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Research Article

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During the second phase of observation we subjected the hypoxemic dogs to stepwise increments in arterial carbon dioxide tension in order to evaluate the effects of the low oxygen tension on the acid—base adjustments to a chronic state of hypercapnia. At least 6 days was allowed for extracellular composition to reach a new steady state at each level of inspired carbon dioxide. The data demonstrate a rise in both plasma bicarbonate concentration and renal acid excretion that was not significantly different from that which has been described previously for hypercapnia without hypoxemia. Just as in these earlier studies, plasma hydrogen ion concentration rose with each increment in carbon dioxide tension, each millimeter Hg increment in PCO_2 leading to an increase in hydrogen ion concentration of 0.32 nmole per […]

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Summary. We have carried out balance studies in normal dogs in order to appraise the effects of chronic hypoxemia on acid–base and electrolyte equilibrium. During the first phase of observation we produced a state of "pure" hypoxemia by reducing the oxygen concentration (utilizing nitrogen as a diluent) and by adding carbon dioxide to the environment in a concentration sufficient to keep arterial CO_2 tension (P_{CO_2}) within normal limits. The data demonstrate that such a 9–day period of normocapneic hypoxemia has no effect on electrolyte excretion and is virtually without effect on plasma composition.

During the second phase of observation we subjected the hypoxemic dogs to stepwise increments in arterial carbon dioxide tension in order to evaluate the effects of the low oxygen tension on the acid–base adjustments to a chronic state of hypercapnia. At least 6 days was allowed for extracellular composition to reach a new steady state at each level of inspired carbon dioxide. The data demonstrate a rise in both plasma bicarbonate concentration and renal acid excretion that was not significantly different from that which has been described previously for hypercapnia without hypoxemia. Just as in these earlier studies, plasma hydrogen ion concentration rose with each increment in carbon dioxide tension, each millimeter Hg increment in P_{CO_2} leading to an increase in hydrogen ion concentration of 0.32 nmole per L. It thus appears that the chronic "carbon dioxide response curve" is not significantly influenced by moderately severe hypoxemia.

Introduction

The effects on the mammalian organism of low oxygen tensions have long attracted the attention of physiologists and clinical investigators, yet virtually no data are available which define the influence of chronic hypoxemia per se on electrolyte and acid–base equilibrium. All maneuvers that have been used to produce chronic hypoxemia (e.g., altitude, decompression) also induce hyperventilation and respiratory alkalosis; as a result, the specific effects of a sustained reduction in oxygen tension have not been separated from those of the accompanying hypocapnia. The first purpose of the present study has been to investigate the influence of chronic hypoxemia on electrolyte and acid–base equilibrium under circumstances in which arterial carbon dioxide tension is main-

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TABLE I

Balance data for a representative study illustrating the response

	Day	Body wt	Intake					Urine					
			Na	Cl	K	N	H_2O	Volume	pH	HCO_3	Cl	Na	K
		kg	*mEq/day*			*g/day*	*ml/day*	*ml/day*			*mEq/day*		
	1	19.5	86	83	65	11.4	1,200	1,440	5.99	2	88	75	85
	2		86	83	65	11.4	1,200	1,300	5.87	1	81	75	64
Control	3		86	83	65	11.4	1,200	1,390	6.00	3	82	80	67
	4	19.5	86	83	65	11.4	1,200	1,130	6.07	2	80	77	62
	5		86	83	65	11.4	1,200	1,170	5.90	1	60	55	51
	6	19.0	86	83	65	11.4	1,200	1,620	6.13	5	104	113	90
	7		86	83	65	11.4	1,200	950	5.89	1	65	57	54
	8	19.0	86	83	65	11.4	1,200	600	6.03	1	52	56	46
9% O_2	9		86	83	65	11.4	1,200	1,070	5.73	1	93	88	67
4% CO_2	10		86	83	65	11.4	1,200	1,100	5.79	1	77	69	66
	11	19.5	86	83	65	11.4	1,200	920	5.83	2	80	72	64
	12		86	83	65	11.4	1,200	950	5.73	1	91	79	70
	13	19.5	86	83	65	11.4	1,200	1,050	5.63	1	85	82	59
	14		86	83	65	11.4	1,200	690	5.64	1	58	50	66
	15	19.0	86	83	65	11.4	1,200	470	6.08	2	82	83	81
	16		86	83	65	11.4	1,200	550	5.54	0	97	67	67
	17	18.5	86	83	65	11.4	1,200	480	5.62	0	60	54	43
9% O_2	18		86	83	65	11.4	1,200	980	5.98	6	122	100	75
7% CO_2	19		86	83	65	11.4	1,200	660	5.94	1	79	67	63
	20	18.5	86	83	65	11.4	1,200	520	5.87	1	53	49	46
	21		86	83	65	11.4	1,200	700	6.06	2	69	63	55
	22	18.5	86	83	65	11.4	1,200	790	6.20	3	88	79	64
	23		86	83	65	11.4	1,200	720	6.18	3	127	108	95
	24		86	83	65	11.4	1,200	320	5.66	0	62	46	57
	25	19.0	86	83	65	11.4	1,200	280	5.92	1	53	46	37
9% O_2	26		86	83	65	11.4	1,200	910	5.99	3	140	113	72
10% CO_2	27	18.5	86	83	65	11.4	1,200	640	6.28	5	77	70	65
	28		86	83	65	11.4	1,200	640	6.15	5	91	75	65
	29	18.5	86	83	65	11.4	1,200	520	6.20	3	73	65	55
	30		86	83	65	11.4	1,200	580	6.37	8	70	59	61
	31		85	82	64	11.2	1,181	430	6.59	9	66	73	92
	32		83	80	63	11.0	1,163	350	5.96	1	86	63	63
	33		84	81	64	11.2	1,177	280	6.14	3	44	41	55
9% O_2	34	18.0	85	82	64	11.2	1,183	700	6.04	3	146	111	70
13% CO_2	35	18.0	84	81	64	11.1	1,166	530	6.14	3	76	68	47
	36	18.0	84	81	64	11.2	1,177	710	6.16	5	99	85	55
	37		85	82	64	11.2	1,183	500	6.15	2	66	49	52
	38	17.5	85	82	64	11.2	1,180	660	6.37	7	114	111	81

* Abbreviations: TA = titratable acid, P_{CO_2} = CO_2 tension, and S_{aO_2} = O_2 saturation.

tained at normal levels (normocapneic hypoxemia).

The second purpose of the study has been to examine the effects of chronic hypoxemia on the adjustments of acid–base equilibrium to graded degrees of chronic hypercapnia. Previous studies in animals have defined a "carbon dioxide response curve" in dogs exposed chronically to increasing degrees of hypercapnia (1), but the possible influence of coexistent hypoxemia on the ability of the kidney to increase acid excretion and bicarbonate reabsorption has not been evaluated. In view of the possibility that hypoxemia might alter tubular cell function and that the consequent carbon dioxide response curve might therefore be modified, it has seemed desirable to re-examine the response to hypercapnia at levels of oxygen tension of 45 to 55 mm Hg. This range was chosen because it encompasses the great majority of values encountered in patients with chronic and reasonably constant degrees of pulmonary insufficiency.

Methods

Studies were carried out in eight female mongrel dogs ranging in weight from 14 to 21 kg. Detailed metabolic studies were done on six of the dogs; in the remaining two animals measurements were restricted to the composition of plasma. After a control period of 5 to 9 days the animals were placed in an environmental chamber (2) in which oxygen concentration had been lowered

TABLE I

*to chronic hypercapnia in the presence of hypoxemia (dog 57)**

Urine				Stool				Plasma								
NH_4	TA	PO_4	N	Na	Cl	K	N	P_{CO_2}	pH	H	HCO_3	Na	Cl	K	P_{O_2}	Sa_{O_2}
mEq/day		*mmoles/day*	*g/day*	*mEq/day*			*g/day*	*mm Hg*		*nmoles/L*		*mEq/L*			*mm Hg*	*%*
50	48	71	12.8	7	1	1	0.3	34	7.40	40	20.6	147	112	4.3		97
37	38	54	9.6	7	1	1	0.3									
33	37	55	9.5	7	1	1	0.3									
28	33	50	8.0	7	1	1	0.3	32	7.43	37	20.8	147	111	4.6		97
27	27	39	7.3	7	1	1	0.3	35	7.41	39	21.5	147	109	4.5		
37	43	68	12.2	10	2	3	0.5	35	7.43	37	22.3	149	110	4.1	48	78
25	29	41	6.6	10	2	3	0.5									
26	25	39	8.2	10	2	3	0.5									
42	42	59	10.1	10	2	3	0.5									
38	41	59	9.1	10	2	3	0.5									
39	37	55	9.0	10	2	3	0.5	38	7.34	46	19.7	148	109	4.6	47	71
37	36	52	9.8	10	2	3	0.5									
34	40	55	8.8	10	2	3	0.5	38	7.36	44	20.6	151	113	4.7	50	75
36	38	52	8.9	10	2	3	0.5	34	7.41	39	20.8	151	113	4.3	46	76
32	36	60	9.2	7	1	2	0.5	51	7.31	49	24.8	152	112	4.1	53	79
77	56	78	11.7	7	1	2	0.5									
35	31	44	5.9	7	1	2	0.5									
59	43	66	13.0	7	1	2	0.5	53	7.34	46	27.6	153	109	4.4	54	80
42	36	55	9.2	7	1	2	0.5	52	7.34	46	27.4	150	107	4.7		
34	22	33	7.1	7	1	2	0.5	51	7.35	45	27.1					
45	31	50	9.2	7	1	2	0.5	52	7.34	46	27.4	152	108	4.6	57	81
51	29	52	10.0	7	1	2	0.5	56	7.31	49	27.4	153	110	4.3		
42	36	66	10.7	5	1	2	0.4	75	7.23	59	30.3	157	109	4.1	56	76
57	39	57	9.4	5	1	2	0.4									
41	24	38	6.4	5	1	2	0.4	69	7.28	52	31.3					
61	44	70	11.3	5	1	2	0.4	71	7.29	51	33.2	150	101	4.1	54	78
63	28	54	11.0	5	1	2	0.4	74	7.28	52	33.7					
69	34	59	10.0	5	1	2	0.4	73	7.30	50	35.0		102	3.9	54	
48	26	47	8.5	5	1	2	0.4	74	7.30	50	35.4					78
53	25	52	8.3	5	1	2	0.4	74	7.29	51	33.8	152	104	4.3	54	78
34	21	62	9.7	5	1	1	0.4	92	7.20	63	34.7	151	103	4.2	60	79
63	32	53	10.8	5	1	1	0.4									
43	28	52	8.0	5	1	1	0.4									
91	37	64	14.1	5	1	1	0.4	94	7.23	59	38.1	152	99	4.0	55	74
61	28	50	9.5	5	1	1	0.4	91	7.26	55	39.7	147	97	4.1		
62	31	56	10.5	5	1	1	0.4	91	7.27	54	40.7	147	96	4.2	55	73
50	26	47	9.2	5	1	1	0.4	98	7.23	59	39.9	155	100	4.3		
64	30	66	13.1	5	1	1	0.4	101	7.21	62	39.3	151	97	4.2	55	74

to approximately 9% with nitrogen as a diluent. During the first 9 days of the hypoxemic state, arterial carbon dioxide tension was maintained at a normal level by elevating carbon dioxide concentration in the inspired air to approximately 4%. Bloods were drawn routinely on the first, sixth, eighth, and ninth days of the period. This first phase of the study is defined as normocapneic hypoxemia.

Subsequently, the effects of hypoxemia on the response to chronic hypercapnia were evaluated by superimposing upon the hypoxemic state stepwise increments in arterial carbon dioxide tension; for this purpose environmental CO_2 concentrations of 7, 10, and 13% were utilized. Two of the dogs (dogs 2 and 4) were not exposed to 7% CO_2 but were instead studied only in a 10% and a 13% CO_2 environment. All periods were long enough to permit a new steady state of plasma bicarbonate concentration to be demonstrated, and in most instances studies were continued for several days beyond this point. Of the 19 periods of combined hypoxemia and hypercapnia studied in the eight dogs, 17 lasted 7 to 12 days, and the remaining two were 6 days long. During each period of hypercapnia blood samples were drawn on the first, third, and all subsequent days of exposure. The gas concentrations within the chamber were maintained within $\pm$ 0.5% of the desired level by automatic control systems, the nature of which has been been described previously (2).

The animals were fed 30 g per kg of an artificial diet (homogenized with twice its weight of water) the composition of which has been described earlier (3); dogs that did not eat spontaneously were tube fed. The intrinsic electrolyte content of the diet was as follows: sodium, 1 mEq per 100 g; potassium, 0.1 mEq per 100 g; and chloride, less than 1 mEq per 100 g. In the initial studies the diet was supplemented with 4 mEq per kg of

NaCl and 3 mEq per kg of potassium as neutral phosphate (4 HPO_4/1 H_2PO_4); in the last several studies the sodium supplement was 2 mEq per kg, as was the potassium supplement.

The details of the balance technique and most of the calculations have been previously described, as have the majority of the analytic methods (3). In addition the following methods were employed: Oxygen saturations on blood were performed by means of an American Optical oximeter, which was calibrated by manometric determinations of oxygen saturation according to the method of Van Slyke and Neill. We calculated P_{O_2} from the observed oxygen saturation, utilizing the hemoglobin dissociation curve for the dog and appropriate correction factors (4). No attempt was made to correct either pH or calculated P_{CO_2} for the slight difference in temperature between the electrode (37° C) and the observed temperature of the dog (38 to 39° C rectal).

Daily balances were calculated as the net intake minus the combined outputs in urine and stool. The change in net external balance was calculated as the difference between the balance on an experimental day and the mean daily balance during the control period.

Results

A) Normocapneic hypoxemia

General remarks. Mean arterial P_{O_2} was 47 mm Hg (range 43 to 51 mm Hg), and mean saturation was 75% (range 68 to 80%). None of the dogs showed untoward effects during the period of normocapneic hypoxemia. There was no change in motor activity, and the animals appeared alert and in most instances ate their diets spontaneously. A representative study is shown in detail in Table I (dog 57). Electrolyte and acid–base data for all dogs appear in Tables II and III.

Acid–base. The average P_{CO_2} for the eight dogs was 36 mm Hg as compared to a control value of 35. The mean arterial P_{CO_2} in no instance differed by more than 2 mm Hg from the mean value observed for that animal during the control period. Mean plasma bicarbonate concentration fell

TABLE II

*Changes in balance during chronic exposure to normocapneic hypoxemia and to hypoxemia combined with hypercapnia**

Period	Dog	Days	Na	Cl	Cl − (Na/1.3)	K	Kn†	N
					mEq			*g*
A. Normocapneic hypoxemia								
	4	9	−36	−17	+ 11	−32	−31	0
4% CO_2	57	9	−43	−15	+ 18	− 6	−13	+ 3
9% O_2	59	9	+12	+ 6	− 3	+13	+21	− 3
	74	9	−12	−69	− 60	+49	+34	+ 6
	77	9	+18	−10	− 24	+38	+34	+ 1
	Average		−12	−21	− 12	+12	+ 9	+ 1
B. Hypoxemia plus hypercapnia								
	57	8	+ 9	−33	− 40	+26	+30	− 1
7% CO_2	59	8	+10	−32	− 40	− 2	+ 8	− 4
9% O_2	74	7	−40	−65	− 34	−17	−18	0
	77	7	+15	−12	− 24	− 6	+17	− 9
	Average		− 2	−36	− 35	0	+ 9	− 4
	4	7	+20	−93	−108	+28	+19	+ 3
10% CO_2	57	8	+ 1	−79	− 80	+21	+28	− 3
9% O_2	59	8	+14	−51	− 62	+12	+26	− 5
	74	10	+23	−24	− 42	− 2	+35	−14
	77	10	+31	−12	− 36	− 3	+39	−16
	Average		+18	−52	− 66	+11	+29	− 7
	4	11	+97	+19	− 56	+23	+22	0
13% CO_2	57	8	0	−87	− 87	+ 7	+42	−13
9% O_2	59	8	+35	−10	− 37	−14	+20	−13
	74	7	+58	− 3	− 48	−49	+ 3	−19
	77	10	+24	−17	− 35	−16	+17	−12
	Average		+43	−20	− 53	−10	+21	−11

* Data for each period have been accumulated separately.
† Kn = K corrected for N.

TABLE III

*Changes in urinary titratable acid, ammonium, bicarbonate, and net acid excretion during chronic exposure to normocapneic hypoxemia and to hypoxemia combined with hypercapnia**

Period	Dog	Days	TA	NH_4	HCO_3	Net acid
				mEq		
A. Normocapneic hypoxemia						
	4	9	+ 6	+ 43	+ 1	+ 48
4% CO_2	57	9	+ 7	− 1	− 4	+ 10
9% O_2	59	9	− 10	− 12	−12	− 10
	74	9	− 16	− 4	− 3	− 17
	77	9	− 25	− 17	+ 4	− 45
	Average		− 8	+ 2	− 3	− 3
B. Hypoxemia plus hypercapnia						
	57	8	− 4	+ 95	− 1	+ 92
7% CO_2	59	8	+ 2	+ 59	−12	+ 73
9% O_2	74	7	+ 2	+ 62	+ 6	+ 58
	77	7	− 29	+ 69	+15	+ 25
	Average		− 7	+ 71	+ 2	+ 62
	4	7	− 9	+193	+ 2	+182
10% CO_2	57	8	− 32	+154	+12	+110
9% O_2	59	8	− 40	+135	− 2	+ 97
	74	10	− 39	+152	+21	+ 92
	77	10	− 79	+148	+37	+ 32
	Average		− 40	+156	+14	+103
	4	11	−108	+202	+18	+ 76
13% CO_2	57	8	− 55	+188	+17	+116
9% O_2	59	8	− 88	+196	+35	+ 73
	74	7	− 12	+ 55	+ 1	+ 42
	77	10	−103	+177	+89	− 15
	Average		− 73	+164	+32	+ 58

* Data for each period have been accumulated separately.

slightly; after 1, 6, and 9 days of exposure the mean values were, respectively 1.1, 1.6, and 1.5 mEq per L below control. The latter two values were significantly different from the control levels. There was no significant change in urine pH or excretion of ammonium, titratable acidity, or net acid at any time during the period.

Electrolytes and miscellaneous data. Plasma sodium concentration rose significantly ($p < 0.01$) by a mean of 3 mEq per L, but plasma potassium, chloride, and phosphate concentrations were unchanged. There were no significant changes in the urinary excretion of these electrolytes. Unmeasured anion concentration rose by 2 to 3 mEq per L. There was no change in organic acid excretion (measured in two dogs) or in plasma lactate or pyruvate concentrations. Internal balance calculations indicated that there were only small shifts of electrolytes between extra- and intracellular fluid. Hematocrit rose by 4 to 8%, presumably in response to the hypoxemia. There was no change in weight.

B) Hypoxemia plus hypercapnia

General remarks. Six of the animals completed uneventfully the entire cycle of study, i.e., exposure to normocapneic hypoxemia and to the subsequent periods of hypercapnia superimposed on hypoxemia. However, the two remaining animals developed severe vomiting, one at a CO_2 level of 10%, the other at a level of 13%, and these studies were discontinued. Data from these dogs are included only for those periods before the first episode of vomiting.

Sixty-eight of the seventy-one arterial Po_2 values were in the range of 45 to 56 mm Hg. The mean Po_2 for the three periods of hypercapnia was 52 mm Hg, compared with the mean of 47 that was observed during normocapneic hypoxe-

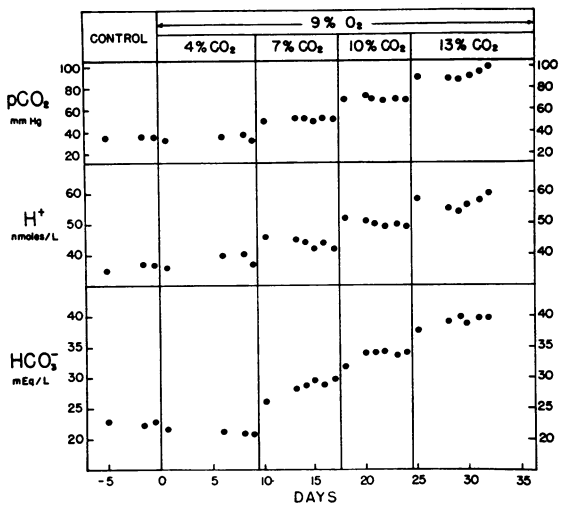

FIG. 1. PLASMA HYDROGEN ION CONCENTRATION, BICARBONATE CONCENTRATION, AND CARBON DIOXIDE TENSION (P_{CO_2}) DURING A REPRESENTATIVE STUDY. Each point represents a single arterial blood sample. Note that during the period of normocapneic hypoxemia (9% O_2, 4% CO_2) the only change was a slight (1.5 mEq per L) fall in plasma bicarbonate concentration. Note also that during the three subsequent periods of hypoxemia plus hypercapnia a steady state was achieved with 4 to 5 days of exposure to each new level of carbon dioxide.

mia; this difference was presumably due to an increase in ventilation associated with the rises in carbon dioxide tension. Despite this slight increase in P_{O_2}, the arterial oxygen saturation remained unchanged or fell because of the reduction in extracellular pH associated with the hypercapnia. The range of oxygen saturations during the three periods of hypercapnia was 68 to 81%, and the mean was 74%.

Acid–base. Plasma. Figure 1 presents the day-to-day changes in acid–base parameters of plasma for a representative study (dog 57). Detailed balance data for this dog are shown in Table I. The changes after each increment in carbon dioxide tension can be summarized as follows: plasma bicarbonate concentration rose, in nearly all instances reaching a new steady state in 3 to 5 days. Plasma hydrogen concentration also reached a new steady state in approximately 3 to 5 days; any subsequent slight fluctuations resulted from small variations in the arterial P_{CO_2}. Statistical analysis of observations from all experiments demonstrated no significant change in plasma bicarbonate concentrations over the last 3 days of each period of hypercapnia; the average change in bicarbonate concentration for all dogs over this interval was 0.4 mEq per L or less at each level of carbon dioxide tension. This pattern of response was virtually identical to that seen in previous studies of chronic hypercapnia without hypoxemia (1).

In Figure 2 is shown the steady state bicarbonate–P_{CO_2} relationship for all eight animals. The response of each animal to a given level of hypercapnia is represented by a single point obtained by averaging the observations made on the last 3 days of each period. Note that there was a marked rise in plasma bicarbonate concentration with each elevation of inspired P_{CO_2}, the increment in bicarbonate tending to diminish slightly at the higher P_{CO_2} levels. The line drawn through the points has been taken from previous observations of hypercapnia without hypoxemia (1). It is evident from the fit of the data to this line that hypoxemia is without significant effect on the bicarbonate response.

Companion data for change in plasma hydrogen ion concentration are shown in Figure 3.

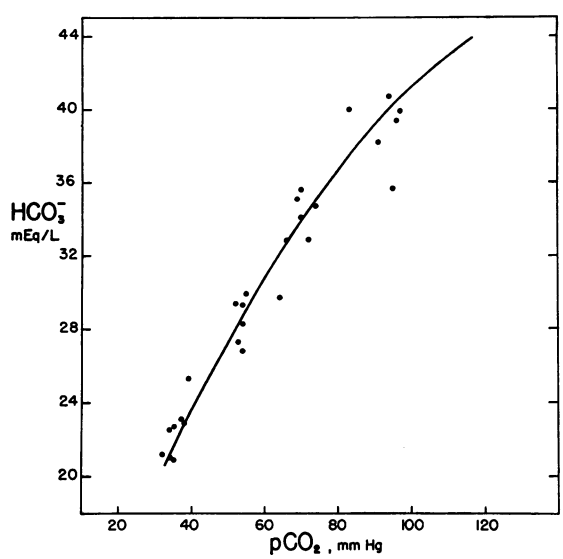

FIG. 2. STEADY STATE RELATIONSHIP BETWEEN PLASMA BICARBONATE CONCENTRATION AND P_{CO_2} DURING CHRONIC HYPOXEMIA COMBINED WITH HYPERCAPNIA OF INCREASING SEVERITY. Steady state bicarbonate values for all eight studies are shown. Each point represents the average of the plasma bicarbonate concentrations observed on the last 3 days at each level of exposure to CO_2. The line was obtained from previously reported studies of hypercapnia without hypoxemia (1). Note that the points representing the current observations fit closely around the line.

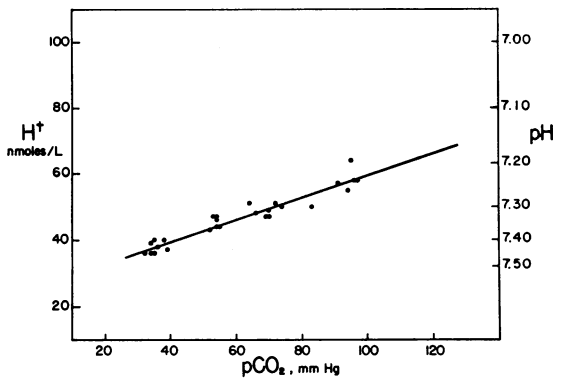

FIG. 3. STEADY STATE RELATIONSHIP BETWEEN PLASMA HYDROGEN ION CONCENTRATION AND P_{CO_2} DURING CHRONIC HYPOXEMIA COMBINED WITH HYPERCAPNIA OF INCREASING SEVERITY. Steady state hydrogen ion values are shown for all eight studies. Each point represents the average of the plasma hydrogen ion concentrations observed on the last 3 days at each level of exposure to CO_2. As in Figure 2, the line was obtained from previously reported studies of hypercapnia without hypoxemia (1).

Note that there was a rise in plasma hydrogen ion concentration with each rise in P_{CO_2}, each millimeter Hg increment in P_{CO_2} leading to an increase of 0.32 nmole of hydrogen per L. The line in this Figure, as in Figure 2, was obtained from the previous study of hypercapnia in which inspired oxygen tension was normal (1).

Urine. The changes in the acid–base parameters of the urine were also similar to those which have been described previously in nonhypoxemic hypercapnia. At each new level of carbon dioxide there was an augmentation in the excretion of net acid; this resulted from a large rise in ammonium excretion, which more than offset a simultaneous increase in the excretion of bicarbonate and reduction in the excretion of titratable acid. Dog 77 showed an unexplained fall in net acid excretion at a level of 13% CO_2. The mean increment in net acid excretion per period was 62 mEq at 7% exposure, 103 mEq at 10% exposure, and 58 mEq at 13% exposure (Table III).

On the first day of exposure to 13% CO_2 there was a slight decrease in net acid output, analogous to the response that was seen previously on the first day of exposure to 11 and 17% CO_2 in dogs breathing a normal oxygen concentration (1).

Electrolytes. Plasma chloride concentration decreased significantly ($p < .02$) with each increase in carbon dioxide tension from a control value of 111 mEq per L to a level of 101 mEq per L at the end of the 13% CO_2 period. There was at the same time a significant negative chloride balance (Table II); "selective" chloride balance calculated by using the ratio of sodium to chloride in the extracellular fluid (arbitrarily taken as 1.3) averaged − 35, − 66, and − 53 mEq for the three periods of hypercapnia.

Plasma sodium concentration increased from a mean control value of 147 mEq per L to 154 at the end of the study. Sodium balance was unremarkable during the 7% period but slightly positive at the two higher levels of carbon dioxide exposure (Table II).

Serum potassium concentration did not change significantly throughout the study. Potassium excretion increased above the mean control level on the first day of each period of hypercapnia by amounts ranging from 10 to 40 mEq. Potassium was subsequently retained so that by the end of the period over–all balance was restored to normal. Potassium balance, corrected for nitrogen, was slightly positive during both the 10 and 13% CO_2 periods (Table II). Phosphate excretion followed a pattern similar to that of potassium, rising above control levels (mean increment + 8 mmoles per day) on the first day of each hypercapnia period but returning to control levels on subsequent days. There were no significant changes in the plasma creatinine or "unmeasured anion" concentration, nor were there any appreciable shifts of sodium, potassium, or chloride between the extra- and intracellular fluids.

Miscellaneous. Organic acid excretion (measured in two dogs) did not change significantly, and plasma lactate and pyruvate concentrations were unchanged. There was virtually no change in hematocrit between the end of the period of normocapneic hypoxemia and the end of the study. Nitrogen balance became negative during the last two periods of hypercapnia (Table II). All animals lost weight, the average being 2.3 kg.

Discussion

Despite the widespread interest in the physiologic effects of chronic hypoxemia, there has been virtually no effort to define the effects of hypoxemia per se on the steady state adjustments of acid–base and electrolyte equilibrium. In all

studies designed to produce a sustained reduction in oxygen tension, an accompanying respiratory alkalosis has served to complicate the evaluation of the specific role of oxygen. This problem has been circumvented in the present study by adding carbon dioxide to the inspired air in a concentration sufficient to maintain arterial P_{CO_2} at control levels. The most notable finding has been that 9 days of normocapneic hypoxemia (arterial oxygen tensions in the range of 43 to 51 mm Hg) had virtually no effect on the electrolyte or acid–base composition of either plasma or urine. Furthermore, there was no change in plasma concentrations of either lactate or pyruvate. The latter observations are consistent with data from patients with pulmonary insufficiency which suggest that, expressed in metabolic terms, chronic hypoxemia does not cause cellular hypoxia (5).

The absence of any significant change in electrolyte excretion during the first day of hypoxemia is consistent with observations from the one study of acute hypoxemia in which carbon dioxide was administered in concentrations sufficient to prevent hypocapnia (6). In other studies said to show a specific effect of hypoxemia on electrolyte excretion (i.e., increased output of sodium, potassium, and chloride), either measurements of blood pH were not carried out (7), or the pH values suggested that respiratory alkalosis had developed (8). At present, therefore, there appears to be no convincing evidence that hypoxemia per se exerts a significant effect on electrolyte excretion during acute hypoxemia.

The second phase of the present study is concerned with the possible influence of hypoxemia on the acid–base adjustments to chronic hypercapnia. Previous studies have shown that a small generation of bicarbonate by body buffer stores and a larger generation by augmented renal acid excretion serve to raise plasma bicarbonate concentration and to mitigate significantly the acidifying effects of an increased carbon dioxide tension. These studies characterized the quantitative relationship between the degree of hypercapnia and the change in plasma pH and bicarbonate concentration and permitted construction of chronic carbon dioxide response curves (1). Since the sole purpose of these earlier experiments was to examine the effects of hypercapnia per se, oxygen concentrations were maintained at a normal level, and the possible influence of hypoxemia on the adaptive process was not explored.

An evaluation of the specific role of hypoxemia in the response to chronic hypercapnia is not only of physiologic interest, but of potential clinical importance. Only by knowing the anticipated physiologic response to a given degree of hypercapnia can one determine whether a complicating metabolic acidosis or alkalosis is present (9). Dulfano and Ishikawa (10) and Refsum (11) have suggested, on the basis of observations in patients with chronic pulmonary insufficiency, that hypoxemia exerts no important effects on the response to chronic hypercapnia; however, their data do not allow this conclusion, since the only way in which the role of oxygen tension can be critically assessed is under circumstances in which it has been determined that there is a steady state of uncomplicated chronic hypercapnia. In neither of the above studies has this goal been achieved. Evidence for a steady state of hypercapnia is lacking, since measurements of arterial P_{CO_2} over several days were not carried out (9). Moreover, the presence of a complicating metabolic alkalosis (e.g., caused by vomiting or by diuretics and a low salt diet) was not adequately excluded. Data on urinary chloride excretion were not given, and the possible role of chloride deficiency in maintaining an abnormally high plasma bicarbonate concentration was thus not adequately excluded (9, 12). Under such circumstances it is impossible to determine whether the acid–base equilibrium in chronic hypercapnia was influenced by the level of oxygen tension.

On the basis of the above physiological and clinical considerations it appeared desirable to evaluate the influence of hypoxemia on the response to graded degrees of hypercapnia under the controlled conditions that can be achieved in studies on the normal dog. As was mentioned earlier, a level of 45 to 55 mm Hg arterial oxygen tension was chosen because this degree of hypoxemia encompasses the majority of values encountered in patients with chronic pulmonary insufficiency. The results indicate that, just as in hypercapnia without hypoxemia, a period of 3 to 5 days is usually sufficient to establish a new steady state of acid–base equilibrium. Further-

more, these new steady state values for plasma bicarbonate concentration and pH are indistinguishable from those seen in animals exposed to normal oxygen tensions (1). Each increment of P_{CO_2} induced a proportional rise in hydrogen ion concentration, the increase averaging 0.32 nmole of H^+ per mm Hg increase of carbon dioxide tension. The renal adjustments in hypercapnia are also unaffected by hypoxemia, i.e., there is a rise in net acid excretion at each level of hypercapnia, which is far in excess of that necessary to account for the rise in extracellular bicarbonate concentration and even in excess of the amount necessary to account for an equivalent rise in intracellular alkali stores (1). In addition, there was a transient loss of potassium and phosphorus on the first day of exposure to each carbon dioxide concentration (1).

By extrapolating from the present physiologic studies, we conclude that it seems unlikely that hypoxemia is an important variable in the appraisal of acid–base equilibrium in patients with chronic pulmonary insufficiency.[1] It thus appears that a correction factor related to oxygen tension will not be required in appraising the appropriateness of a given set of values for pH and bicarbonate to a given elevation of arterial P_{CO_2}. The possibility cannot be excluded, of course, that more severe hypoxemia than that studied here (that is, oxygen concentrations of less than 45 mm Hg) might exert a significant influence on the adaptive process.

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[1] Recent observations have demonstrated that oxygen tensions in the same range as reported here (45 to 50 mm Hg) do not affect the response to acute hypercapnia as defined by the carbon dioxide titration curve of the normal dog (13).

References

1. Schwartz, W. B., N. C. Brackett, Jr., and J. J. Cohen. The response of extracellular hydrogen ion concentration to graded degrees of chronic hypercapnia: the physiologic limits of the defense of pH. J. clin. Invest. 1965, **44**, 291.
2. Schwartz, W. B., and L. Silverman. A large environmental chamber for the study of hypercapnia and hypoxia. J. appl. Physiol. 1965, **20**, 767.
3. Tannen, R. L., H. L. Bleich, and W. B. Schwartz. The renal response to acid loads in metabolic alkalosis; an assessment of the mechanisms regulating acid excretion. J. clin. Invest. 1966, **45**, 562.
4. Rossing, R. G., and S. M. Cain. A nomogram relating P_{O_2}, pH, temperature, and hemoglobin saturation in the dog. J. appl. Physiol. 1966, **21**, 195.
5. Huckabee, W. E. Metabolic consequences of chronic hypoxia. Ann. N. Y. Acad. Sci. 1965, **121**, 723.
6. Ullmann, E. Acute anoxia and the excretion of water and electrolyte. J. Physiol. (Lond.) 1961, **155**, 417.
7. Berger, E. Y., M. Galdston, and S. A. Horwitz. The effect of anoxic anoxia on the human kidney. J. clin. Invest. 1949, **28**, 648.
8 Thurau, K. Renal Na–reabsorption and O_2-uptake in dogs during hypoxia and hydrochlorothiazide infusion. Proc. Soc. exp. Biol. (N. Y.) 1961, **106**, 714.
9. Cohen, J. J., and W. B. Schwartz. Evaluation of acid–base equilibrium in pulmonary insufficiency: an approach to a diagnostic dilemma. Amer. J. Med. 1966, **41**, 163.
10. Dulfano, M. J., and S. Ishikawa. Quantitative acid–base relationships in chronic pulmonary patients during the stable state. Amer. Rev. resp. Dis. 1966, **93**, 251.
11. Refsum, H. E. Acid-base status in patients with chronic hypercapnia and hypoxaemia. Clin. Sci. 1964, **27**, 407.
12. Kassirer, J. P., and W. B. Schwartz. Correction of metabolic alkalosis in man without repair of potassium deficiency; a re-evaluation of the role of potassium. Amer. J. Med. 1966, **40**, 19.
13. Levine, D. Z., D. G. Sapir, and W. B. Schwartz. Unpublished observations.