The Influence of Graded Degrees of Chronic Hypercapnia on the Acute Carbon Dioxide Titration Curve

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ABSTRACT Studies were carried out to determine the influence of the chronic level of arterial carbon dioxide tension upon the buffering response to acute changes in arterial carbon dioxide tension. After chronic adaptation to six levels of arterial CO_2 tension, ranging between 35 and 110 mm Hg, unanesthetized dogs underwent acute whole body CO_2 titrations. In each instance a linear relationship was observed between the plasma hydrogen ion concentration and the arterial carbon dioxide tension. Because of this linear relationship, it has been convenient to compare the acute buffering responses among dogs in terms of the slope, $dH^+/dPaco_2$. With increasing chronic hypercapnia there was a decrease in this slope, i.e. an improvement in buffer capacity, which is expressed by the equation $dH^+/dPaco_2 = -0.005 (Paco_2)_{chronic} + 0.95$. In effect, the ability to defend pH during acute titration virtually doubled as chronic $Paco_2$ increased from 35 to 110 mm Hg.

The change in slope, $dH^+/dPaco_2$, was the consequence of the following two factors: the rise in plasma bicarbonate concentration which occurs with chronic hypercapnia of increasing severity, and the greater change in bicarbonate concentration which occurred during the acute CO_2 titration in the animals with more severe chronic hypercapnia. These findings demonstrate the importance of the acid-base status before acute titration in determining the character of the carbon dioxide titration curve. They also suggest that a quantitative definition of the interplay between acute and chronic hypercapnia in man should assist in the rational analysis of acid-base disorders in chronic pulmonary insufficiency.

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INTRODUCTION

Recent studies of the "whole body" carbon dioxide titration curve have provided a physiologic description of the buffer characteristics of normal dog and man (1–5). They have left unanswered, however, the question of how, and to what extent, preexisting abnormalities in the acid-base status of the organism might influence the ability to defend pH during acute changes in arterial carbon dioxide tension. In the present study, we make a first approach to this problem using chronic hypercapnia as an instrument for creating change in body composition. Chronic hypercapnia was chosen as a point of departure not only because it is a potent tool for altering the acid-base status of the organism but also because it allows simulation of the interplay between acute and chronic respiratory acidosis that is frequently encountered in patients with chronic pulmonary insufficiency.

The experimental protocol consisted of, first, the chronic adaptation of normal dogs to one of six levels of arterial CO_2 tension and, second, the acute titration of these dogs over a range of carbon dioxide tensions between 35 and 110 mm Hg. The results indicate that with chronic hypercapnia of increasing severity there was a progressive improvement in the acute defense of pH. This improvement was a function of the initial plasma bicarbonate concentration and of the change in plasma bicarbonate concentration that occurred during the acute titration.

METHODS

Dogs to be studied during chronic hypercapnia were placed in an environmental chamber (6) that allows the percentage of carbon dioxide in the atmosphere to be controlled automatically within ±5%. The chamber was maintained at environmental carbon dioxide tensions designed to produce arterial $Paco_2$ levels of approximately 45, 55, 70, 90, and 110 mm Hg. The percentage of the oxygen in the environment

was maintained between 20 and 21% in all studies. The animals were kept at a given level of arterial carbon dioxide tension for 6 days, a period which has been demonstrated to be adequate for the development of a new steady state of acid-base equilibrium (7). All dogs were fed commercial dog chow with normal electrolyte content and allowed food and water ad lib. before and during the period of chronic adaptation. Any dog which failed to eat spontaneously was tube fed twice daily and dogs which vomited were excluded from the study. On the day of the acute experiment, food and water were withheld. Arterial blood samples were drawn percutaneously on the 5th and 6th days of exposure to hypercapnia to insure that the acid-base composition of plasma was in the range characteristic of the chronic steady state (7). In a group of dogs studied without prior exposure to hypercapnia (chronic Pa_{CO_2} approximately 35 mm Hg), arterial blood samples were drawn on the 2 days preceding the acute study.

On the day of the acute study, arterial samples were obtained from all dogs via a Teflon catheter placed in the femoral artery. Dogs were considered acceptable for the acute titration study only if (*a*) the first arterial Pa_{CO_2} on the day of the acute study and the values obtained on the previous days were within a range of 6 mm Hg, and (*b*) the first plasma bicarbonate concentration on the day of study did not differ by more than 3 mEq/liter from the value obtained on the previous day. 4 of 31 dogs failed to satisfy these criteria and were therefore excluded.

Acute titrations with carbon dioxide. The acute titrations with carbon dioxide were carried out over a range of carbon dioxide tensions between 35 and 110 mm Hg. The sequence and direction of the titrations were varied, depending upon the initial chronic Pa_{CO_2} level (Table I). Those dogs with initial arterial carbon dioxide tensions of 35 and of 45 mm Hg were exposed to stepwise increments in Pa_{CO_2} terminating with a Pa_{CO_2} level of approximately 110 mm Hg. Conversely, those dogs with initial chronic values of 110 mm Hg were exposed to stepwise decrements in arterial carbon dioxide tension, terminating in exposure to room air. The dogs with intermediate chronic arterial carbon dioxide tensions were first titrated to one extreme and then underwent sequential titration in the opposite direction. The titrations were designed to limit the change in arterial carbon dioxide tension between any two periods to no more than 30 mm Hg.

All the acute titrations were carried out in the following manner. Three control blood samples were drawn at intervals of 20 min. The carbon dioxide tension in the environmental chamber was then altered over a period of 15 min and an additional 30 min was allowed to permit the dogs to reach a new acute steady state.[1] Three further blood samples were then drawn at 20-min intervals. This entire procedure was repeated for each subsequent period. A period was considered to be representative of an acute steady state only if (*a*) the range of plasma bicarbonate concentrations in the three samples did not exceed 3 mEq/liter, and (*b*) the range of Pa_{CO_2} values did not exceed 6 mm Hg at Pa_{CO_2} levels less than 100 mm Hg, and did not exceed 10 mm Hg at Pa_{CO_2} levels greater than 100 mm Hg. Acceptance of the slightly less rigorous criteria for Pa_{CO_2} at high carbon dioxide levels was necessary because of the greater variability encountered with severe hypercapnia. In 22 of 27 studies all of the periods satisfied the above criteria. In each of the remaining five studies, a single period that did not meet the criteria of the acute steady state was excluded.

[1] Cohen, J. J., N. C. Brackett, Jr., and W. B. Schwartz. Unpublished data.

TABLE I

Sequence and Magnitude of the Acute Changes in Pa_{CO_2} during Titration of Dogs Chronically Exposed to Each of Six Levels of Arterial CO_2 Tension

Group	Approximate chronic Pa_{CO_2} level	Acute carbon dioxide titration, approximate Pa_{CO_2} during each period			
		Period 1	Period 2	Period 3	Period 4
	mm Hg	*mm Hg*			
1	35	60	85	110	—
2	45	60	85	110	—
3	55	35	55	80	110
4	70	100	70	50	35
5	90	110	90	65	35
6	110	90	65	35	—

Studies with ureteral obstruction. Preliminary studies were carried out in dogs chronically adapted to a Pa_{CO_2} of 110 mm Hg to determine whether significant renal alkali excretion occurred during acute reductions of Pa_{CO_2} in dogs with a markedly elevated plasma bicarbonate concentration. These preliminary studies demonstrated an average net alkali excretion of 15 mEq during the acute CO_2 titration; net alkali excretion during an identical time interval 2 days earlier (during which the CO_2 tension was maintained at a constant hypercapnic level) was 6 mEq.

The following studies were undertaken to evaluate the influence of this renal alkali loss upon the acute CO_2 response curve. Dogs in which Jacobson cuffs (Davol Inc., Providence, R. I.) had been placed around both ureters were chronically adapted to a Pa_{CO_2} of 110 mm Hg. Immediately before acute titration, bilateral ureteral obstruction was produced by inflating the cuffs percutaneously. A group of nonobstructed dogs was studied simultaneously. In dogs with ureteral obstruction all of the urine proximal to the obstructing cuffs was aspirated postmortem. In the nonobstructed dogs, all urine formed during the acute titration was collected via a bladder catheter.

Analytical methods. The pH of blood and urine was measured anaerobically at 39°C. (Radiometer Co., PHM 26, with capillary microelectrode, Copenhagen, Denmark). The CO_2 content of plasma and urine was determined using the Technicon Auto Analyzer (Technicon Co., Inc., Tarrytown, N. Y.) by a modification of the technique of Gambino and Schreiber (8). The automated analysis of CO_2 content was monitored daily by duplicate determination of a randomly chosen specimen using the manometric technique of Peters and Van Slyke. The automated system was considered to be functioning satisfactorily if it differed from the manometric method by no greater than 1.0 mEq/liter for CO_2 values less than 40 mEq/liter and no greater than 1.5 mEq/liter for values greater than 40 mEq/liter. Beta-hydroxybutyrate and acetoacetate levels were measured by a modification of the method of Williamson and Mellanby (9). The remaining analytical methods (sodium, potassium, chloride, ammonia, phosphate, creatinine, and lactate) have been described previously (10, 11). The pH, pK′, and solubility coefficient of CO_2 were corrected to the temperature of the dogs (which was measured by rectal thermometer at the time each blood sample was drawn) employing the data

TABLE II

*Plasma Pa_{CO_2}, Hydrogen Ion, and HCO_3 Values in Dogs Adapted to Various Levels of Chronic Arterial Carbon Dioxide Tension**

Group	No. of dogs	Pa_{CO_2}	H^+	HCO_3
		mm Hg	*nmoles/liter*	*mEq/liter*
1	6	35–40	41–45	20–21
2	4	43–46	43–46	23–26
3	4	56–58	49–51	27–28
4	3	66–67	53–54	29–30
5	4	87–91	56–58	36–38
6	6	108–113	60–71	38–45

* The ranges are based on the mean chronic steady-state values for each dog.

of Rosenthal (12) and Severinghaus, Stupfel, and Bradley (13, 14).

RESULTS

Acid-base status before acute titrations with carbon dioxide. The ranges of arterial $Paco_2$, hydrogen ion, and plasma bicarbonate concentrations obtained before the acute titrations in animals studied at the six levels of arterial carbon dioxide tension are presented in Table II. A regression line relating hydrogen ion concentration and $Paco_2$ calculated from these data yielded the equation, $H^+ = 0.27Paco_2 + 32.9$; this equation is closely similar to that previously reported in dogs adapted to chronic hypercapnia ($H^+ = 0.32\,Paco_2 + 26.9$ [7]).

Evaluation of the steady-state periods during acute titration with carbon dioxide. To determine whether there was a unidirectional trend in either $Paco_2$ or bicarbonate concentration within the criteria established for an acute steady state, the differences between the first and third blood values were analyzed for each period. The periods after an acute increase in $Paco_2$ ("upgoing") were considered separately from those after an acute reduction in $Paco_2$ ("downgoing"). In the case of the $Paco_2$, the mean difference was not significantly[2] different from zero, regardless of the direction of the change. In the case of the plasma bicarbonate concentration, the mean difference was not significantly different from zero in the "downgoing" periods, but in the "upgoing" periods, the mean difference was +0.5 mEq/liter. This slight difference was ignored, and a steady state was assumed to be present.

Character of the acute carbon dioxide titration curves. Fig. 1 presents two representative studies; in panel A is shown the carbon dioxide titration curve of a dog in which the chronic $Paco_2$ level was approximately 40 mm Hg, and in panel B (and Table III) is shown the titration curve of a dog in which the chronic $Paco_2$ level was approximately 110 mm Hg. Note that in both studies the relationship between the hydrogen ion concentration and the $Paco_2$ appears to be linear, but that there was a smaller change in hydrogen ion concentration for any given acute change in $Paco_2$ in the dog with chronic hypercapnia. It can also be seen that the animal with chronic hypercapnia underwent the larger change in plasma bicarbonate concentration during the acute titration.

Evidence for a linear relationship between hydrogen ion concentration and $Paco_2$. For each acute titration, a linear regression relating the hydrogen ion concentration to the level of arterial carbon dioxide tension was calculated using the method of least squares. The possibility that this linear function best described the relationship between hydrogen ion concentration and $Paco_2$ was evaluated for each titration by the insertion of the quadratic term (15). In 24 of 27 studies, the insertion of this term did not significantly improve the goodness of fit when compared to the linear function. In the three cases in which there was statistically significant improvement, the introduction of the quadratic term did not appreciably alter the predictive value of the linear function; the difference in predicted change in hydrogen ion concentration in the worst case was, for a 70 mm Hg change in $Paco_2$, less than 2 nmoles/liter.

Influence of the chronic level of $Paco_2$ on the relationship between hydrogen ion concentration and $Paco_2$.

TABLE III

Acute CO_2 Titration of a Dog Chronically Adapted to a $Paco_2$ of Approximately 110 mm Hg (Dog No. 581)

Time	H^+	pH	Pa_{CO_2}	HCO_3
min	*nmoles/liter*		*mm Hg*	*mEq/liter*
	Ambient CO_2, 14%			
0	61	7.22	110	43.2
20	61	7.22	111	43.6
40	58	7.23	107	43.2
41–55	Ambient CO_2 changed to 12%			
85	54	7.27	94	41.8
105	54	7.27	94	41.7
125	54	7.27	94	41.7
126–140	Ambient CO_2 changed to 7%			
170	43	7.37	69	37.9
190	43	7.37	70	38.5
210	44	7.36	66	35.9
211–225	Chamber opened to room air			
255	34	7.47	44	31.3
275	32	7.49	44	33.2
295	31	7.50	43	33.3

[2] Throughout this paper, the term "significant" will be used to describe a difference which has a P value of less than 0.01.

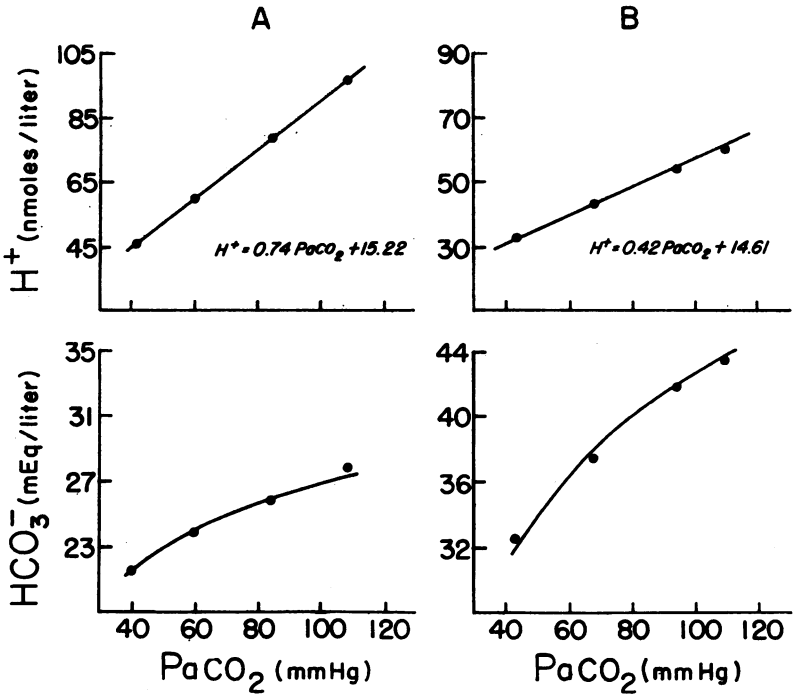

FIGURE 1 Comparison of changes in hydrogen ion and bicarbonate concentrations during acute CO_2 titration in a normal dog and in a dog with severe chronic hypercapnia. Panel A represents the titration in a dog (No. 137) in which the chronic $Paco_2$ was approximately 40 mm Hg. Panel B represents the titration in a dog (No. 581) in which the chronic $Paco_2$ was approximately 110 mm Hg. The curves drawn through the observed bicarbonate values were plotted using the bicarbonate values predicted from the corresponding H^+ — $Paco_2$ regression equations.

Fig. 2 presents the slope of the acute H^+ — $Paco_2$ regression line, $dH^+/dPaco_2$, for each dog plotted against the chronic arterial carbon dioxide tension. It is evident by inspection that the acute slope decreased progressively as the chronic level of arterial carbon dioxide tension increased. The regression line calculated from these data, $Y = -0.005X + 0.952$, has a slope significantly different from zero, and the insertion of the quadratic term did not significantly improve the goodness of fit.

Influence of the chronic level of $Paco_2$ on the acute change in plasma bicarbonate concentration. Fig. 3 depicts the relationship between the acute change in plasma bicarbonate concentration and the chronic arterial carbon dioxide tension. The delta bicarbonate concentration in each case was calculated for an arbitrarily chosen change in $Paco_2$ of 60 mm Hg, i.e., for an acute titration between 40 and 100 mm Hg. The values for these specific $Paco_2$ levels were determined from the individual H^+ — $Paco_2$ regression lines. Note that up to a chronic $Paco_2$ level of 60 mm Hg the change in plasma bicarbonate concentration is virtually constant (approximately 5 mEq/liter). Above this level, however, delta bicarbonate concentration becomes progressively larger with the result that at a chronic arterial CO_2 tension of 110 mm Hg an acute change in $Paco_2$ of 60 mm Hg results in a change of approximately 12 mEq/liter in plasma bicarbonate concentration.

Acute carbon dioxide titrations after ureteral obstruction. Studies of renal bicarbonate excretion during acute reduction in $Paco_2$ were carried out in seven dogs chronically adapted to a $Paco_2$ of approximately 110 mm Hg (four dogs with ureteral obstruction and three nonobstructed controls). In the course of acute titration (total reduction in $Paco_2$ of approximately 60 mm Hg) the nonobstructed dogs demonstrated net alkali excretions of 7, 8, and 17 mEq, (mean, 11 mEq) and the obstructed dogs, excretions of less than 1.5 mEq. The mean reduction in plasma bicarbonate concentration was 10 and 7.5 mEq/liter, respectively, in the two groups of dogs. The slopes of the H^+ — $Paco_2$ regression lines in the obstructed dogs, 0.459, 0.456, 0.468, and 0.468, were not significantly different from the slopes of the nonobstructed dogs, 0.454, 0.412, and 0.460. In addition, there was no significant difference between the acute slopes of the cuffed dogs and the six dogs shown

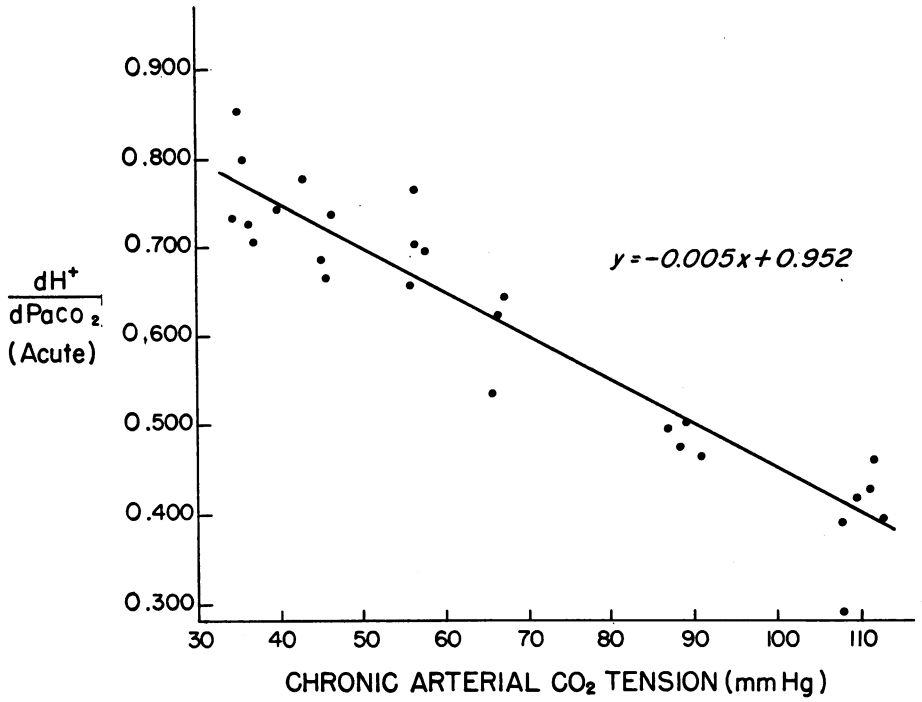

FIGURE 2 Relationship between the chronic arterial CO_2 tension and the slope of the acute H^+ — $Paco_2$ regression line, $dH^+/dPaco_2$. The line drawn through the data was calculated by the method of least squares.

in Fig. 2 which were also chronically adapted to a $Paco_2$ of 110 mm Hg.

Miscellaneous. In the acute carbon dioxide titrations in normal dogs, the increase in plasma bicarbonate concentration was accompanied by a significant increase (4 mEq/liter) in plasma sodium concentration. There was no significant change in plasma chloride or potassium concentration. In the dogs chronically adapted to

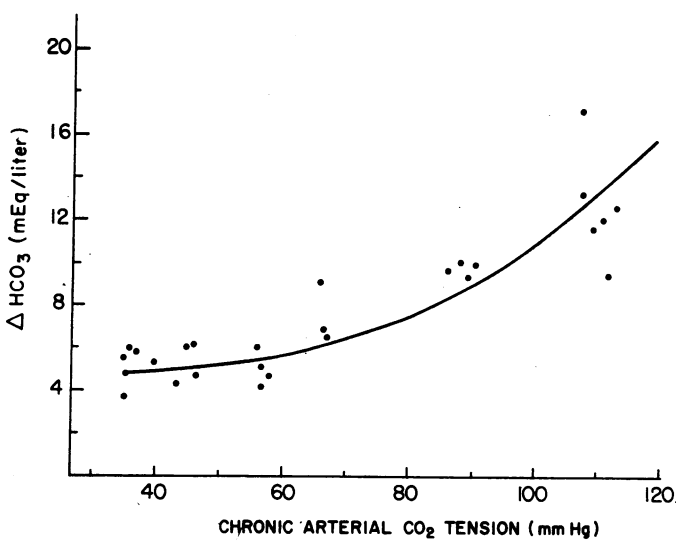

FIGURE 3 Changes in plasma bicarbonate concentration induced by an arbitrarily chosen change in $Paco_2$ (60 mm Hg) in animals chronically adapted to carbon dioxide tensions ranging between 35 and 110 mm Hg. The curve through the individual data points was drawn by inspection.

110 mm Hg, the acute reduction in arterial CO_2 tension and plasma bicarbonate concentration was not associated with any significant change in plasma electrolytes. The changes in plasma electrolyte composition in the dogs titrated from intermediate $Paco_2$ levels demonstrated a transition between the observations at the two extremes.

During acute hypercapnia in the normal dogs, the unmeasured anions ($Na - [HCO_3 + Cl]$) decreased from 11 to 7 mEq/liter, whereas during the acute reduction in $Paco_2$ in dogs chronically adapted to a $Paco_2$ of 110 mm Hg there was an increase in unmeasured anions from 13 to 18 mEq/liter. There was a mean *increase* in the blood lactate concentration of 2.5 mEq/liter after acute reduction in $Paco_2$ in the dogs with severe chronic hypercapnia, a value almost identical to the *decrease* in blood lactate concentration (1.8 mEq/liter) previously reported in normal dogs subjected to acute hypercapnia (1). Beta-hydroxybutyrate and acetoacetate levels were also determined before and after acute carbon dioxide titration in six dogs chronically adapted to a $Paco_2$ of 110 mm Hg; no significant changes were observed. No significant difference in the hematocrit was noted among the six groups of dogs before acute carbon dioxide titration. There was no significant change in hematocrit during the acute titration except in the normal dogs in which the hematocrit increased from 39 to 45%. The blood pressure was monitored in 12 dogs during the acute carbon dioxide titrations; regardless of the chronic $Paco_2$ level or the direction of the acute change in $Paco_2$, no significant changes in blood pressure were noted.

DISCUSSION

The present study demonstrates that the chronic level of carbon dioxide tension in the body fluids has a major influence upon the response to superimposed acute changes in $Paco_2$. As illustrated in Fig. 2, the ability of the organism to protect extracellular pH against acute changes in $Paco_2$ increased progressively as a function of the increasing degree of chronic hypercapnia. This behavior appears to be accounted for by two factors: the level of bicarbonate concentration in the plasma before acute alterations in $Paco_2$, and the change in bicarbonate concentration which occurred during the acute titration.

On the basis of the Henderson-Hasselbalch equation, it is evident that the rise in plasma bicarbonate concentration that accompanies increasing degrees of chronic hypercapnia (Table II) in itself acted as an important factor in minimizing the change in pH in response to acute changes in $Paco_2$. This effect is illustrated by the dashed line in Fig. 4, labeled "theoretical," which depicts the situation which would exist if the plasma bicarbonate

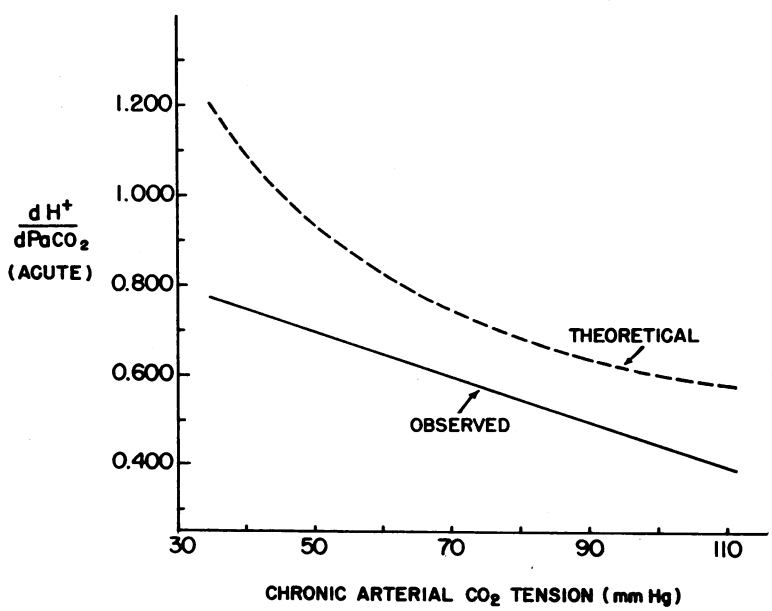

FIGURE 4 Theoretical and observed relationship between the chronic arterial CO_2 tension and the slope of the acute $H^+ - Paco_2$ regression line, $dH^+/dPaco_2$. The dashed line, labeled "theoretical," was calculated for the hypothetical situation in which plasma bicarbonate at any given level of chronic hypercapnia remains constant during acute titration with carbon dioxide. The observed line was taken from experimental data shown in Fig. 2.

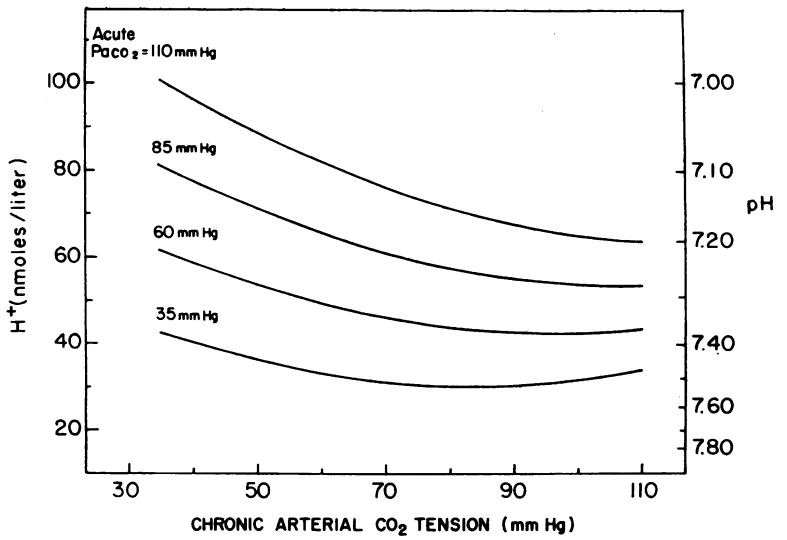

FIGURE 5 Predicted effect of acute changes in $Paco_2$ on the plasma hydrogen ion concentration in dogs with chronic $Paco_2$ levels ranging between 35 and 110 mm Hg. The horizontal lines represent the spectrum of hydrogen ion concentrations which would occur after an acute titration to the indicated $Paco_2$ levels.

concentration were held constant at its chronic value during the acute titration. Note that in the presence of a bicarbonate concentration fixed at the level appropriate to a given degree of chronic hypercapnia the slope of the $H^+ - Paco_2$ relationship, $dH^+/dPaco_2$, decreases sharply, the majority of the change taking place between chronic $Paco_2$ levels of 35 and 70 mm Hg.[3]

The influence of the second factor, the change in plasma bicarbonate concentration which occurred during the acute carbon dioxide titration, can now be readily appreciated by a comparison of the dashed theoretical line with the solid line which depicts the observed defense of pH. The wide divergence of the two lines in the range of normal and slightly elevated arterial carbon dioxide tensions indicates that the in vivo buffering response is markedly improved by the acute change in plasma bicarbonate concentration. On the other hand, the close proximity of the lines above a chronic $Paco_2$ level of 70 mm Hg gives evidence that in severe chronic hypercapnia the acute change in plasma bicarbonate concentration plays a relatively small role in augmenting the buffer capacity of the organism.

These findings, when viewed in light of the absolute change in plasma bicarbonate concentration, pose a seeming paradox. In the severely hypercapnic state, the small improvement in the in vivo slope as compared to the "theoretical" slope is achieved at the price of a greater absolute change in plasma bicarbonate concentration than is the large improvement in the mildly or moderately hypercapnic animals. Of course, upon examination of the Henderson-Hasselbalch equation the physicochemical explanation for this finding becomes clear. One must still ask, however, *why* the change in plasma bicarbonate concentration in response to a standard acute change in $Paco_2$ is approximately 7 mEq/liter larger in animals with severe chronic hypercapnia than in the normal dogs. The answer appears to lie in part with the kidney. In the dogs with severe hypercapnia, 2–3 mEq/liter of the acute reduction in plasma bicarbonate concentration is accounted for by renal alkali excretion, whereas none of the acute increase in plasma bicarbonate concentration in the normal or mildly hypercapnic dogs can be accounted for by renal acid excretion (1, 7). The remaining discrepancy is not as easily accounted for, however, because the combined contribution of extracellular buffers and lactic acid in both the normal and high CO_2 groups is about equal in magnitude, though opposite in direction. In severe hypercapnia, tissue buffering or production of some organic acid other than lactic must be invoked as the most

[3] The curvilinear configuration of the theoretical line depicted in Fig. 4 cannot be attributed solely to the fact that the bulk of the increment in plasma bicarbonate concentration occurs with slight to moderate degrees of chronic hypercapnia. Even if the plasma bicarbonate concentration were to increase in a linear manner in chronic hypercapnia of increasing severity, the "theoretical" relationship between the chronic $Paco_2$ level and the acute slope would still have the same general configuration, although it would be slightly less concave.

likely sources for the unexplained increment in buffering capacity.

The discussion thus far has concerned itself with the pattern of change in hydrogen ion concentration during titrations with carbon dioxide rather than with the absolute levels of plasma hydrogen ion concentration. Fig. 5 depicts in an idealized fashion the spectrum of anticipated hydrogen ion concentrations during acute titration of dogs chronically adapted to a wide range of arterial carbon dioxide tensions. The curves shown in the figure were constructed from values calculated at each chronic $Paco_2$ level using the slope of the appropriate $H^+ - Paco_2$ regression lines. As would be expected from the relationship between the acute slope, $dH^+/dPaco_2$, and the chronic arterial CO_2 tension (Fig. 2), the range of predicted hydrogen ion concentrations becomes progressively narrower as the degree of chronic hypercapnia becomes more severe. Thus, the change in hydrogen ion concentration during titration of the normal dog is approximately 60 nmoles/liter whereas in the most hypercapnic dog it is only 30 nmoles/liter. Furthermore, from this representation of the data it can be seen that although severe acidosis is a feature of acute hypercapnia in the normal dog (pH 7.0) severe alkalosis, at least under our experimental conditions, is not a feature of acute reductions of $Paco_2$ in dogs with moderate or even severe chronic hypercapnia. As can be seen in Fig. 5, the anticipated pH after acute reduction in $Paco_2$ to 35 mm Hg is only slightly greater than 7.5 regardless of the level of chronic hypercapnia. Indeed, the highest pH in any dog after acute reduction of the $Paco_2$ was 7.55.

Whether the interplay of acute and chronic changes in arterial carbon dioxide tension in humans with pulmonary insufficiency is the same as in the normal dog obviously cannot be deduced from the present study. It is evident that the behavior of the patient with long-standing pulmonary failure might be influenced not only by species differences but also by many complicating factors that did not exist in our experimental setting. The presence of hypoxemia, potassium depletion, and other abnormalities might well lead to an $H^+ - Paco_2$ relationship notably different from that observed here. It is of interest, however, to note that in the one published study designed to assess the influence of chronic pulmonary insufficiency upon acute changes in arterial carbon dioxide tension the gross behavior appeared to be similar to that which we have found in the dog, i.e., pH was seemingly defended more effectively than in normal volunteers (16). Unfortunately, a detailed analysis of these data is not possible, because only mean values are presented, because data demonstrating a chronic steady state are not included, and because no effort was made to relate the level of chronic hypercapnia to the character of the acute carbon dioxide titration curve. It seems reasonable to predict, however, that a rigorous quantitative definition of the interplay between acute and chronic respiratory acidosis should provide a more rational basis for the analysis of mixed acid-base disorders than is currently available (17–20).

It will be recalled that the present study was undertaken as a step towards determining how and to what extent preexisting abnormalities in the acid-base status of the organism might influence the ability to defend extracellular pH during acute changes in arterial carbon dioxide tension. The results have provided a clear answer to this question for the specific case of chronic hypercapnia. They have, in addition, suggested a range of factors which can well be expected to modify the carbon dioxide titration curve in a variety of other acid-base disorders.

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