potassium content might be found if K_e were expressed in units of lean body mass (21, 47). The high incidence of hepatic disease may have been a complicating factor in this group of patients; the liver probably participates in changes of K_p during respiratory disturbances since the initial rise in K_p in early respiratory alkalosis is abolished in hepatectomized animals (9, 41, 48). The number of cases with respiratory disturbances was relatively small and it was not feasible to study any severe cases of this type. Finally there may be specific influences on K_p such as the effects of epinephrine secretion or other hormonal factors which may alter potassium gradients across cell membranes independent of the effect of hydrogen ion or body potassium content (40, 49–51).

SUMMARY

The relationships of plasma potassium concentration (K_p), plasma sodium concentration (Na_p), extracellular fluid pH, and body potassium content, expressed as exchangeable potassium per kilogram of dry body weight (K_e/DBW), were explored by simultaneous measurements in a heterogeneous group of chronically ill patients with a variety of acid-base disturbances.

Plasma potassium concentration correlates poorly or slightly with Na_p, plasma pCO_2 and K_e/DBW. A modest correlation exists between K_p and arterial blood hydrogen ion concentration (H_a) which is enhanced significantly when K_p is plotted against $\frac{H_a \times K_e/DBW}{Na_p}$. Striking differences in correlation appear between subgroups of patients with metabolic and respiratory acid-base disturbances. In the group of patients with metabolic disturbances a close correlation was found between K_p and $\frac{H_a \times K_e/DBW}{Na_p}$ which is not apparent in the group with respiratory acid-base disturbances.

The physiological implications of these findings are discussed, and possible differential mechanisms in these two types of acid-base disturbance are presented.

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