Respiratory Adjustment to Chronic Metabolic Alkalosis in Man

ROBERTA M. GOLDRING, PAUL J. CANNON, HENRY O. HEINEMANN, and ALFRED P. FISHMAN

From the Departments of Medicine, Presbyterian and Francis Delafield Hospitals, College of Physicians and Surgeons, Columbia University, New York

ABSTRACT This study examined the ventilatory adjustment to chronic metabolic alkalosis induced under controlled conditions in normal human volunteers. Metabolic alkalosis induced by buffers (sodium bicarbonate, trishydroxymethylamine methane) or ethacrynic acid was associated with alveolar hypoventilation, as evidenced by a rise in arterial P_{CO_2}, a fall in arterial P_{O_2}, a reduced resting tidal volume, and a diminished ventilatory response to CO_2 inhalation. Alveolar hypoventilation did not occur when metabolic alkalosis was induced in the same subjects by thiazide diuretics or aldosterone despite comparable elevations of the arterial blood pH and bicarbonate concentration.

The different ventilatory responses of the two groups could not be ascribed to differences among individuals comprising each group, pharmacological effects of the alkalinizing agents, differences in the composition of the lumbar spinal fluid, changes in extracellular fluid volume, or sodium and chloride balance.

The differences in ventilatory adjustments were associated with differences in the patterns of hydrogen and potassium ion balance during the induction of alkalosis. Alveolar hypoventilation occurred when hydrogen ions were buffered (sodium bicarbonate, trishydroxymethylamine methane) or when renal hydrogen ion excretion was increased (ethacrynic acid). Alveolar hypoventilation did not occur when induction of similar degrees of extracellular alkalosis was accompanied by marked potassium loss and no demonstrable increase in external hydrogen loss (thiazides and aldosterone).

These observations suggest that respiratory depression does not necessarily accompany extracellular alkalosis but depends on the effect of the mode of induction of the alkalosis on the tissues involved in the control of ventilation.

INTRODUCTION

Chronic metabolic alkalosis is commonly associated with alveolar hypoventilation (1–3). However, there are many unexplained exceptions to this generalization (4–6). The absence of respiratory compensation in metabolic alkalosis may be due to: (*a*) acute hyperventilation at the time of blood sampling because of anxiety; (*b*) secondary effects on respiration of the agents causing the alkalosis; (*c*) the effects of alkalosis upon the composition of cerebrospinal fluid (7, 8), and (*d*) effects of the alkalinizing agents or physiologic disturbances on the hydrogen ion or electrolyte concentration or buffering capacity of the tissues involved in the control of ventilation (9, 10).

The present study was designed to determine the patterns of respiratory adjustment to chronic metabolic alkalosis in man. For this purpose, chronic metabolic alkalosis was induced in normal subjects under controlled conditions by the administration of buffers, diuretics, and aldosterone.

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The pattern of ventilation during the metabolic alkalosis produced by these different agents fell into two groups: alveolar hypoventilation occurred when metabolic alkalosis was effected by sodium bicarbonate, trishydroxymethylamine methane (THAM), or ethacrynic acid; alveolar hypoventilation *did not* occur after the thiazide diuretics or aldosterone.

After it was established that neither acute hyperventilation at the time of sampling nor pharmacological effects of the alkalinizing agents on the respiratory apparatus were involved, the third and fourth possible reasons for the disparate pattern of respiratory adjustment were investigated by analysis of lumbar cerebrospinal fluid removed during alkalosis and by examination of the patterns of hydrogen ion and electrolyte excretion in balance studies during the induction of alkalosis.

GENERAL PROCEDURES

13 normal male volunteers, ranging in age from 27 to 40 yr, served as subjects. The subjects were housed on a metabolic ward where they were given fixed diets of known protein, carbohydrate, potassium, and sodium content during control and test periods. The composition of the diets varied somewhat with the agent under study and will be indicated subsequently at appropriate places. Distilled water was allowed ad lib. Fluid intake and body weight were recorded daily. None of the subjects had nausea, vomiting, or diarrhea during the study.

All urine was collected under mineral oil with toluene added as preservative, and stored at 4°C. The 24 hr excretion of creatinine was used to check the reliability of the 24 hr collection of urine. The urinary excretion rates of sodium, potassium, chloride, and hydrogen ion (titratable acid plus ammonia minus bicarbonate) were determined daily (see Analytical Methods). Cumulative electrolyte balances were calculated as the sums of the urinary excretion of the ion on each experimental day minus the mean excretion of control days. In 4 of the subjects, the urinary excretion of nitrogen was also measured during the control and experimental periods. Venous blood samples were obtained at preset times for the determination of sodium, chloride, potassium, and bicarbonate concentrations.

All subjects were trained for the ventilatory studies by prior "runs" in the laboratory. The ventilatory studies, before and after induction of alkalosis, were performed under "steady-state" conditions as assessed by measurements of respiratory quotient and oxygen consumption. The respiratory quotients ranged from 0.74 to 0.89; a difference in respiratory quotient of less than 0.13 between control and test runs for each individual was required for inclusion in the study. The oxygen consumption ranged from 115 to 156 ml/min per m^2 of body surface area, and varied less than ± 10 ml on successive studies in any one individual. During these ventilatory studies, brachial arterial blood was drawn anaerobically into heparinized syringes from an indwelling needle which had been placed under local procaine anesthesia. The samples were analyzed for pH, oxygen saturation and tension, and carbon dioxide content.

Lumbar puncture was performed in 7 subjects after induction of alkalosis. The spinal fluid was collected anaerobically for determination of pH and carbon dioxide, sodium, potassium, and chloride content. The concentration of bicarbonate and P_{CO_2} in cerebrospinal fluid was calculated from the Henderson-Hasselbalch equation, using a pK′ of 6.13 and solubility coefficient of 0.0312. Arterial blood was sampled immediately before and during the lumbar puncture for comparison with cerebrospinal fluid.

Induction of alkalosis

After a control period (3–6 days) for the stabilization of the arterial pH, the serum concentration of bicarbonate, and the excretion of hydrogen ion in the urine, metabolic alkalosis was induced by either buffers (sodium bicarbonate and trishydroxymethylamine methane), diuretics (ethacrynic acid, chlorothiazide, or hydrochlorothiazide), or aldosterone in the following ways:

Sodium bicarbonate was administered on four occasions to 4 subjects; 290–1954 mmoles/day were given by continuous intravenous infusion for periods of 1–5 days. The infusion was discontinued 2 hr before ventilatory studies were carried out. The daily intake of sodium chloride was 90 mmoles/day.

Trishydroxymethylamine methane (THAM) was given orally as a syrup for 4–7 days in doses of 36 g/day to 2 subjects. The daily intake of sodium chloride was 90 mmoles/day.

Ethacrynic acid was given orally on nine occasions to 6 subjects for periods ranging from 3 to 8 days in a dose of 200 mg/day. These subjects were maintained on a constant low sodium chloride diet (less than 22 mmoles/day) during the control and experimental periods.

Chlorothiazide, 2 g/day, or hydrochlorothiazide, 250 mg/day, was administered orally on 11 occasions to 10 subjects for a period of 5–11 days. These subjects were maintained on a low sodium chloride intake (less than 22 mmoles/day) during control and experimental periods.

Aldosterone was infused continuously on four occasions in three subjects for a period of 6–11 days. 1–2.5 mg in 750 ml of 5% dextrose in water was given per 24 hr. These subjects were maintained on a high sodium chloride intake (more than 90 mmoles/day) during control and experimental periods.

ANALYTICAL METHODS

The sodium and potassium concentration in serum and urine was measured by standard flame photometry; chloride in serum and urine was measured by potentiometric titration (11); ammonia was measured by means of the diffusion technique of Seligson and Hirahara (12); creatinine was analyzed by the method of Bonsnes and

TABLE I

Summary of Multiple Determinations of Arterial Blood pH, P_{CO_2}, and Serum Electrolyte Concentrations during Control Periods and during Metabolic Alkalosis Induced by Different Agents

Protocol	No. of subjects		pH	HCO_3^-	Na^+	K^+	Cl^-	P_{aCO_2}
					mmoles/liter			*mm Hg*
Control	13	Average	7.41	24	140	4.4	102	39
		Range	(7.38–7.43)	(22–26)	(135–144)	(3.9–5.7)	(95–107)	(37–44)
		SD ±	0.02	1.6	1	0.2	3	2.4
		*n**	31	31	17	17	17	31
Sodium bicarbonate	4	Average	7.44	30	141	3.9	102	46
		Range	(7.41–7.45)	(26–31)	(138–150)	(3.3–4.5)	(99–108)	(43–49)
		SD ±	0.17	0.5	1.4	0.4	0.8	2.3
		n	11	11	8	8	8	11
THAM	2	Average	—	—	—	—	—	—
		Range	(7.40, 7.41)	(30, 31)	(137, 139)	(4.4, 4.5)	(103, 108)	(45, 47)
		SD ±	—	—	—	—	—	—
		n	2	2	2	2	2	2
Ethacrynic acid	6	Average	7.46	34	137	3.5	92	48
		Range	(7.43–7.52)	(28–36)	(131–143)	(2.4–4.7)	(81–103)	(44–51)
		SD ±	0.02	0.8	3.6	1.4	5.2	0.8
		n	14	14	14	14	14	14
Chlorothiazide	10	Average	7.48	31	134	2.9	90	41
hydrochlorothiazide		Range	(7.44–7.51)	(28–33)	(132–143)	(2.4–3.3)	(92–99)	(39–43)
		SD ±	0.02	0.6	4.5	0.2	4.4	2.4
		n	21	21	20	19	20	21
Aldosterone	3	Average	7.48	30	144	2.7	102	38
		Range	(7.44–7.52)	(26–32)	(140–147)	(2.4–2.9)	(100–104)	(36–42)
		SD ±	—	—	—	—	—	—
		n	4	4	3	3	3	4

* *n*, number of observations.

Taussky (13). The titratable acid of the urine was obtained by titration to pH 7.4. The concentration of nitrogen in urine was determined by a modification of the method of Kjeldahl. The carbon dioxide and oxygen contents of arterial blood, as well as the carbon dioxide content of the urine and cerebrospinal fluid, were determined by the method of Van Slyke and Neil (14). The partial pressure of oxygen and carbon dioxide in arterial blood was measured either by the bubble-equilibration technique of Riley et al. (15), or by specific electrodes (glass electrode for carbon dioxide and platinum electrode for oxygen). The pH of arterial blood and urine was measured anaerobically at 37.5°C with a glass electrode. The carbon dioxide and oxygen content of expired air were determined by the method of Scholander (16).

RESULTS

Arterial blood composition and serum electrolytes during induced metabolic alkalosis

The effects of the different agents on the arterial pH and P_{CO_2} and on certain electrolytes in serum are shown in Table I. The control values of the 13 subjects are presented as the average and range of repeated determinations. Multiple observations were made during the course of induced alkalosis in each subject, and several subjects underwent a second induction of alkalosis with the same agent to verify the consistency of observed results. However, statistical analysis of changes from con-

trol as presented below are based on single observations in each subject obtained at the end of the period of induced alkalosis.

In each individual, alkalosis was induced using more than one agent, and 9 of the 13 individuals received agents of both the groups to be described below.

Serum bicarbonate and arterial blood pH. The serum bicarbonate concentration increased appreciably after each of the agents. However, comparable increments in serum bicarbonate concentration (to a range of 30–34 mmoles/liter) with the different agents were associated with variations of arterial pH: the alkalosis of sodium bicarbonate and THAM was associated with little or no increase in pH above control, whereas similar increments in serum bicarbonate concentration during thiazide or aldosterone administration were associated with elevated values of blood pH, averages ranging between 7.46 and 7.48.

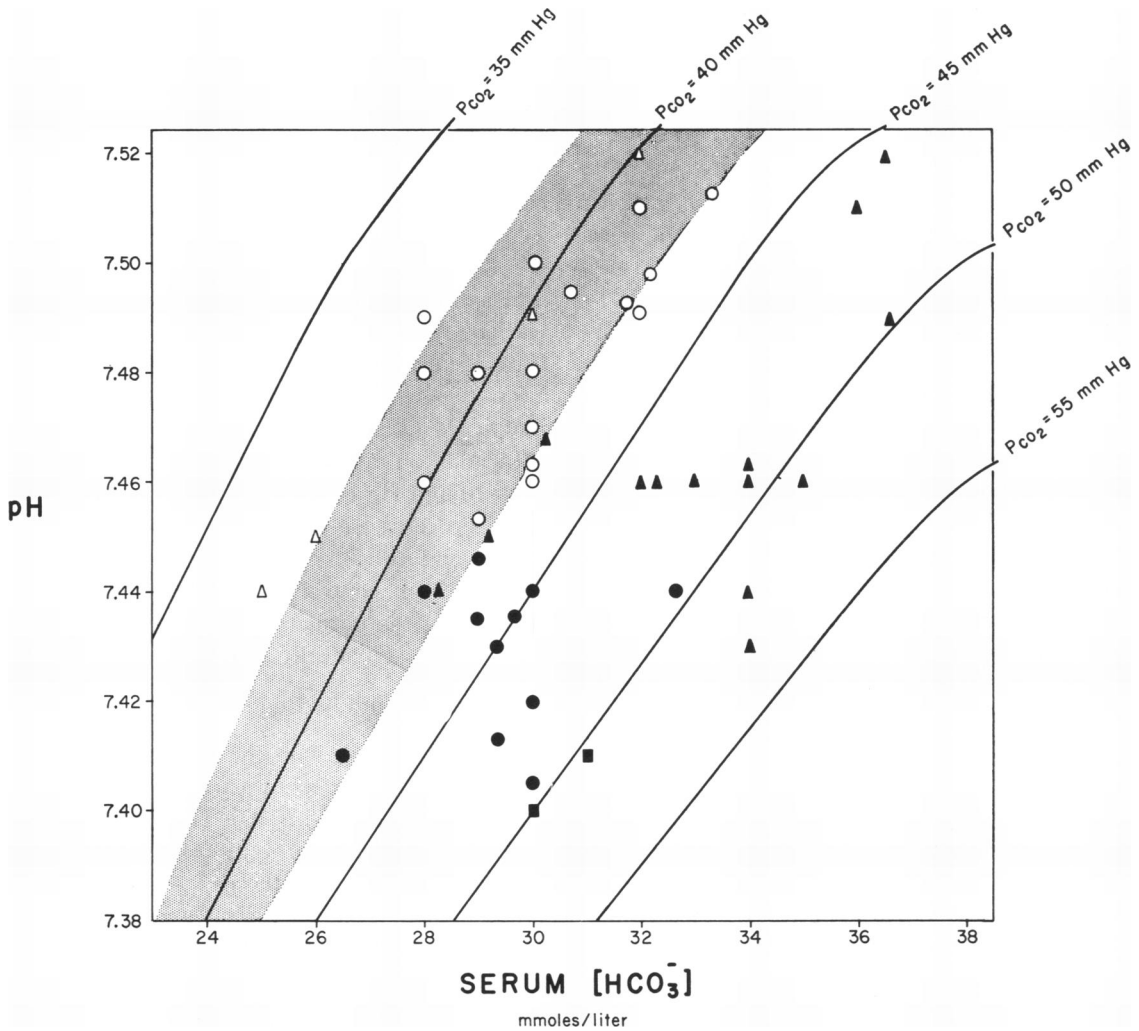

FIGURE 1 Relationship between the concentration of bicarbonate in arterial serum, the arterial blood P_{CO_2}, and the arterial blood pH during induced metabolic alkalosis. P_{CO_2} isobars are plotted from the Henderson-Hasselbalch equation. The *normal arterial* P_{CO_2} group is shown by open symbols; the *high arterial* P_{CO_2} group is shown by the solid symbols. Shaded area represents the control range of P_{CO_2} for all subjects. Alkalosis induced by the administration of sodium bicarbonate (dark circles), THAM (dark squares), and ethacrynic acid (dark triangles) is associated with high values for arterial blood P_{CO_2}; alkalosis induced by thiazide diuretics (open circles) and by aldosterone (open triangles) is associated with normal values for arterial blood P_{CO_2}, despite comparable increases in serum bicarbonate concentration and pH.

Serum electrolytes: sodium, chloride, and potassium. None of the agents caused striking changes in the concentration of sodium in the serum; the lowest value (average 134 mmoles/liter) followed the use of thiazide diuretics. Similarly, only the thiazides and ethacrynic acid caused appreciable decrements in the concentration of chloride in the serum (mean values 90–92 mmoles/liter). The concentration of potassium in the serum was unchanged after the administration of THAM, and decreased slightly after sodium bicarbonate and ethacrynic acid. On the other hand, serum potassium concentration was consistently decreased following thiazide diuretics and aldosterone. The lowest values (average of 2.7 mmoles/liter) were effected by aldosterone.

Arterial blood P_{CO_2} *and* P_{O_2}. These results (Table I) fell into two groups: (*a*) *high arterial* P_{CO_2}, after the administration of sodium bicarbonate, THAM, or ethacrynic acid; in this group, the arterial blood pH averaged 7.45 (range 7.41–7.52), the serum bicarbonate concentration averaged 32 mmoles/liter (range 26–36), the average arterial blood P_{CO_2} was 49 mm Hg (range 44–51); in addition, the average arterial blood P_{O_2} was 69 mm Hg (range 62–82); and (*b*) *normal arterial* P_{CO_2}, after the administration of chlorothiazide, hydrochlorothiazide, or aldosterone; in this group, the arterial blood pH was also increased (mean value of 7.48, with a range of 7.44–7.53) and the serum bicarbonate concentration was increased to an average of 30 mmoles/liter (range 26–33); but the arterial blood P_{CO_2} and P_{O_2} remained virtually unchanged from control (mean $P_{CO_2} = 39$ mm Hg, range 36–43; mean $P_{O_2} = 86$ mm Hg, range 80–96).

The relationship between arterial pH, P_{CO_2}, and serum bicarbonate concentration for individual determinations during alkalosis is illustrated in Fig. 1. As pH and bicarbonate concentration increased in the "normal P_{CO_2}" group (open symbols), the values for P_{CO_2} remained within the control range (shaded area). In contrast, in the "high P_{CO_2}" group (solid symbols), the increase in P_{CO_2} was associated with less of a rise in pH for a given increase in serum bicarbonate concentration. The arterial blood P_{CO_2} values from all studies in which serum bicarbonate concentration was similar in the two groups were subjected to statistical analysis. The difference in P_{CO_2} between the two groups at comparable elevations of serum bicarbonate concentration (28–33 mmoles/liter) was statistically significant with a P value of < 0.001.

Further analysis of the P_{CO_2} values during alkalosis involved comparison of each individual's change from his own control in the two groups of studies. Control values were analyzed statistically. The dissimilar P_{CO_2} during alkalosis could not be ascribed to differences in the patient population, because analysis of the control values showed no statistically significant differences ($P < 0.4$) between the mean control P_{CO_2} in the two groups. (Mean control P_{CO_2} was 40.0 ± 2 mm Hg in the high P_{CO_2} group and 39.4 ± 2 mm Hg in the normal P_{CO_2} group.) In addition, 9 of the 13 individuals were subjects for both groups of studies. During alkalosis, there was a mean change in the P_{CO_2} of each individual from his own control of $+ 9 \pm 3.2$ mm Hg in the high P_{CO_2} group. In contrast, in the normal P_{CO_2} group, there was essentially no change from control ($+ 0.1 \pm 1.2$ mm Hg) during alkalosis. The difference between the mean changes in the two groups was statistically significant ($P < 0.001$).

In addition, arterial blood P_{O_2} which averaged 86 ± 10 mm Hg in both groups during the control periods decreased during alkalosis in the high P_{CO_2} group by 17 ± 11 mm Hg and remained unchanged from control (0 ± 4.3 mm Hg) during alkalosis in the normal P_{CO_2} group. These differences were statistically significant ($P < 0.001$).

Electrolyte and hydrogen balances

Sequential changes in the composition of urine and blood after the administration of each of the agents are illustrated in Table II and Figs. 2 and 4.

High arterial P_{CO_2} *group.* Of the three agents in this group, two of these, sodium bicarbonate (administered intravenously) and THAM (administered orally), exerted similar effects on urinary hydrogen ion excretion (Table II A, B); the urinary excretion of titratable acid and ammonium ion decreased, and the excretion of bicarbonate increased.

The pattern of excretion of hydrogen ions produced by the third agent, ethacrynic acid, differed from that of the two exogenous buffers. The urinary excretion of hydrogen ions involved two phases (Table IIC and Fig. 2): for the first few

TABLE II

Representative Examples of Daily Electrolyte and H^+ Excretion, Arterial Blood pH and P_{CO_2}, and Serum Electrolytes during the Induction of Alkalosis by Different Agents

Subject	Day	Diet Na^+/K^+	Weight	Urine volume	Urine pH	Urine T.A.	Urine NH_4^+	Urine HCO_3^-	Urine H^+	Urine Na^+	Urine K^+	Urine Cl^-	Blood pH	Blood P_{CO_2}	Serum HCO_3^-	Serum Na^+	Serum K^+	Serum Cl^-
		mmoles/ 24 hr	*kg*	*liters/ 24 hr*	*mmoles/24 hr*									*mm Hg*	*mmoles/liter*			
A. THAM p.o. 36 g/24 hr																		
W.G.	C	50/60	55.3	3988	5.5	30	64	5	89	44	42	107	7.40	42	24	142	5	104
	1	50/60	55.2	4085	7.0	13	32	27	18	50	92	163						
	2	50/60	56.1	3505	7.3	8	22	64	−34	33	72	110						
	3	50/60	55.2	3724	7.6	0	21	12	9	34	81	44						
	4	50/60	55.6	3856	7.5	0	15	12	3	25	86	32	7.41	47	29	147	—	—
B. $NaHCO_3$ i.v. 330 mmoles/24 hr																		
W.Gr.	C	80/120	74.3	1800	6.5	23	44	8	59	74	107	88	7.40	38	23	139	4.3	107
	1	80/120	74.2	2070	7.9	0	22	63	−41	193	108	56						
	2	80/120	75.4	3250	7.8	0	37	258	−221	370	102	73						
	3	80/120	74.6	2840	7.4	0	34	93	−59	256	98	132						
	4	80/120	74.2	2115	6.7	27	24	15	36	141	105	142						
	5	80/120	74.1	3380	7.9	0	36	313	−277	392	162	55	7.42	47	29	139	4.1	108
C. Ethacrynic acid p.o. 200 mg/24 hr																		
J.W.	C	14/116	79.3	1393	6.3	20	54	3	71	5	61	13	7.41	41	25	136	4.4	97
	1	14/116	79.4	2650	5.7	43	91	2	132	53	194	215						
	2	14/116	79.2	2710	5.6	54	94	3	145	42	195	174						
	3	14/116	79.2	3300	6.4	35	87	12	110	74	175	156	7.46	48	33	137	2.8	87
D. Chlorothiazide p.o. 2 g/24 hr																		
J.W.	C	14/116	79.6	1135	6.5	25	31	5	51	4	97	19	7.40	39	23	141	5.3	104
	1	14/116	79.7	2540	7.2	1	46	67	−20	92	261	254						
	2	14/116	79.3	2260	6.9	18	57	17	58	60	211	168						
	3	14/116	77.5	1976	6.7	20	51	12	59	59	183	94						
	4	14/116	77.4	2680	6.7	38	43	16	65	13	158	60	—	—	33*	136	4.0	93
	5	14/116	77.5	3175	6.8	27	54	27	54	10	152	43						
	6	14/116	77.5	3480	7.1	12	75	36	51	7	156	38						
	7	14/116	77.3	4360	7.1	8	92	25	76	6	123	27	—	—	35*	132	3.3	87
	8	14/116	77.0	2200	7.0	3	44	13	34	4	63	14						
	9	14/116	77.4	3500	7.1	7	52	28	31	12	113	24						
	10	14/116	77.5	4020	7.0	14	80	40	54	15	111	21	7.51	41	31	136	3.5	89
E. Aldosterone i.v. 2.5 mg/24 hr																		
W.G.	C	100/104	55.4	2665	6.3	9	27	5	31	111	90	112	7.41	41	24	138	5.2	100
	1	100/104	55.6	1950	5.6	12	28	1	39	15	108	48						
	2	100/104	55.6	2980	6.7	7	27	3	31	8	133	45						
	3	100/104	55.7	3140	6.3	9	28	2	35	19	116	56						
	4	100/104	57.0	2780	6.6	8	21	11	18	101	149	152						
	5	100/104	56.2	2020	6.2	10	19	5	24	16	89	57						
	6	100/104	56.6	2330	6.4	7	15	13	9	87	107	123	7.52	40	32	144	3.3	104
	7	100/104	56.2	2400	6.5	7	21	16	12	94	110	117						
	8	100/104	56.2	2380	6.6	6	20	12	14	71	97	91					3.2	
	9	100/104	56.6	2630	6.7	5	30	17	18	91	115	115						
	10	100/104	57.2	2200	6.5	8	43	8	43	44	80	50	7.48	42	30	141	2.9	100

T.A., titratable acid.

* Venous serum HCO_3^-.

days (phase 1) the net output of hydrogen ions into the urine increased above control values as a result of an increase in the excretion of titratable acid and ammonium with little change in the excretion of bicarbonate in the urine. The calculated hydrogen balance was negative. Once alkalosis was established (phase 2), bicarbonate excretion increased and the net excretion of hydrogen ion into the urine declined toward control values. Since the administration of exogenous buffers inactivates free hydrogen ions in body fluids, and since the administration of ethacrynic acid led to an increase in urinary hydrogen output above control values, the induction of alkalosis with these agents was regularly associated with a reduction of free hydrogen ions in body fluids, i.e., "hydrogen ion depletion." [1]

[1] The term "hydrogen ion depletion" is used to indicate buffering or increased renal loss of hydrogen ions.

In contrast, the effects of these agents upon electrolyte excretion were less consistent (Tables II and III). The administration of buffers led to the retention of sodium and chloride and to a gain in weight; ethacrynic acid led to increased excretion of sodium chloride and to loss of weight. The excretion of potassium by the kidney either remained unchanged from control values or in-

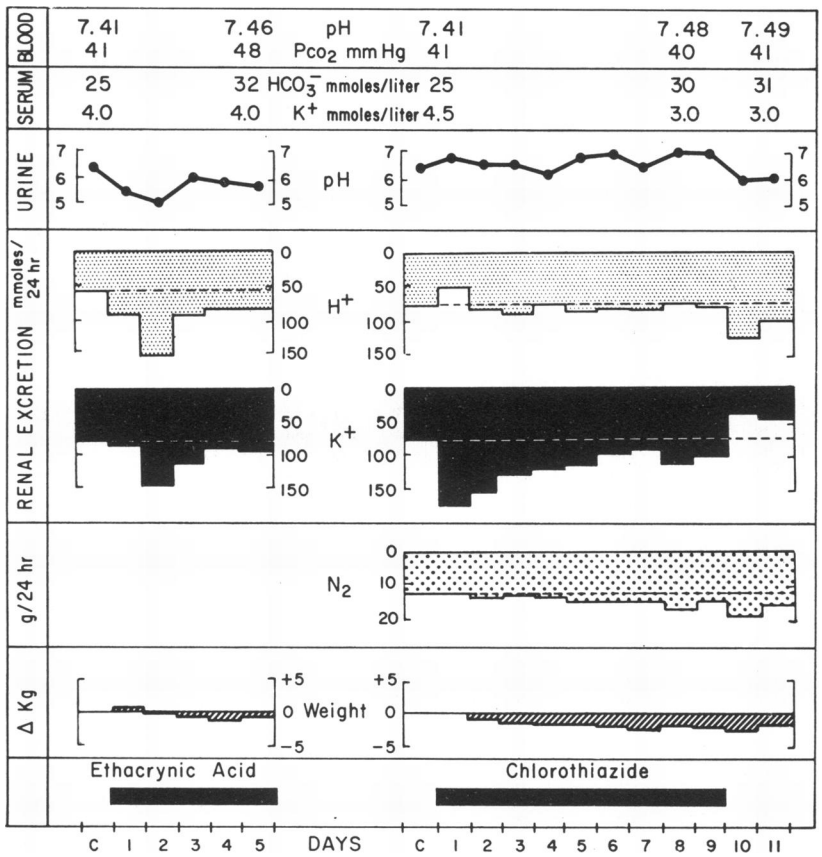

FIGURE 2 Effect of different diuretics on acid-base balance in the same subject W.P. *Ethacrynic acid* (200 mg p.o. daily) was administered on days 1–5. The pH and P_{CO_2} in arterial blood and the bicarbonate concentration in serum increased. The hydrogen ion excretion in the urine (titratable acid + NH_4^+ − HCO_3^-) increased; the cumulative hydrogen ion balance was negative (−193 mmoles) during the 5 day period in which the alkalosis developed. Cumulative renal potassium loss for the 5 day period was −132 mmoles. The serum potassium concentration did not change. Body weight fell by 1.0 kg. *Chlorothiazide* (2 g p.o. daily) was administered in the second study on days 1–9. The pH of arterial blood and the bicarbonate concentration in serum increased, but the P_{CO_2} in arterial blood remained within the normal range. Cumulative renal potassium loss for the 9 day period was −309 mmoles. The serum potassium concentration fell from 4.5 to 3.0 mmoles/liter. The hydrogen ion excretion in the urine (titratable acid + NH_4^+ − HCO_3^-) declined initially because of increased bicarbonate excretion, but returned subsequently to control levels; the cumulative hydrogen ion balance was essentially zero (−6 mmoles) during the 9 day period in which the alkalosis developed. Nitrogen excretion in the urine increased during chlorothiazide administration. Body weight fell by 2.2 kg. On discontinuing the diuretic (days 10 and 11), potassium excretion decreased, hydrogen ion and nitrogen excretion increased, and the pH and P_{CO_2} of arterial blood, as well as the bicarbonate content of serum, remained unchanged. Note that in this representative individual, the P_{CO_2} increased during alkalosis induced by ethacrynic acid and did not change after chlorothiazide.

TABLE III

*Effect of Inducing Metabolic Alkalosis by Different Agents on Plasma Electrolyte Concentrations and Cumulative Electrolyte Balance**

Agent	No. of studies	Δ Plasma			Cumulative balance			Δ Weight
		Na^+	K^+	Cl^-	Na^+	K^+	Cl^-	
		mmoles/liter			*mmoles*			*kg*
Buffers	6	+2	−0.5	−3	+224	−61	+55	+1.5
Ethacrynic acid	7	−4	−0.3	−7	−139	−135	−272	−1.1
Thiazides	11	−3	−1.5	−10	−237	−324	−422	−1.8
Aldosterone	2	+5	−1.3	−2	+306	−107	+81	+1.4

* Data derived from those studies in which serum bicarbonate concentrations during alkalosis ranged from 28 to 33 mmoles/liter.

creased during the induction of alkalosis. Cumulative potassium loss during the administration of buffers averaged 61 mmoles (range 0–103) and 135 mmoles (range 5–372) during the administration of ethacrynic acid. The renal loss of potassium could not be related to the degree of alkalosis (Fig. 3).

Normal arterial P_{CO_2} *group.* There were two types of agents in this group, the thiazides and aldosterone.

The thiazides regularly produced an initial increase in urinary pH and in the excretion of bicarbonate; the excretion of titratable acid decreased but, despite the high pH of the urine, the excretion of ammonium increased. Thus, as indicated in Table II and Fig. 2, the rate of net hydrogen ion excretion decreased to levels below control during the first few days of administration and subsequently returned to control levels. Fig. 2 also shows that the decrease in the excretion of hydrogen ion in the urine occurred despite a small increase in nitrogen excretion during chlorothiazide administration. The mean cumulative balances of sodium, potassium, and chloride during chlorothiazide diuresis were more negative than during the administration of ethacrynic acid (Table III). There was an average weight loss of 1.8 kg. When the renal effects of the thiazides on acid-base balance were prevented by the administration of either a high sodium chloride diet (8 g/24 hr) or potassium supplements, comparable doses of chlorothiazide failed to change the arterial pH, P_{CO_2}, or the concentration of bicarbonate in the serum.

The effects of infusing aldosterone on urinary electrolyte and hydrogen ion excretion are illustrated both in Table II and in Fig. 4. Even though extracellular alkalosis developed, aldosterone produced no consistent change in urinary pH or the excretion rates of titratable acid, ammonium, or bicarbonate. Nitrogen balance remained unchanged. Sodium and chloride retention occurred and was

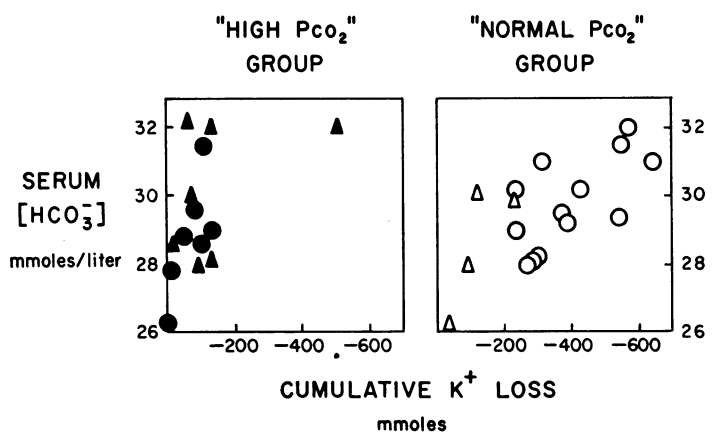

FIGURE 3 The relationship of the increase in serum bicarbonate concentration during alkalosis to the renal potassium loss induced by the different agents. Sodium bicarbonate, dark circles; ethacrynic acid, dark triangles; chlorothiazide, open circles; aldosterone, open triangles. Alkalosis developed independently of renal potassium excretion with agents of the high P_{CO_2} group. A greater increase in serum bicarbonate concentration was associated with increased renal potassium loss in the normal P_{CO_2} group.

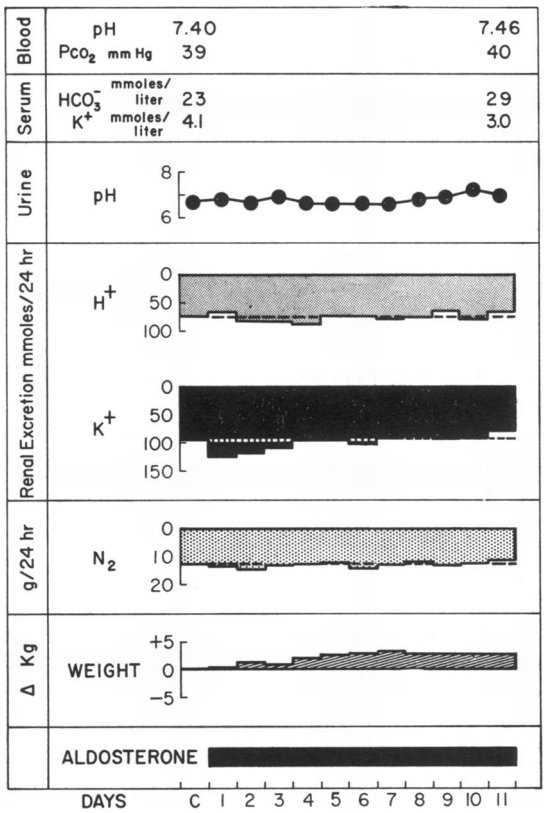

FIGURE 4 The effect of a continuous intravenous aldosterone infusion, 1.5 mg/day (days 1–11) on acid-base balance, body weight, and renal potassium and nitrogen excretion. The pH of arterial blood and the bicarbonate concentration in serum increased, but the P_{CO_2} in arterial blood remained within the normal range. Serum potassium concentration decreased, although urinary potassium loss was small. (Loss of potassium in stool not quantitated, but presumed increased (17).) Urinary H^+ excretion did not increase during the induction of alkalosis.

associated with a mean gain in weight of 1.4 kg, an increase in serum sodium concentration, and a reduction in plasma potassium concentration (Table III). The negative potassium balance, averaging 107 mmoles, calculated from urinary excretion rates, is probably an underestimation of total potassium loss since the excretion of potassium in the stool was not determined and has been shown by others to increase during the administration of aldosterone (17). When the renal effects of aldosterone on potassium excretion were prevented by a low sodium diet (less than 11 mmoles/day), the administration of aldosterone caused no change in arterial blood pH, P_{CO_2}, or serum bicarbonate concentration.

During the induction of alkalosis with agents comprising the normal P_{CO_2} group, sodium and chloride retention and weight gain were induced by aldosterone; opposite effects were induced by chlorothiazide (Table III). Despite these differences, both agents produced insignificant changes in the urinary excretion of hydrogen ion during the period that alkalosis was developing. Also, both induced hypokalemia and cumulative losses of potassium were linearly related to the degree of alkalosis (Fig. 3).

Time of onset and duration of alkalosis varied with different individuals and different agents, but, because of considerable overlap between the two groups, they could not be related to observed differences in patterns of electrolyte or hydrogen ion excretion.

Ventilation during induced metabolic alkalosis

Resting ventilation. Control values for alveolar ventilation, tidal volume, and frequency did not differ between the two groups. Mean control alveolar ventilation in the high P_{CO_2} group was 4.1 ± 0.9 liters/min, and 4.6 ± 1.3 liters/min in the normal P_{CO_2} group. These values were not significantly different ($P = 0.3$).

In the high P_{CO_2} group, the calculated alveolar ventilation decreased after induction of alkalosis in all but one instance; the average decrease from each individual's own control was -0.8 liters/min ± 0.9 (range $+0.1$ to -2.8 liters). This decrease was entirely attributable to a reduction in resting tidal volume, averaging -99 ± 54 ml (range -10 to -210 ml), since there was no change in respiratory frequency. The decrease in tidal volume was significantly related to the increase in serum bicarbonate concentration ($r = -0.75$; $P < 0.01$) but not to the arterial blood pH ($r = -0.23$; $P > 0.05$. These changes in ventilation did not occur with administration of these agents until after alkalosis had developed.

In the normal P_{CO_2} group the alveolar ventilation did not decrease after induction of alkalosis, and there was no change in the pattern of breathing. The average change from each subject's own control was $+0.2 \pm 0.5$ liter/min for alveolar ventilation and $+15 \pm 45$ ml for tidal volume.

The changes in alveolar ventilation and tidal volume which occurred in the high P_{CO_2} group were significantly different ($P < 0.001$ for both)

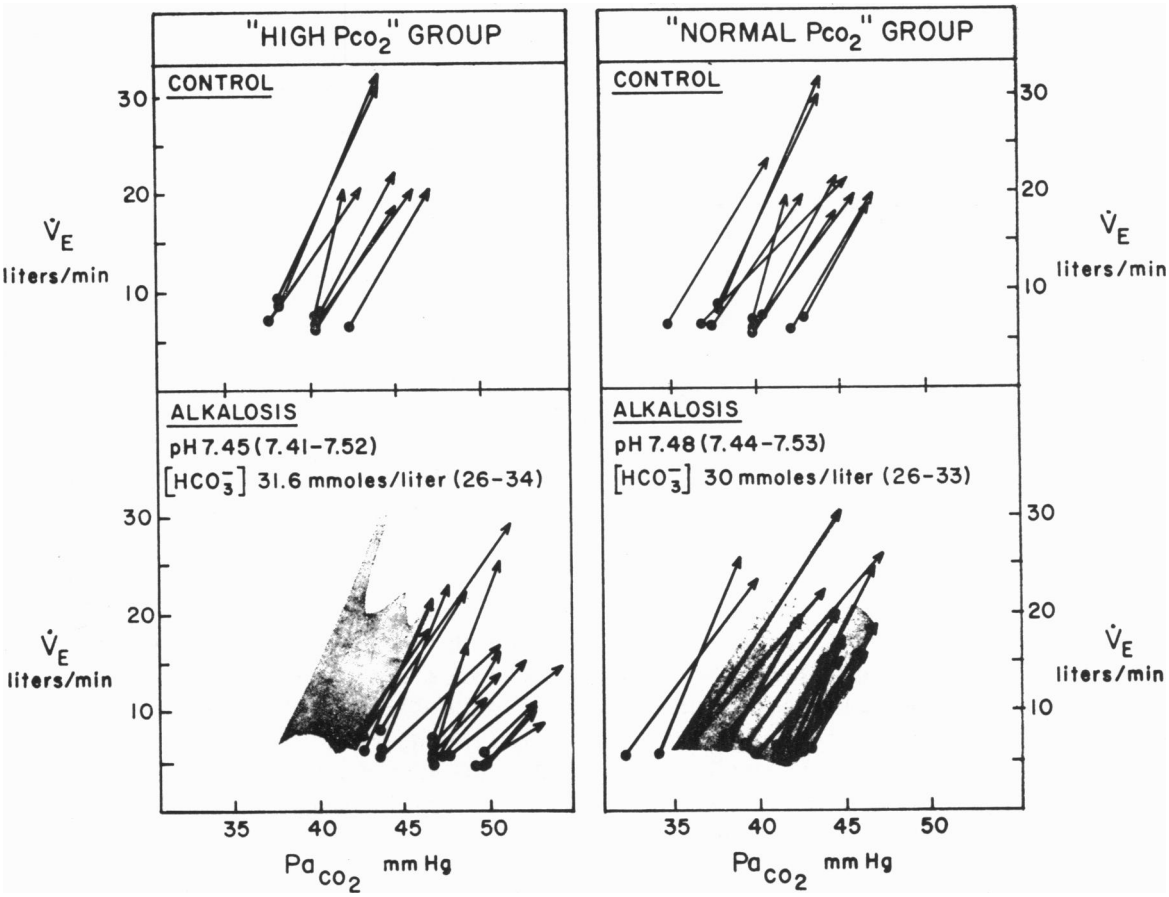

FIGURE 5 Ventilatory response to 5% CO_2 inhalation. Minute ventilation ($\dot{V}_E$) is plotted against the arterial blood P_{CO_2}. The two upper panels show control response curves. Each slope represents an average of two to four measurements in each subject. The two lower panels shown individual CO_2-response curves obtained at repeated intervals during alkalosis. In these panels the range of control values is indicated by the shaded area for reference. The response curves are uniformly shifted to the right in the high P_{CO_2} group and are reduced in amplitude when the P_{CO_2} exceeds 46 mm Hg. In contrast, the ventilatory response curves of the normal P_{CO_2} group during alkalosis (right lower panel) superimpose on the control curves.

from the minimal changes during alkalosis in the normal P_{CO_2} group, despite similar levels of arterial pH and bicarbonate concentration.

Ventilatory response to breathing CO_2. The ventilatory response to breathing an inspired gas mixture containing 5% CO_2 in air is plotted in Fig. 5 for each subject during the control and alkalotic periods. The control response curves represent the average of two to four control measurements obtained before and after periods of alkalosis. It may be seen that the response curves of the high P_{CO_2} group during metabolic alkalosis are to the right of those obtained before alkalosis was induced. During alkalosis, the resting minute ventilation was at control, or below control values,

TABLE IV

Changes in the Arterial Blood P_{CO_2} and Hydrogen Ion Concentration while Breathing 5% CO_2 during Metabolic Alkalosis

		Metabolic alkalosis*	
	Control*	High P_{CO_2}	Normal P_{CO_2}
Arterial blood pH	7.41 (7.38–7.44)	7.45 (7.41–7.52)	7.48 (7.44–7.53)
Serum HCO_3^-, *mmoles/liter*	24 (23–27)	31.6 (26–34)	30 (26–33)
Increase in arterial P_{CO_2}, *mm Hg*	5.5 (3–9)	4 (2–9)	5 (2–8)
Increase in arterial H^+, *nmoles/liter*	3.1 (0.9–5.4)	2.2 (0.2–5.5)	2.5 (0.7–6.1)

* Values are expressed as average and range.

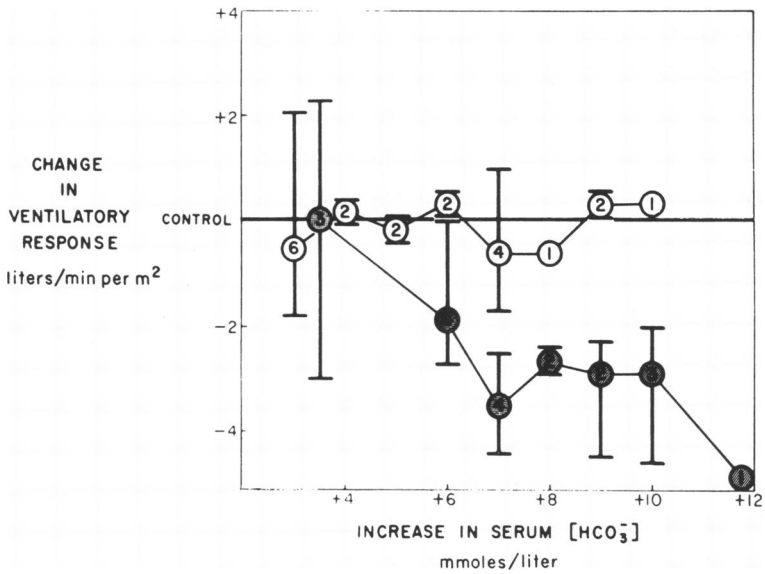

FIGURE 6 Increment in minute ventilation during 5% CO_2 breathing. The changes from each subject's own control values during alkalosis are averaged and compared for the two groups at comparable increases in serum bicarbonate concentration. High P_{CO_2} group represented by shaded circles; normal P_{CO_2} group represented by open circles. Number in circle indicates number of observations; bars indicate the range. There is a progressive decrease in the magnitude of ventilatory response to 5% CO_2 breathing with increasing serum bicarbonate concentration in the high P_{CO_2} group and no change from control when comparable increases in serum bicarbonate concentration were effected by the alkalinizing agents of the normal P_{CO_2} group.

even though the values for arterial P_{CO_2} were higher than those which induced large increments in ventilation during CO_2 breathing in the control state. When the initial P_{CO_2} exceeded 46 mm Hg, the shift to the right of the response curve was associated with a progressive diminution of the ventilatory response for a given change in P_{CO_2} (i.e., decrease in slope). In contrast, the ventilatory response curves of the normal P_{CO_2} group during alkalosis superimpose on the control curves despite comparable increments in serum bicarbonate concentration and higher levels of arterial pH.

The changes in arterial blood P_{CO_2} and hydrogen ion concentration which occurred acutely during CO_2 breathing were similar in both groups of subjects during alkalosis (Table IV) and did not differ significantly ($P > 0.2$, $P > 0.1$, respectively) from control. Despite this, the increment in minute ventilation (ventilatory response) which resulted from CO_2 breathing declined from control values in the high P_{CO_2} group, but did not change from control in the normal P_{CO_2} group. The mean change in ventilatory response (i.e. change from each individual's own control response) which occurred in the 9 individuals of the former group, was -2.8 ± 1.8 liters/min per m², a value significantly different ($P < 0.001$) from the minimal change observed in

TABLE V

Cerebrospinal Fluid (CSF) and Arterial Blood pH, P_{CO_2}, and HCO_3^- during Induced Alkalosis

Agent	Cerebrospinal fluid			Arterial blood			Ratio of CSF to blood HCO_3^-
	pH	HCO_3^-	P_{CO_2}	pH	HCO_3^-	P_{CO_2}	
		mmoles/liter	*mm Hg*		*mmoles/liter*	*mm Hg*	
High P_{CO_2}							
Sodium bicarbonate	7.31	26	57	7.47	31	45	0.85
	7.32	28	57	7.44	29	46	0.96
Ethacrynic acid	7.34	29	57	7.48	32	45	0.93
	7.31	31	65	7.48	32	46	0.98
Normal P_{CO_2}							
Chlorothiazide	7.35	28	53	7.52	29	36	0.94
	7.34	27	53	7.49	30	37	0.90
	7.32	26	53	7.49	28	38	0.91

the 11 individuals of the latter group (-0.3 ± 1.2 liters/min per m^2). Although not shown, the reduced ventilatory response in the high P_{CO_2} group during alkalosis was effected by a reduced tidal volume rather than a change in respiratory rate.

Finally, these changes from each subject's own control values during alkalosis are averaged and compared in Fig. 6 for the two groups of studies at comparable increases in serum bicarbonate concentration. There was a progressive decrease in the ventilatory response to CO_2 breathing with increasing serum bicarbonate concentration in the high P_{CO_2} group. This is in contrast to the lack of change in ventilatory response observed when similar increases in serum bicarbonate concentration and greater increase in arterial blood pH were effected by the alkalinizing agents of the normal P_{CO_2} group.

Cerebrospinal fluid acid-base relationships during alkalosis

Simultaneous determinations of arterial blood and cerebrospinal fluid (CSF) pH, bicarbonate concentration, and P_{CO_2} were obtained during alkalosis in 4 subjects of the high P_{CO_2} group and in 3 of the normal P_{CO_2} group (Table V). During alkalosis, the pH of CSF did not differ in the two groups of subjects. CSF bicarbonate concentrations tended to be slightly higher in the high P_{CO_2} group, but the ratio of CSF to blood bicarbonate concentration was similar for all subjects. The P_{CO_2} of CSF was higher in the high P_{CO_2} group, paralleling changes in the arterial P_{CO_2}.

Examination of electrolyte concentrations in the CSF during alkalosis revealed no differences between the two groups, despite the observed variation in serum concentrations; CSF sodium ranged from 137 to 147 mmoles/liter, CSF chloride ranged from 110 to 127 mmoles/liter and CSF potassium ranged from 2.6 to 3.8 mmoles/liter.

DISCUSSION

The present study examined the ventilatory adjustment to chronic metabolic alkalosis induced under controlled conditions in normal human subjects. The results indicate that chronic metabolic alkalosis produced by one group of agents (sodium bicarbonate, THAM, and ethacrynic acid) was associated with alveolar hypoventilation, as evidenced by an abnormally high P_{CO_2} and abnormally low P_{O_2} in the arterial blood, a reduced tidal volume and alveolar ventilation at rest while breathing ambient air, and a diminished ventilatory response to inspired CO_2. On the other hand, chronic metabolic alkalosis produced by a second group of agents (thiazides and aldosterone) was not associated with alveolar hypoventilation. Statistical analysis of these data in terms of each individual's change from his own control indicated that these differences between the two groups during alkalosis were significant.

These differences in ventilatory response to alkalosis could not be ascribed to variations among the subjects comprising the two groups, because in the control observations there were no inherent differences between the groups with reference to the initial arterial P_{CO_2}, P_{O_2}, pattern of breathing, or response to CO_2 inhalation. In addition, 9 of the 13 individuals served as subjects for both groups. Thus, subjects who were uniform in their pattern of breathing during control periods exhibited different patterns of response during experimental alkalosis depending on the method of induction of the alkalosis. Since alveolar hypoventilation occurred in the first group and not in the second, despite similar elevations of pH and bicarbonate concentration of arterial blood, these observations indicate that respiratory compensation in metabolic alkalosis is not determined by the pH, the P_{CO_2}, or the bicarbonate concentration of arterial blood.

Acute hyperventilation due to anxiety can be excluded as a basis for the different ventilatory responses in the two groups, since the respiratory quotient of each subject was within normal limits during both control and test periods. Also, pharmacological effects of the alkalinizing agents upon the respiratory center, either direct or through carbonic anhydrase inhibition (i.e. thiazides), did not appear to be responsible since: (*a*) acute administration of ethacrynic acid did not cause hypoventilation, and acute administration of thiazides or aldosterone did not induce hyperventilation; (*b*) the observed patterns of ventilation persisted throughout the course of the induced alkalosis after discontinuation of the inducing agents.

Examination of lumbar cerebrospinal fluid revealed no differences in pH, electrolyte composition, or ratio of CSF to blood bicarbonate concentration. In addition, the CSF P_{CO_2} was higher in

the group with alveolar hypoventilation than in the group without hypoventilation. Differences in CSF composition can therefore also not explain the observed differences in ventilatory response, a conclusion similar to that of Fencl, Miller, and Pappenheimer (18). Although cisternal fluid was not analyzed, extrapolation of values obtained from lumbar fluid to those obtained by cisternal sampling during chronic acid-base disturbances has been shown to be valid (19).

Finally, the different ventilatory responses of the two groups could not be attributed to changes in extracellular fluid volume or to differences in sodium or chloride balance, since each of the two groups included at least one agent which induced metabolic alkalosis and expanded the extracellular fluid volume as well as at least one other which reduced the extracellular fluid volume; also, at least one agent in each group caused sodium and chloride retention whereas another caused sodium and chloride diuresis. However, consistent differences were observed between the two groups with respect to hydrogen and potassium balance. These differences are discussed below.

Alveolar hypoventilation after buffers or ethacrynic acid. During induction of alkalosis in the high P_{CO_2} group, slight to moderate potassium losses were accompanied by hydrogen ion depletion. This "depletion" was accomplished in two different ways: (*a*) by inactivation of free hydrogen ions within body fluids by the administration of buffer anions (20, 21); this was reflected in the balance studies by reduced hydrogen ion excretion in the urine; or (*b*) by ethacrynic acid which promoted the excretion of hydrogen ion in the urine under conditions of unchanged endogenous formation of metabolic hydrogen (22); the assumption that the formation of metabolic hydrogen was unchanged in the present study is based upon unchanged excretion of urinary nitrogen.

Two independent types of observations indicate that the sensitivity of the respiratory center was abnormally low in the high P_{CO_2} (hydrogen ion depletion) group: (*a*) the resting minute ventilation was the same or less than control even though the level of arterial P_{CO_2} was higher; and (*b*) the increment in minute ventilation while breathing 5% CO_2 was less during metabolic alkalosis than during the control periods, even though the acute changes in arterial pH and P_{CO_2} produced by CO_2 inhalation were virtually the same during the control periods and during the periods of metabolic alkalosis.

In this group the decrease in resting tidal volume and in the ventilatory response to carbon dioxide inhalation was directly related to the increase in serum bicarbonate concentration and (by inference) extracellular buffering capacity rather than to the increased pH of arterial blood. Since the method of hydrogen ion depletion used in the present group of chronic acid-base disturbances presumably effects corresponding increases in the buffering capacities of all body fluid compartments (23, 24), the decrease in responsiveness of the respiratory center was probably associated with an increase in intracellular, as well as extracellular, buffering capacity (25, 26).

Metabolic alkalosis without alveolar hypoventilation. Alveolar hypoventilation did not occur when chronic metabolic alkalosis was induced by the administration of thiazides or of aldosterone (normal P_{CO_2} group). The preservation of the sensitivity of the respiratory center in this group, despite levels of extracellular alkalosis which were comparable to those of the high P_{CO_2} group, could not be attributed to differences in arterial pH or in extracellular buffering capacity, nor could it be attributed to differences in the acid-base or electrolyte composition of cerebrospinal fluid. On the other hand, the normal sensitivity of the respiratory center did seem to be related to the difference between these two groups in the hydrogen and potassium ion balances. First, the normal P_{CO_2} group had larger cumulative potassium losses and lower serum potassium concentrations than the high P_{CO_2} group; second, there was a direct relationship between cumulative potassium losses and the elevations in serum bicarbonate concentration; and third, aldosterone and thiazides induced extracellular alkalosis during a period in which no external loss of hydrogen ion could be demonstrated. These differences suggest two possible mechanisms for the absence of alveolar hypoventilation despite extracellular alkalosis in this group. First, there may have been redistribution of hydrogen ions into cells of the respiratory center as a consequence of hypokalemia, and second, potassium depletion per se may have changed the respiratory neuronal activity.

In favor of the first possibility is experimental

evidence in animals (27, 28) and man (5, 29) which suggests that, as a consequence of intracellular potassium losses, hydrogen ions shift from extracellular fluid into cells. Potassium loss during induction of alkalosis in this group was not associated with measurable changes in renal hydrogen ion excretion. This observation is consistent with the thesis (5, 28) that redistribution of hydrogen ions into cells was involved in the development of alkalosis. It is conceivable that such a shift of hydrogen ions into cells of the respiratory center may have prevented hypoventilation in this group. A redistribution of hydrogen ions into cells does not necessarily imply a change in intracellular pH. The inherent buffering capacity of cells may prevent a pH change. Furthermore, bicarbonate may equilibrate into cells once extracellular concentration is increased. Finally, the normal, rather than increased, ventilatory responsiveness of these subjects suggests that intracellular acidosis does not occur.

With regard to the second possibility, it is known that alterations in cell potassium concentration or transmembrane concentration gradients affect the threshold for excitation of nerve tissues (30). Whether potassium depletion indeed modifies the threshold for excitation in neurons comprising the respiratory center cannot be evaluated from the present study.

Finally, it is of interest to consider the effects of combined depletion of hydrogen ions and potassium ions. During the induction of alkalosis by ethacrynic acid, considerable amounts of potassium as well as of hydrogen were lost in the urine. Since these subjects developed alveolar hypoventilation, the hydrogen ion depletion seemed to exert the predominant effect on the respiratory adjustment. Nevertheless, the degree of hypoventilation, reflected by the increment in arterial P_{CO_2} for a given increment in serum bicarbonate, was less in patients with combined hydrogen and potassium loss (ethacrynic acid) than in those subjects who were hydrogen-depleted without significant potassium losses (buffers) (Fig. 1). Such interrelationships between the tendency of hydrogen ion depletion to induce hypoventilation and of potassium loss to prevent it may explain some of the variations in respiratory compensation in more prolonged clinical states of metabolic alkalosis, or in experimental situations where mechanisms for producing depletion of both ions coexist (6, 31).

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