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Research Article

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This observation raised the possibility that the secondary hypocapnia which normally accompanies metabolic acidosis, if persistent, might induce an analogous renal response and thereby contribute to the steady-state decrement in plasma $[\text{HCO}_3^-]$ observed during HCl feeding. We reasoned that if sustained secondary hypocapnia provoked the kidney to depress renal bicarbonate reabsorption, the acute salutary effect of hypocapnia on plasma acidity might be seriously undermined.

To isolate the possible effects of secondary hypocapnia from those of the hydrogen ion load, per se, animals were maintained in an atmosphere of 2.6% CO_2 during an initial 8-day period of acid feeding (7 mmol/kg per day); this maneuver allowed Paco_2 to be held constant at the control level of 36 mm Hg despite the hyperventilation [...]

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ABSTRACT It has generally been thought that homeostatic mechanisms of renal origin are responsible for minimizing the alkalemia produced by chronic hypocapnia. Recent observations from this laboratory have demonstrated, however, that the decrement in $[\text{HCO}_3^-]$, which "protects" extracellular pH in normal dogs, is simply the by-product of a non-specific effect of PaCO_2 on renal hydrogen ion secretion; chronic primary hypocapnia produces virtually the same decrement in plasma $[\text{HCO}_3^-]$ in dogs with chronic HCl acidosis as in normal dogs ($\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2 = 0.5$), with the result that plasma $[\text{H}^+]$ in animals with severe acidosis rises rather than falls during superimposed forced hyperventilation.

This observation raised the possibility that the secondary hypocapnia which normally accompanies metabolic acidosis, if persistent, might induce an analogous renal response and thereby contribute to the steady-state decrement in plasma $[\text{HCO}_3^-]$ observed during HCl feeding. We reasoned that if sustained secondary hypocapnia provoked the kidney to depress renal bicarbonate reabsorption, the acute salutary effect of hypocapnia on plasma acidity might be seriously undermined.

To isolate the possible effects of secondary hypocapnia from those of the hydrogen ion load, per se, animals were maintained in an atmosphere of 2.6% CO_2 during an initial 8-day period of acid feeding (7 mmol/kg per day); this maneuver allowed PaCO_2 to be held constant at the control level of 36 mm Hg despite the hyperventilation induced by the acidemia. Steady-state bicarbonate concentration during the

period of eucapnia fell from 20.8 to 16.0 meq/liter, while $[\text{H}^+]$ rose from 42 to 55 neq/liter. During the second phase of the study, acid feeding was continued but CO_2 was removed from the inspired air, permitting PaCO_2 to fall by 6 mm Hg. In response to this secondary hypocapnia, bicarbonate concentration fell by an additional 3.0 meq/liter to a new steady-state level of 13.0 meq/liter. This reduction in bicarbonate was of sufficient magnitude to more than offset the acute salutary effect of the hypocapnia on plasma hydrogen ion concentration; in fact, steady-state $[\text{H}^+]$ rose as a function of the adaptive fall in PaCO_2 , $\Delta[\text{H}^+]/\Delta\text{PaCO}_2 = -0.44$. That the fall in bicarbonate observed in response to chronic secondary hypocapnia was the result of the change in PaCO_2 was confirmed by the observation that plasma bicarbonate returned to its eucapnic level in a subgroup of animals re-exposed to 2.6% CO_2 .

These data indicate that the decrement in plasma $[\text{HCO}_3^-]$ seen in chronic HCl acidosis is a composite function of (a) the acid load itself and (b) the renal response to the associated hyperventilation. We conclude that this renal response is maladaptive because it clearly diminishes the degree to which plasma acidity is protected by secondary hypocapnia acutely. Moreover, under some circumstances, this maladaptation actually results in more severe acidemia than would occur in the complete absence of secondary hypocapnia.

INTRODUCTION

It is commonly assumed that secondary hyperventilation is of critical importance to the homeostatic defense of pH during metabolic acidosis. As generally envisioned, some "metabolic" process initiates this acid-base disturbance by causing plasma bicarbonate

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to fall; this bicarbonate decrement, in turn, reduces the level of plasma pH because of its immediate effect on the Henderson-Hasselbalch equation. As a consequence of the acidemia, ventilation is stimulated and the resulting, adaptive fall in arterial carbon dioxide tension (P_{aCO_2}) returns the bicarbonate/carbonic acid ratio, and hence pH, toward normal.

Implicit in this formulation is the assumption that plasma bicarbonate concentration, once reduced by the metabolic process, undergoes little or no further reduction as a consequence of the secondary hypocapnia. This thesis, however, has never been subjected to direct experimental confirmation. In fact, recent evidence from our laboratory has demonstrated that the renal response to chronic primary (forced) hypocapnia of prolonged duration results in the same large reduction in renal bicarbonate reabsorption in dogs with chronic HCl acidosis as in normal dogs; in both groups, each mm Hg reduction in P_{aCO_2} led, on the average, to a 0.5 meq/liter decrement in steady-state plasma bicarbonate concentration (1). Thus, it seemed reasonable to speculate that secondary hypocapnia, if sufficiently prolonged, might suppress renal bicarbonate reabsorption and, as in primary hypocapnia, be responsible for a significant fall in plasma bicarbonate concentration. If such a renal response were to contribute importantly to the overall decrement in bicarbonate concentration in metabolic acidosis, it is evident that the acute effect of secondary hypocapnia in protecting plasma pH would be seriously compromised.

The present studies were carried out in order to isolate the effects of an acid load from those of secondary hypocapnia and, thus, to fully define the homeostatic role of hyperventilation during metabolic acidosis. To accomplish this goal, the response of acid-base equilibrium to the chronic administration of HCl (7 mmol/kg per day) was examined by the following two-phase protocol. In an initial phase, the effects of the acid load, per se, were evaluated by forcing dogs to breathe 2.6% carbon dioxide in an environmental chamber, thus preventing the reduction in P_{aCO_2} which ordinarily accompanies acidosis-induced hyperventilation. In a second phase, the specific effect of hypocapnia on acid-base equilibrium was evaluated by removing carbon dioxide from the chamber, thus allowing secondary hypocapnia to develop.

The results indicate that, contrary to the usual view, chronic secondary hypocapnia produces a significant reduction in plasma bicarbonate concentration, accounting for nearly 40% of the total bicarbonate decrement seen in HCl acidosis. It is thus evident that the optimal benefit to be derived from the secondary hypocapnia induced by metabolic acidosis is seen only during the acute phases of this disorder; when the

secondary hypocapnia of metabolic acidosis is sustained, the defense of plasma pH is undermined by a further, maladaptive reduction in plasma bicarbonate concentration.

METHODS

Studies were carried out on 35 female mongrel dogs, ranging in weight from 11.3 to 24.8 kg. All animals were fed 30 g/kg per day of a synthetic diet for at least 3 days before the control period and throughout the period of study. The diet contained <1.0 meq sodium/100 g, <0.1 meq potassium/100 g, and <0.5 meq chloride/100 g (2). The daily diet was homogenized with twice its weight of distilled water and supplemented with 2.5 meq/kg body wt of potassium as neutral phosphate and 2.5 mmol/kg body wt of sodium chloride. Animals that did not eat spontaneously were tube-fed, and animals that vomited were excluded from further study. Blood samples were obtained by percutaneous arterial puncture; rectal temperature was measured at the time of blood sampling. During each period of study, an animal was judged to be in a steady state when plasma values obtained on three consecutive days varied by no more than 2 meq/liter for bicarbonate and by no more than 5 mm Hg for P_{aCO_2} .

Experimental design

Studies were conducted according to the following three protocols.

PROTOCOL I—CHRONIC HCL ACIDOSIS: EUCAPNIA VS. HYPOCAPNIA (14 DOGS)

This protocol, depicted schematically in Fig. 1, was designed to determine whether the decrement in plasma bicarbonate concentration observed during chronic HCl feeding is, in part, the result of the secondary (acidosis-induced) decrement in P_{aCO_2} .

Control period. A control period of at least 3 days duration was obtained in order to establish a normal base line.

Chronic eucapnic acidosis. Chronic metabolic acidosis was induced by the daily feeding of HCl, 7 mmol/kg body wt. At the onset of acid feeding, the animals were placed in a large environmental chamber (3) containing approximately 2.6% CO_2 . During preliminary studies, this level of ambient CO_2 was found to be sufficient to prevent hypo-

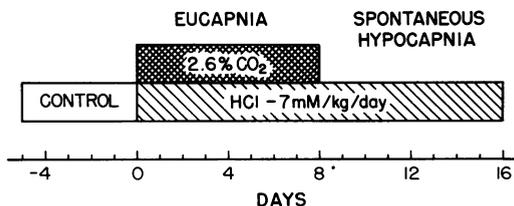


FIGURE 1 Protocol for isolating the effects of an acid load per se from those of secondary hypocapnia in animals fed 7 mmol/kg HCl/day. The development of secondary hypocapnia was thwarted by forcing the animals to breathe 2.6% CO_2 in an environmental chamber. After a steady state of eucapnic acidosis was achieved, the animals were allowed to breathe room air, thereby permitting secondary hypocapnia to emerge.

capnia from occurring in response to secondary (acidosis-induced) hyperventilation. Oxygen concentration was maintained at 21%. Observations were carried out for 8 days, by which time a new steady-state of acid-base equilibrium had been established in all animals.

Chronic hypocapnic acidosis. Acid feeding was continued but the animals were returned to a room-air environment. This maneuver allowed arterial carbon dioxide tension to fall in response to the acidosis-induced hyperventilation. An 8-day period of observation was then carried out. At the end of this period, five of the animals remained under study for an additional 7 days during which acid feeding was continued and chronic eucapnic acidosis was reestablished by reexposure to 2.6% CO₂.

No attempt was made to measure changes in urinary acid excretion because previous studies have indicated that the day-to-day variation in ammonium and titratable acid excretion during HCl-feeding are far too large to permit experimental detection of small changes such as those anticipated in the present study (1).

PROTOCOL II—ACUTE HYPOCAPNIA SUPERIMPOSED ON CHRONIC EUCAPNIC ACIDOSIS (4 DOGS)

This protocol was designed to assess the influence of acute hypocapnia on acid-base equilibrium in animals with chronic eucapnic acidosis. As a base line for this assessment, a steady state of chronic eucapnic acidosis was first induced, using the technique described in protocol I.

Acute hypocapnia. On the day of the acute study, the diet was withheld and three control blood samples were obtained at 30-min intervals; animals were accepted for study only if arterial carbon dioxide tension and plasma bicarbonate concentration fell within 5 mm Hg and 2 meq/liter, respectively, of the individual steady-state values obtained during eucapnic acidosis. Two levels of acute hypocapnia were induced in order to encompass the range of PaCO₂ values observed during chronic HCl-acidosis (protocol I). A mild degree of acute hypocapnia was created by abruptly replacing the CO₂-rich atmosphere within the chamber with room air; after a 30-min equilibration period, three arterial blood samples were obtained at 30-min intervals. A more severe degree of acute hypocapnia was then induced by lowering the oxygen concentration of the chamber (over a 30-min period) to 14%, using nitrogen as a diluent; after an additional 30-min equilibration period, three final blood samples were obtained at 30-min intervals.

An acute steady-state was judged to be present only if the PaCO₂ and bicarbonate values of the three blood samples obtained in a given period varied by no more than 5 mm Hg and 2 meq/liter, respectively.

PROTOCOL III—HCL DOSE-RESPONSE CURVE DURING EUCAPNIA

This protocol was designed to determine, under eucapnic conditions, the quantitative relationship between the daily dose of HCl and the resulting steady-state decrement of plasma bicarbonate concentration.

Data defining the response of plasma bicarbonate concentration to prolonged acid feeding at a dose of 7 mmol/kg per day were available from the eucapnic period of protocol I. To obtain comparable data at higher levels of acid ingestion, two additional groups of dogs were studied in the following fashion. After a control period of at least 3 days, 10 animals were fed 10.5 mmol/kg and 7 animals were fed 14

mmol/kg per day of hydrogen ion. Preliminary observations indicated that diets containing such large amounts of HCl frequently caused vomiting; this problem was obviated by feeding only 7 mmol/kg per day of the dietary acid supplement as HCl itself and the remainder as L-lysine monohydrochloride (Sigma Chemical Co., St. Louis, Mo.).

Eucapnic conditions were maintained throughout the period of acid ingestion by the same technique employed in protocols I and II. Observations were carried out until steady-state conditions were well established (6–8 days).

In eight of the animals fed 10.5 mmol/kg per day of acid, an 8-day period of chronic hypocapnic acidosis was also obtained (as in protocol I) after the period of eucapnia. Efforts to obtain a similar period of spontaneous hypocapnia in the animals fed 14 mmol/kg per day of acid were unsuccessful because all of the animals vomited within a few days after having been removed from the CO₂-rich atmosphere.

Analytical methods

Methods used for determining sodium, potassium, chloride, phosphorus, and creatinine have been reported previously (4). Total CO₂ and pH were measured directly; bicarbonate concentration and PaCO₂ were calculated from the Henderson-Hasselbalch equation. pH, pK' and the solubility coefficient of CO₂ were corrected for temperature; pK' was also corrected for pH (5–7). Blood lactate and pyruvate were determined by specific enzymatic methods (8–9).

RESULTS

Steady-state plasma values for the control period and each experimental period were obtained for each animal by averaging the three plasma determinations made during the respective steady-state intervals. Statistical evaluation was carried out by means of analysis of variance for paired data. Throughout the text the terms "significant" or "significantly different" will be used to describe a difference which has a *P* value of <0.01, unless otherwise noted.

Protocol I—Chronic HCl acidosis: Eucapnia vs. hypocapnia

Mean, steady-state plasma values for the group as a whole are presented in Table I and Fig. 2.

Chronic eucapnic acidosis. Exposure of the animals to a 2.6% CO₂ atmosphere during administration of HCl (7 mmol/kg per day) was effective in maintaining mean PaCO₂ virtually unchanged from the control value of 36 mm Hg. In the face of this stable level of PaCO₂, plasma bicarbonate concentration decreased significantly during acid feeding, falling from a mean control value of 20.8 to 16.0 meq/liter (Fig. 2). As a consequence, mean plasma hydrogen ion concentration increased significantly from a control value of 42 to a value of 55 neq/liter.

Plasma sodium concentration remained virtually unchanged. Plasma potassium concentration decreased significantly from 4.0 to 3.3 meq/liter, and plasma

TABLE I
Changes in Plasma Composition during Chronic Eucapnic and Chronic Hypocapnic HCl Acidosis* (HCl, 7 mmol/kg per day)

Period	PaCO ₂ mm Hg	HCO ₃ ⁻ meq/liter	H ⁺ neq/liter	Na meq/liter	K meq/liter	Cl meq/liter	Unmeasured anions† meq/liter
Control	36±0.6	20.8±0.3	42±0.3	145±0.7	4.0±0.1	111±0.9	17±0.6
Eucapnic HCl acidosis	36±0.6	16.0±0.4	55±1.1	145±0.3	3.3±0.1	117±0.5	16±0.5
Hypocapnic HCl acidosis	30±0.7	13.0±0.5	57±2.0	145±0.4	3.2±0.1	120±1.2	15±0.6

* Values shown are the means±1 SE; n = 14.

† (Na + K) - (HCO₃⁻ + Cl).

chloride concentration increased significantly from 111 to 117 meq/liter. Unmeasured anion concentration (defined as the sum of sodium and potassium minus the sum of bicarbonate and chloride) decreased significantly from 17 to 16 meq/liter. Phosphate concentration rose significantly from 1.4 to 1.5 mmol/liter and plasma creatinine fell significantly from 0.8 to 0.7 mg/100 ml. No significant change in hematocrit was noted.

Chronic hypocapnic acidosis. When HCl-fed animals were returned to room air, there was a significant decrease in mean steady-state PaCO₂ from 36 to 30 mm Hg. In association with this degree of secondary hypocapnia, mean plasma bicarbonate concentration fell significantly from 16.0 to 13.0 meq/liter (Fig. 2). As a consequence of these changes in PaCO₂ and bicarbonate concentration, mean plasma hydrogen ion concentration rose from 55 to 57 neq/liter ($P < 0.02$).

Plasma sodium concentration remained virtually unchanged. Plasma potassium concentration decreased significantly from 3.3 to 3.2 meq/liter ($P < 0.05$), and plasma chloride concentration increased significantly from 117 to 120 meq/liter. No significant changes in unmeasured anion or phosphate concentrations or in hematocrit were noted. Plasma creatinine increased significantly from 0.7 to 0.8 mg/100 ml.

5 of the 14 HCl-fed animals included in the above analysis were re-exposed to 2.6% CO₂ in an effort to reestablish chronic eucapnic conditions. In this subgroup, mean steady-state PaCO₂ increased significantly from 31±0.7 mm Hg (mean±1 SE) during chronic hypocapnic acidosis to 39±0.7 mm Hg, a value identical to that obtained during the initial period of eucapnic acidosis. In association with the reappearance of eucapnia, mean plasma bicarbonate increased significantly from 13.9±0.6 to 16.3±0.5 meq/liter, a value not significantly different from the 17.1±0.2 meq/liter value observed before the development of hypocapnia. Mean plasma hydrogen ion concentration did not change significantly, stabilizing at 54±1.0 neq/liter during the initial period of eucapnia, 54±1.3 neq/liter during secondary hypocapnia, and 58±1.3 neq/liter during the reestablishment of eucapnia. Mean plasma potassium concentration during the reestablishment of eucapnia was 3.0±0.1 meq/liter, a value not significantly different from the value of 3.2±0.1 meq/liter during secondary hypocapnia but significantly different from the value of 3.3±0.1 meq/liter during the initial eucapnic period ($P < 0.05$). No significant changes in mean plasma sodium concentration (144±0.5, 144±0.5, and 144±0.6 meq/liter) or in mean

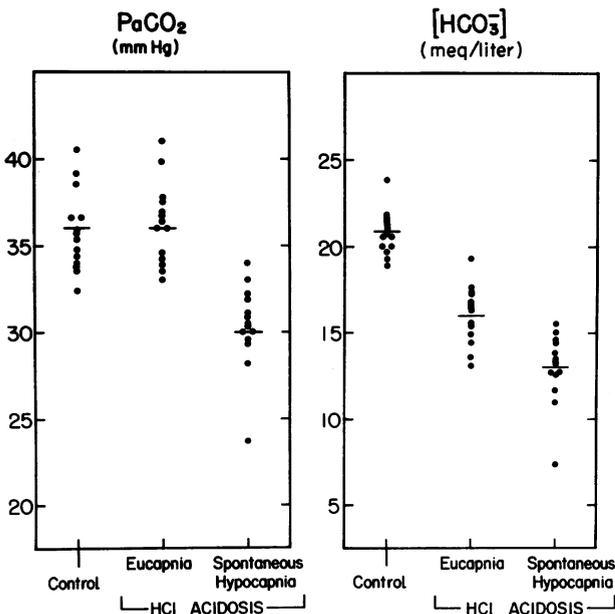


FIGURE 2 Effects of persistent spontaneous hypocapnia on plasma bicarbonate concentration during chronic HCl acidosis. Steady-state values for PaCO₂ are shown on the left and for bicarbonate concentration on the right. Each point represents the average of three observations obtained on consecutive days in a single dog. PaCO₂ was maintained at control levels during eucapnic HCl acidosis but fell significantly during the period of spontaneous hypocapnia (mean Δ PaCO₂ = 6 mm Hg). Note that bicarbonate concentration, which was reduced significantly by HCl feeding during the eucapnic period, fell even further when spontaneous hypocapnia was allowed to occur.

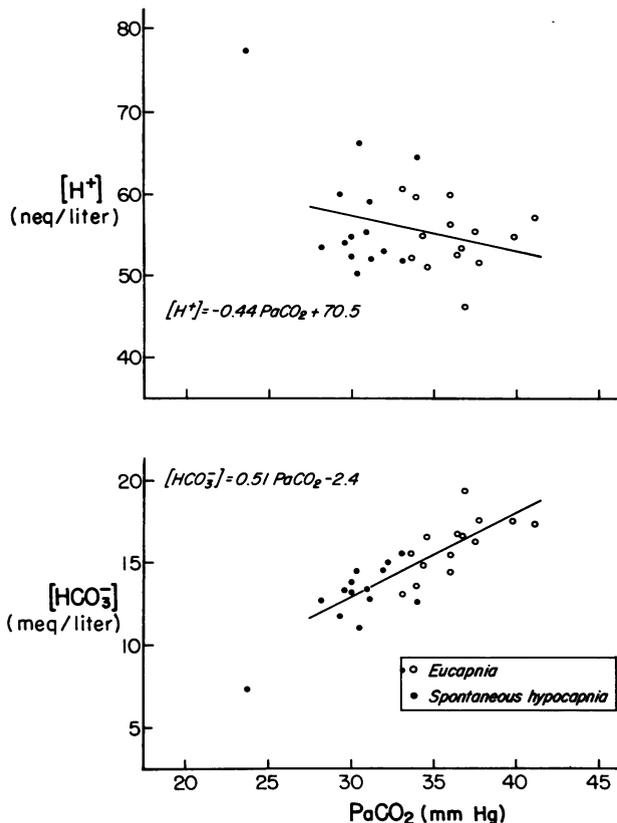


FIGURE 3 Relationship between persistent spontaneous hypocapnia and plasma bicarbonate and hydrogen ion concentrations during chronic HCl acidosis. Each point represents the average of three observations obtained on consecutive days in a single dog; open symbols denote values obtained during eucapnia and closed symbols denote values obtained during spontaneous hypocapnia. The equations for the least squares regression lines are shown in the respective panels; the value for the slope of each line was significantly different from zero ($P < 0.01$).

plasma chloride concentration (116 ± 0.2 , 116 ± 1.0 , and 115 ± 0.4 meq/liter) were noted.

Regression of bicarbonate and hydrogen ion concentrations on PaCO₂. Fig. 3 depicts the steady-

state values for acid-base parameters obtained from all 14 animals during eucapnic and hypocapnic metabolic acidosis. Both plasma bicarbonate concentration (lower panel) and plasma hydrogen ion concentration (upper panel) are shown as a function of steady-state PaCO₂. The regression lines drawn through the points were calculated from the pooled data by the method of least squares. As can be seen, the relationship between bicarbonate concentration and PaCO₂ has a slope value of 0.51 meq/liter per mm Hg and that between hydrogen ion concentration and PaCO₂, a slope value of -0.44 neq/liter per mm Hg; both values are significantly different from zero. The correlation coefficient was 0.83 for bicarbonate vs. PaCO₂ and -0.29 for hydrogen ion vs. PaCO₂.

Protocol II—Acute hypocapnia superimposed on chronic eucapnic acidosis (Table II)

The sudden restoration of a room-air environment led to a small but significant decrease in mean PaCO₂ from 37 to 34 mm Hg. Plasma bicarbonate concentration remained unchanged. As a consequence, mean plasma hydrogen ion concentration fell significantly from 59 to 54 neq/liter.

During subsequent exposure to 14% oxygen, mean PaCO₂ fell from 34 to 29 mm Hg; mean plasma bicarbonate concentration, however, did not differ significantly either from the value obtained during the preceding period of spontaneous hypocapnia or from the value obtained during the period of eucapnia. As a consequence, there was a further significant fall in mean plasma hydrogen ion concentration from 54 to 47 neq/liter.

Plasma sodium, chloride, unmeasured anion, and phosphate concentrations remained virtually constant throughout this protocol. Plasma potassium concentration fell significantly from 3.1 meq/liter during eucapnia to 3.0 meq/liter during spontaneous hypocapnia ($P < 0.02$) and to 2.7 meq/liter during exposure to 14% oxygen.

Plasma lactate and pyruvate concentrations were

TABLE II
Changes in Plasma Composition After Superimposition of Acute Hypocapnia on Chronic Eucapnic HCl Acidosis* (HCl, 7 mmol/kg per day)

HCl acidosis	PaCO ₂	HCO ₃ ⁻	H ⁺	Na	K	Cl	Unmeasured anions†
	mm Hg	meq/liter	neq/liter	meq/liter	meq/liter	meq/liter	meq/liter
Eucapnia	37 ± 0.6	15.2 ± 0.8	59 ± 1.9	143 ± 1.1	3.1 ± 0.1	116 ± 0.9	16 ± 1.0
Acute hypocapnia							
Room air	34 ± 0.6	15.3 ± 0.6	54 ± 1.2	144 ± 0.8	3.0 ± 0.1	115 ± 1.3	16 ± 1.3
14% O ₂	29 ± 1.1	14.8 ± 0.7	47 ± 0.8	145 ± 0.6	2.7 ± 0.1	115 ± 0.4	17 ± 0.6

* Values shown are the means ± 1 SE; $n = 4$.

† $(Na + K) - (HCO_3 + Cl)$.

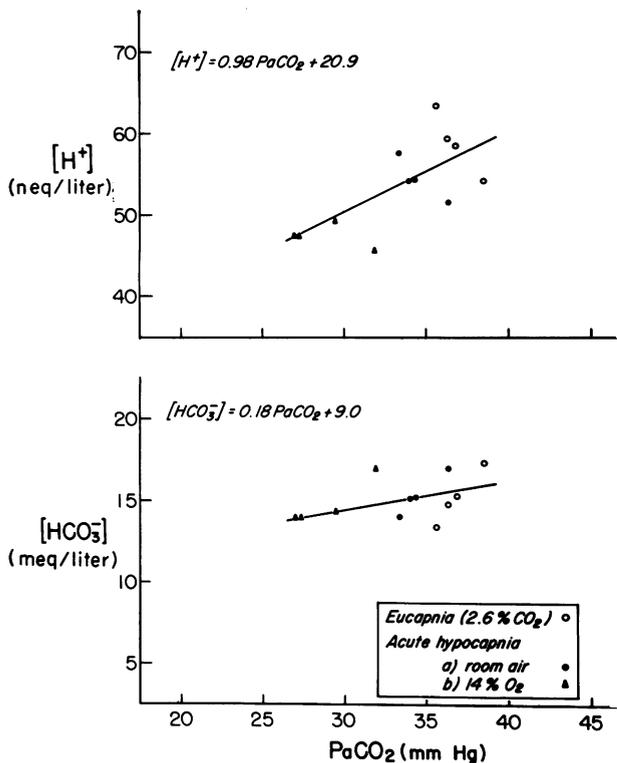


FIGURE 4 Effects of acute hypocapnia on plasma bicarbonate and hydrogen ion concentrations during chronic HCl acidosis. Eucapnia values (open circles) represent the average of three observations obtained on consecutive days. Acute hypocapnia values represent the average of three observations obtained (a) within 2 h after removal of the animals from the CO₂-rich atmosphere (closed circles) and (b) during the subsequent 2 h when ventilation was mildly stimulated by reducing the oxygen concentration of the inspired air to 14% (closed triangles). The equations for least squares regression lines are shown in the respective panels; the value for the slope of each line is significantly different from zero ($P < 0.01$). Note that plasma bicarbonate concentration falls trivially during physiologic, spontaneous hypocapnia of brief duration (room air); as a consequence, the ameliorating influence of the hypocapnia on the severity of the acidemia is virtually unaffected.

measured in three animals. Plasma lactate averaged 0.6 mmol/liter during the period of eucapnic acidosis, remained unchanged during exposure to room air and increased to 1.1 mmol/liter during exposure to 14% oxygen ($P < 0.05$). Plasma pyruvate averaged 0.1 mmol/liter in each period of the study. Hematocrit remained unchanged.

Regression of bicarbonate concentration and hydrogen ion concentration on PaCO₂. Fig. 4 depicts the steady-state relationship between PaCO₂ and both plasma bicarbonate (lower panel) and plasma hydrogen ion concentrations (upper panel) for the four animals with chronic eucapnic acidosis studied during acute hypocapnia. The regression lines drawn through the

points were calculated from the pooled data by the method of least squares. In both cases the slope value was significantly different from zero. As can be seen, the relationship between bicarbonate concentration and PaCO₂ has a slope value of 0.18 meq/liter per mm Hg and that between hydrogen ion concentration and PaCO₂, a slope value of 0.98 neq/liter per mm Hg. The correlation coefficient was 0.50 for bicarbonate vs. PaCO₂ and 0.67 for hydrogen ion vs. PaCO₂.

Protocol III—HCl dose-response curve during eucapnia

Fig. 5 depicts the changes in plasma bicarbonate and chloride concentrations observed under eucapnic conditions in response to the prolonged feeding of HCl at three levels, 7.0, 10.5, and 14.0 mmol/kg per day. Mean, steady-state plasma values for the three groups studied are presented in Table III. As can be seen, mean PaCO₂ remained unchanged from the control in all three groups. By using the method of least squares, the relationship between Δ plasma bicarbonate concentration (y) and the daily acid load (x) was found to be: $y = -0.722x + 0.1$ ($r = -0.712$, $P < 0.01$). The relationship between plasma chloride concentration (y) and the acid load (x) was: $y = 0.662x + 1.1$ ($r = 0.524$, $P < 0.01$). In neither case was the intercept value significantly different from zero.

DISCUSSION

The results of the present study indicate that chronic HCl acidosis reduces the steady-state level of plasma bicarbonate concentration by two independent but additive effects, one related to the magnitude of the daily acid load, and the other to a heretofore unrecog-

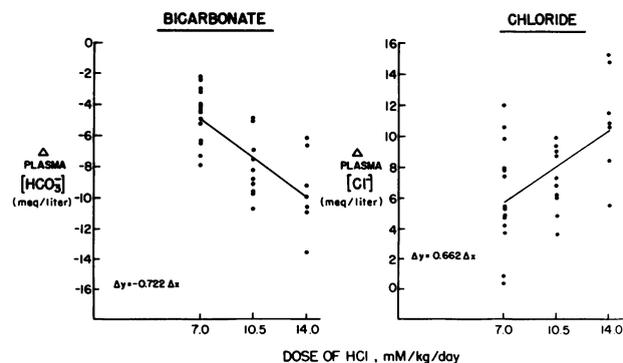


FIGURE 5 Eucapnic HCl dose-response curves. Changes in plasma bicarbonate and plasma chloride concentrations are shown as a function of the daily dose of HCl. Each point represents the mean of three observations obtained on consecutive days during a steady-state period of eucapnic acidosis.

TABLE III
Changes in Plasma Composition during Chronic Eucapnic HCl
Acidosis of Graded Severity*

Period	Number	HCl dose	PaCO ₂	HCO ₃	H ⁺	Cl
		mmol/kg/day	mm Hg	meq/liter	neq/liter	meq/liter
Control	14		36±0.6	20.8±0.3	42±0.3	111±0.9
Eucapnic acidosis		7.0	36±0.6	16.0±0.4‡	55±1.1‡	117±0.5‡
Control	10		37±0.6	20.6±0.4	43±0.5	112±0.5
Eucapnic acidosis		10.5	37±1.0	12.6±0.7‡	71±3.4‡	120±0.7‡
Control	7		36±0.8	21.3±0.4	41±0.7	111±0.5
Eucapnic acidosis		14.0	36±1.6	11.8±0.8‡	75±3.6‡	122±1.1‡

* Values shown are the means±1 SE.

‡ Denotes that the difference between the mean values is significant at a level of $P < 0.01$.

nized reduction in renal bicarbonate reabsorption which is induced by the accompanying secondary hyperventilation. The data also indicate that this renal response not only undermines the beneficial effects of secondary hypocapnia on plasma acidity but, under some circumstances, may actually result in more severe acidemia than would occur in the complete absence of secondary hypocapnia.

The hybrid nature of the bicarbonate decrement observed during chronic HCl acidosis was detected by comparing the steady-state level of acid-base equilibrium achieved under eucapnic conditions with that observed when secondary hypocapnia was subsequently allowed to develop. During the initial eucapnic phase of acid feeding (7 mmol/kg per day), the kidneys maintained a stable level of plasma bicarbonate that was 4.8 meq/liter lower than control. During the later phase of spontaneous hypocapnia (Δ PaCO₂, 6 mm Hg), there was a significant further reduction in plasma bicarbonate (averaging 3 meq/liter), the kidneys now setting the plasma bicarbonate concentration at a level 7.8 meq/liter below control.¹ It is noteworthy that this overall decrement, although arrived at in two distinct steps, is virtually identical to that reached in one step in 20 previously reported animals receiving the same diet and the same dose of HCl but allowed to develop secondary hypocapnia from the outset; neither the decrement in plasma bicarbonate (6.7 meq/liter) nor the decrement in PaCO₂ (5 mm Hg) observed in these animals was significantly different from the respective, overall decrements observed in the present study (1, 10, 11).

¹ A similar response to secondary hyperventilation was observed in animals fed 10.5 mmol/kg per day of HCl; in those animals, plasma bicarbonate fell from 12.9 meq/liter during the period of eucapnia to 9.7 meq/liter during the subsequent period of secondary hypocapnia (Δ PaCO₂, 9 mm Hg).

As can be seen in Fig. 3, the secondary decrement in plasma bicarbonate concentration induced by spontaneous hypocapnia in the present study had a seemingly paradoxical effect on the level of plasma acidity. Hydrogen ion concentration, instead of falling in response to the ventilatory adaptation, actually rose to progressively higher levels as a function of the degree to which PaCO₂ was reduced. The explanation for this dramatic effect is, of course, inherent in the mathematical relationship defined by the Henderson equation and lies in the fact that the percent fall in plasma bicarbonate concentration induced by secondary hypocapnia was greater than the percent fall in PaCO₂ itself.

Quantitative relationship between bicarbonate concentration and PaCO₂

As indicated in Fig. 3, the fall in plasma bicarbonate concentration elicited by prolonged secondary hypocapnia in the present study appeared to be proportional to the decrement in PaCO₂; on the average, each mm Hg reduction in PaCO₂ was responsible for a 0.5 meq/liter fall in the bicarbonate level.² It is noteworthy that precisely the same Δ bicarbonate/ Δ PaCO₂ relationship was observed over a much wider range of PaCO₂ in an earlier study from this laboratory in which dogs receiving the same daily HCl load were exposed to 9% oxygen and thereby forced to

² As pointed out earlier, it is not possible to detect small changes in acid excretion in the face of the large day-to-day fluctuations in urinary acid output characteristic of HCl-fed animals; for this reason, no effort was made to document retention of the 20 meq or so of acid that would be required to account for the observed decrement in plasma bicarbonate. It should be recalled, however, that acid retention can be demonstrated in both HCl-fed and normal animals when greater decrements in PaCO₂ are produced and, hence, when larger reductions in plasma bicarbonate occur (1, 12).

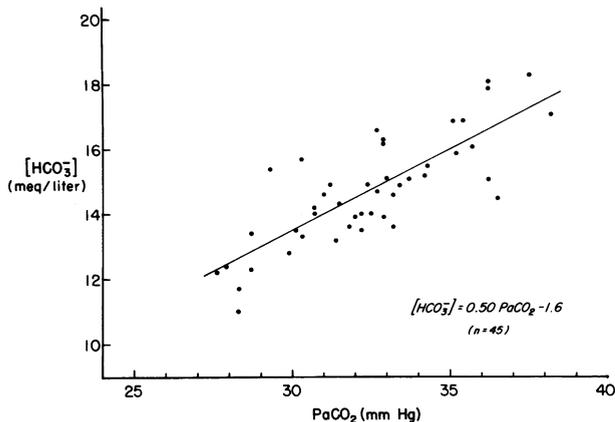


FIGURE 6 Relationship between plasma bicarbonate concentration and PaCO_2 during chronic HCl acidosis. Data are taken from all 45 dogs fed 7 mmol/kg of HCl/day in this laboratory over the past several years. Each point represents the average of three steady-state observations obtained on consecutive days of acid feeding. The slope value of the least squares regression line drawn through the points is 0.5 meq/liter per mm Hg ($P < 0.01$).

hyperventilate to a much greater degree than had been provoked by acidosis alone (1); the further reduction of 17 mm Hg in PaCO_2 led to an 8.6 meq/liter fall in plasma bicarbonate concentration beyond the reduced

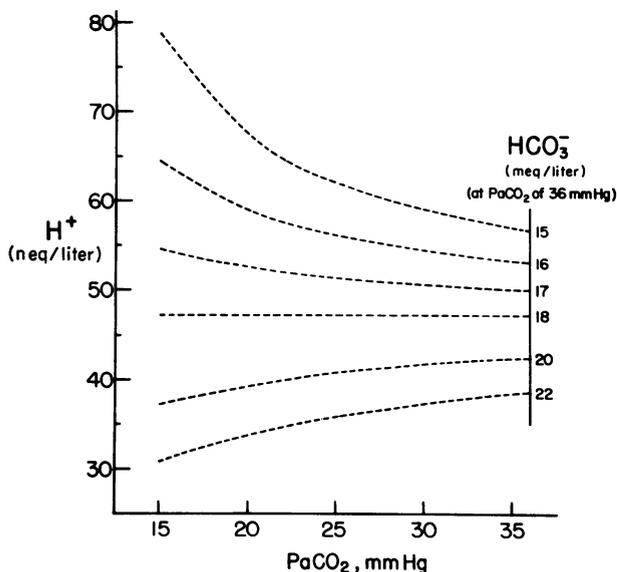


FIGURE 7 Nomogram for predicting the level of hydrogen ion concentration during graded degrees of chronic hypocapnia in normal and HCl-fed dogs. A value of 36 mm Hg was taken as the eucapnic (i.e. normal) level of PaCO_2 and a value of 0.5 meq/liter per mm Hg was used to calculate the bicarbonate decrement induced by prolonged hypocapnia. Note that hypocapnia has the net effect of reducing hydrogen ion concentration only if the eucapnic level of plasma bicarbonate is greater than 18 meq/liter.

level which had already occurred as a result of the prolonged acid feeding. Thus, at a dose level of 7 mmol/kg per day of HCl, prolonged hyperventilation of whatever degree appears to be characterized by a uniform Δ bicarbonate/ Δ PaCO_2 relationship.

The same interpretation can be drawn from observations on the steady-state relationship between PaCO_2 and plasma bicarbonate concentration in a large group of acid-fed dogs (7 mmol/kg per day) in which spontaneous variations in the degree of hyperventilation were sufficient to produce a wide range of values for PaCO_2 . Fig. 6, which depicts data from all 45 animals studied by us in this way, shows that the level to which plasma bicarbonate falls is highly dependent upon the magnitude of the secondary hypocapnia. Once again, the slope of the least squares regression between bicarbonate concentration and PaCO_2 is 0.5 meq/liter per mm Hg.

Presently available data also suggest that this Δ bicarbonate/ Δ PaCO_2 relationship is not influenced importantly by the dose level of HCl. This inference is based on the fact that animals receiving no HCl, when forced to hyperventilate (9% oxygen), exhibit a Δ bicarbonate/ Δ PaCO_2 relationship that is identical to that observed in animals receiving 7 mmol/kg of HCl per day (1, 12). It thus seems unlikely that intermediate dose levels of HCl would significantly alter the animals' response to sustained hypocapnia.

Nomogram for predicting hydrogen ion concentration during graded degrees of chronic hypocapnia in normal and HCl-fed dogs

On the basis of the findings outlined above, a general descriptive framework has been developed which takes into account the complex manner by which sustained reductions in PaCO_2 affect hydrogen ion concentration in normal animals and in animals with HCl-induced metabolic acidosis of variable severity. This framework, presented as the nomogram shown in Fig. 7, allows one to predict the overall impact of graded degrees of sustained hypocapnia on the level of plasma acidity. A value of 36 mm Hg was taken as the eucapnic (i.e. normal) level of PaCO_2 , and a value of 0.5 meq/liter per mm Hg (*vide supra*) was used to calculate the bicarbonate decrement induced by chronic hypocapnia. This formulation indicates that the net effect of prolonged hypocapnia on plasma hydrogen ion concentration is solely a function of the eucapnic level of plasma bicarbonate concentration. In normal animals as well as in animals with metabolic acidosis of mild to moderate severity, in which the eucapnic level of plasma bicarbonate concentration is reduced to levels no lower than 18 meq/liter, sustained hyperventilation causes plasma

hydrogen ion concentration to fall. By contrast, in metabolic acidosis of greater severity, in which the eucapnic level of bicarbonate is reduced below 18 meq/liter, sustained hyperventilation produces progressively higher levels of plasma hydrogen ion concentration.

Physiologic effects of acute vs. chronic secondary hypocapnia

It is clear from the findings in the present study that a sharp distinction must be drawn between the "protective" effects of acute vs. those of chronic secondary hyperventilation. The well-known homeostatic role of the respiratory response in ameliorating the severity of acidemia during acute metabolic acidosis is illustrated in Fig. 4. This figure demonstrates that the effect of acute hypocapnia on plasma bicarbonate is so small that it does little to diminish the protective effect that secondary hyperventilation exerts on plasma acidity.³

If acidosis and secondary hyperventilation persist, however, the kidney begins to dismantle the homeostatic barricade constructed by the respiratory system because of its indiscriminant response to the hypocapnia. As a result of the large fall in plasma bicarbonate concentration, the once unmitigated benefits derived from respiratory adaptation are seriously undermined. In light of this maladaptive behavior of the kidney, it is evident that the traditional view concerning the utility of secondary hyperventilation in clinical disorders of acid-base equilibrium must be reappraised.

³ An acute reduction in carbon dioxide tension would, of course, be expected to titrate nonbicarbonate buffers and thus to produce some decrement in plasma bicarbonate concentration. Indeed, as shown in Fig. 4, plasma bicarbonate does fall in response to acute hyperventilation but only by some 0.18 meq/liter for each mm Hg change in PaCO₂. Although any secondary reduction in the level of bicarbonate is counterproductive from the standpoint of protecting acidity, the changes in bicarbonate induced by acute secondary hypocapnia are too small to have an important physiologic effect on acid-base equilibrium.

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