

Secondary Response to Chronic Respiratory Acidosis in Humans: A Prospective Study



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Introduction: The magnitude of the secondary response to chronic respiratory acidosis, that is, change in plasma bicarbonate concentration ($[\text{HCO}_3^-]$) per mm Hg change in arterial carbon dioxide tension (PaCO_2), remains uncertain. Retrospective observations yielded $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slopes of 0.35 to 0.51 mEq/l per mm Hg, but all studies have methodologic flaws.

Methods: We studied prospectively 28 stable outpatients with steady-state chronic hypercapnia. Patients did not have other disorders and were not taking medications that could affect acid–base status. We obtained 2 measurements of arterial blood gases and plasma chemistries within a 10-day period.

Results: Steady-state PaCO_2 ranged from 44.2 to 68.8 mm Hg. For the entire cohort, mean (\pm SD) steady-state plasma acid–base values were as follows: PaCO_2 , 52.8 ± 6.0 mm Hg; $[\text{HCO}_3^-]$, 29.9 ± 3.0 mEq/l, and pH, 7.37 ± 0.02 . Least-squares regression for steady-state $[\text{HCO}_3^-]$ versus PaCO_2 had a slope of 0.476 mEq/l per mm Hg (95% CI = 0.414–0.538, $P < 0.01$; $r = 0.95$) and that for steady-state pH versus PaCO_2 had a slope of -0.0012 units per mm Hg (95% CI = -0.0021 to -0.0003 , $P = 0.01$; $r = -0.47$). These data allowed estimation of the 95% prediction intervals for plasma $[\text{HCO}_3^-]$ and pH at different levels of PaCO_2 applicable to patients with steady-state chronic hypercapnia.

Conclusion: In steady-state chronic hypercapnia up to 70 mm Hg, the $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slope equaled 0.48 mEq/l per mm Hg, sufficient to maintain systemic acidity between the mid-normal range and mild acidemia. The estimated 95% prediction intervals enable differentiation between simple chronic respiratory acidosis and hypercapnia coexisting with additional acid–base disorders.

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KEYWORDS: CO_2 retention; hypercapnic respiratory failure; hypoxemia; plasma bicarbonate concentration; renal acidification; respiratory acidosis

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Each of the 4 cardinal acid–base disorders comprises a primary change in either of the determinants of blood pH (i.e., PaCO_2 and $[\text{HCO}_3^-]$) and a secondary response in the countervailing determinant.^{1–3} Quantified empirically, these secondary responses are directional and proportional to the primary changes, and tend to minimize the impact on systemic acidity engendered by the primary changes. Knowledge of the quantitative aspects (i.e., the slope) of the secondary response to each cardinal acid–base

disorder is essential to assessing whether the prevailing acid–base status is consistent with a simple versus a mixed acid–base disorder; therefore, such knowledge has both diagnostic and therapeutic implications.^{1–3}

Respiratory acidosis (primary hypercapnia) is initiated by an increase in PaCO_2 , which acidifies body fluids.^{3,4} Acutely, the acidemia is ameliorated within 5 to 10 minutes by a secondary increase in plasma $[\text{HCO}_3^-]$ that originates from titration of non-bicarbonate buffers.^{4–7} Observations in normal dogs and humans within an environmental chamber revealed a $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slope of 0.1 mEq/l per mm Hg.^{5,8} An essentially identical slope is obtained in humans in whom respiratory acidosis is induced by endogenous hypercapnia.⁹

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Chronic hypercapnia (duration of several days to longer) elicits a larger increase in plasma $[\text{HCO}_3^-]$ that reflects stimulation of renal acidification and further ameliorates systemic acidity.^{3,4,9,10} Studies in normal dogs within an environmental chamber revealed that 3 to 5 days of exposure are required for the renal adaptation to reach completion, thereby establishing a new steady state of acid–base equilibrium.^{11,12} Over a PaCO_2 range between 40 and 90 mm Hg, a $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slope of 0.3 mEq/l per mm Hg is obtained.^{3,4,9,11}

The secondary response to chronic respiratory acidosis in humans remains uncertain. Studies in normal humans have been precluded by the severe discomfort produced by prolonged exposure to high fractions of inspired CO_2 . Retrospective observations in the 1960s in hospitalized patients with hypercapnic respiratory failure yielded $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slopes of 0.35 to 0.43 mEq/l per mm Hg.^{13–15} However, not all studies provided evidence for steady-state chronic hypercapnia or absence of other conditions that could affect the patients' acid–base status. Notwithstanding, a $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slope of 0.35 to 0.4 mEq/l per mm Hg has been accepted for chronic hypercapnia.^{3,16}

Contrasted with studies in hospitalized patients, a 2003 retrospective study of 18 outpatients with stable hypercapnic respiratory failure reported a substantially steeper $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slope of 0.51 mEq/l per mm Hg.¹⁷ The patients had no complicating conditions and were not taking medications that could affect acid–base status. However, only a single measurement was available on each of the 18 patients, thereby making questionable the presence of steady-state chronic hypercapnia.³

Because of the prevailing uncertainty, we carried out a prospective study in outpatients with stable hypercapnic respiratory failure and evidencing a steady state of chronic hypercapnia to quantify the secondary response to chronic respiratory acidosis.

METHODS

Study Design

We conducted a prospective, single-center study at the Outpatient Pulmonary Clinic of the Hospital María Ferrer, Buenos Aires, Argentina, from January 2013 through December 2015. Eligible patients were adults (≥ 18 years of age) with known chronic obstructive or restrictive pulmonary disease, chronic CO_2 retention, and adequate kidney function (estimated glomerular filtration rate [eGFR] ≥ 60 ml/min per 1.73 m²), who were attending a routine clinic appointment and were clinically stable. Clinical stability was defined by the absence of worsening of pulmonary symptomatology, vomiting, diarrhea, and changes in prescribed or

over-the-counter medications over the preceding 4 weeks, as well as hemodynamic stability on physical examination at the clinic appointment. In addition, patients should not have taken diuretics, steroids, carbonic anhydrase inhibitors, alkali, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers over the preceding 4 weeks.

Eligible patients were invited to participate in the study, and those who accepted provided signed informed consent. The study involved measurement of arterial blood gases and a panel of plasma chemistries on the day of the appointment, and a repeat measurement within a 10-day period. The repeat measurement was predicated upon the first PaCO_2 level being ≥ 45 mm Hg, and continued clinical stability and avoidance of medications listed above throughout the intervening period. Patients completing both measurements were included in the final cohort if they met the following 2 conditions: (i) evidence for being in a steady state of PaCO_2 (such evidence required that the 2 measurements of PaCO_2 obtained varied by no more than ± 4 mm Hg from the mean PaCO_2 in the given patient); and (ii) adequate kidney function (eGFR ≥ 60 ml/min per 1.73 m²) on both measurements. The study protocol and informed consent were approved by the Institutional Review Board of Hospital María Ferrer.

Laboratory Measurements

Arterial blood gases (pH, PaCO_2 , and oxygen tension, PaO_2) were measured anaerobically with an ABL800 FLEX automatic analyzer (Radiometer, Copenhagen, Denmark). Plasma $[\text{HCO}_3^-]$ was calculated from pH and PaCO_2 using the Henderson–Hasselbalch equation. Plasma Na^+ , K^+ , Cl^- , urea, creatinine, albumin, glucose, and lactate were measured with an Ortho Clinical Vitros 250 Chemistry System. Plasma anion gap (AG) was calculated as $[\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$. Corrected AG (AGc) was calculated as $\text{AG} + 2.5 \times (4.4 - \text{measured plasma albumin [g/dl]})$. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.¹⁸

Statistical Methods

Continuous variables are summarized as mean \pm SD and categorical variables as frequency count (percentage). We used simple linear regression to model the relationship between the following response variables, plasma $[\text{HCO}_3^-]$, pH, and $[\text{H}^+]$, and PaCO_2 as the predictor variable. Using the linear regression model for plasma $[\text{HCO}_3^-]$ and PaCO_2 , we calculated the predicted $[\text{HCO}_3^-]$ and its 95% prediction intervals by varying the PaCO_2 from 40 to 70 by increments of 1 mm Hg. We checked for functional forms of all continuous variables in the linear regression models using restricted cubic

splines in the rms package in R language (version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria). There were no statistically significant deviations from linearity for any continuous variable. We pooled data from the current study with the data from the Martinu *et al.* study¹⁷ to test the equality of the regression lines for plasma $[\text{HCO}_3^-]$ and PaCO_2 , and for plasma pH and PaCO_2 . We used the analysis of covariance method to compare both intercepts and slopes. We first tested for the equality of the slopes while allowing for the intercepts to be different; if the slopes were not statistically significantly different, we tested for the equality of the intercepts by assuming a common slope. Analyses were performed using SAS Enterprise Guide (version 7.12; SAS Institute, Cary, NC) and R language.

RESULTS

A total of 35 patients were invited and agreed to participate in the study. Of these, 29 patients completed both measurements; 6 patients did not report for the second measurement. On completion of the study, 1 patient was excluded because she was not in a steady state of PaCO_2 (values of 63.4 and 54.3 mm Hg, range of 9.1 mm Hg). The remaining 28 patients comprised our analytical set.

Characteristics of the Study Cohort

Patients' mean age was 55.4 ± 12.7 years, and most patients (75%) were men. The mean height was 164.7 ± 8.6 cm, mean weight 76.9 ± 24.8 kg, and mean body mass index (BMI) 28.3 ± 9.6 kg/m². In all, 20 patients had chronic obstructive pulmonary disease, 3 pulmonary interstitial disease, 3 bronchiectasis, and 2 cystic fibrosis. A total of 16 patients were maintained on home oxygen. Three patients had type 2 diabetes mellitus and were maintained on oral antidiabetic medications.

Evidence for a Steady State of PaCO_2

The mean interval between the 2 measurements was 7.2 ± 2.1 days (in 1 patient, the interval was 12 days, exceeding the designated 10-day period). The mean PaCO_2 was 53.5 ± 6.2 and 52.1 ± 6.3 mm Hg on the first and second measurement, respectively ($P = 0.03$). The mean range of PaCO_2 between the 2 measurements of each patient was 2.8 ± 2.1 mm Hg. In 18 patients (64%), the range of PaCO_2 between the 2 measurements was < 3.0 mm Hg. Compared with the first measurement, the second measurement of PaCO_2 decreased by ≥ 1.0 mm Hg in 14 patients (50%), increased by ≥ 1.0 mm Hg in 8 patients (29%), and remained essentially unchanged (change < 1.0 mm Hg) in 6

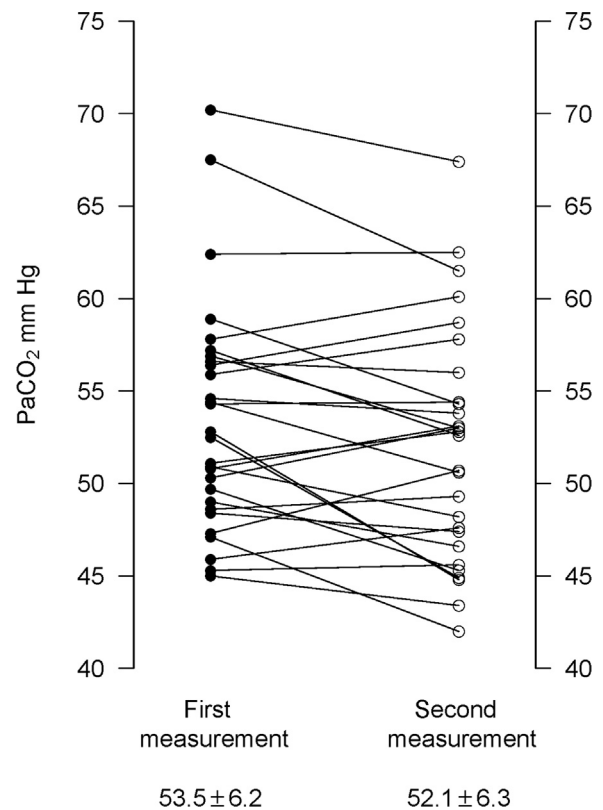


Figure 1. Values for PaCO_2 obtained during the 2 measurements in study patients. Each patient's values are connected with a straight line. Mean and SD of all values obtained in each of the 2 measurements are shown at the bottom of the figure ($P = 0.03$).

patients (21%). **Figure 1** depicts the 2 measurements of PaCO_2 in the 28 patients.

Plasma Data and Correlations

Steady-state plasma values were obtained for each patient by averaging the 2 plasma determinations made. For the group as a whole, **Table 1** provides the mean steady-state values for plasma acid–base and electrolyte composition, and plasma concentrations of lactate, glucose, urea, and creatinine.

Figure 2 depicts the relationship between steady-state values of plasma $[\text{HCO}_3^-]$ and PaCO_2 for the entire cohort. The least-squares regression for this relationship had a slope of 0.476 mEq/l per mm Hg (95% confidence interval [CI] = 0.414–0.538, $P < 0.01$) and a correlation coefficient of 0.95. Using restricted cubic splines, there was no deviation from linearity for this relationship ($P = 0.69$). The limits of the 95% prediction intervals for plasma $[\text{HCO}_3^-]$ at different levels of PaCO_2 applicable to patients with steady-state chronic respiratory acidosis are presented in **Figure 2** and **Table 2**.

Figure 3 depicts the relationship between steady-state values of plasma pH and PaCO_2 (**Figure 3a**) and plasma $[\text{H}^+]$ and PaCO_2 (**Figure 3b**) for the entire cohort. The least-squares regression for the pH versus

Table 1. Steady-state plasma acid–base and electrolyte composition

Variable	Unit	Mean ± SD
PaCO ₂	mm Hg	52.8 ± 6.0
[HCO ₃ ⁻]	mEq/l	29.9 ± 3.0
pH		7.37 ± 0.02
H ⁺	nEq/l	42.5 ± 1.5
PaO ₂	mm Hg	59.8 ± 9.6
Na ⁺	mEq/l	137.8 ± 2.1
K ⁺	mEq/l	4.2 ± 0.2
Cl ⁻	mEq/l	98.3 ± 2.8
AG	mEq/l	9.6 ± 1.8
AGc	mEq/l	10.7 ± 1.5
Albumin	g/dl	4.0 ± 0.3
Lactate	mEq/l	1.0 ± 0.4
Glucose	mg/dl	120.7 ± 29.9
Urea ^a	mg/dl	29.0 ± 7.8
Creatinine	mg/dl	0.7 ± 0.2
eGFR	ml/min per 1.73 m ²	107.1 ± 23.3

AG, anion gap, calculated as $[Na^+] - ([Cl^-] + [HCO_3^-])$; AGc, corrected anion gap, calculated as $AG + 2.5 \times (4.4 - \text{measured plasma albumin [g/dl]})$; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation).

^aTo convert values for urea to blood urea nitrogen (mg/dl), multiply by 0.467.

PaCO₂ relationship had a slope of -0.0012 units per mm Hg (95% CI = -0.0021 to -0.0003 , $P = 0.01$) and a correlation coefficient of -0.47 , whereas that for the [H⁺] versus PaCO₂ relationship had a slope of 0.1138 nEq/l per mm Hg (95% CI = 0.0257 – 0.2019 , $P = 0.01$) and a correlation coefficient of 0.46 . For both relationships, using restricted cubic splines, there was no deviation from linearity ($P > 0.5$ for both). The limits of the 95% prediction intervals for plasma pH and [H⁺] at different levels of PaCO₂ applicable to patients with steady-state chronic respiratory acidosis are presented in Table 2.

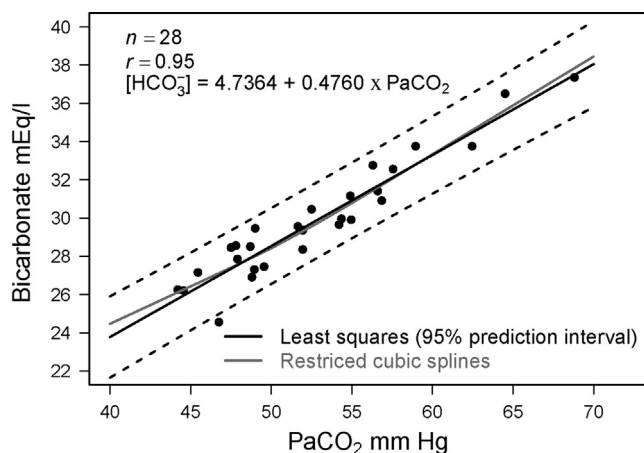


Figure 2. Steady-state relationship between plasma bicarbonate concentration and PaCO₂ in study patients. Each point represents the average of the 2 determinations obtained in each patient. The value for the slope of the least-squares regression line is significantly different from 0 ($P < 0.01$). Using restricted cubic splines, there was no deviation from linearity for this relationship ($P = 0.69$).

Figure 4 juxtaposes the steady-state values of plasma [HCO₃⁻] and PaCO₂ of our 28 patients to the single-per-patient values of the 18 patients reported by Martinu et al.¹⁷ The $\Delta[HCO_3^-]/\Delta PaCO_2$ slopes of the 2 regressions, 0.4760 and 0.5106 mEq/l per mm Hg, respectively, were not significantly different ($P = 0.47$), but the x-axis intercepts, 4.7364 and 5.2366 mEq/l, respectively, were ($P < 0.01$). Similarly, the $\Delta pH/\Delta PaCO_2$ slopes of the 2 regressions, -0.0012 and -0.0014 units per mm Hg, respectively, were not significantly different ($P = 0.76$), but the x-axis intercepts, 7.4337 and 7.4779 , respectively, were ($P < 0.01$) (Figure 5).

The mean steady-state plasma [Na⁺] and [K⁺] were within the normal range, but [Cl⁻] was decreased, as expected in chronic hypercapnia (Table 1). The mean steady-state plasma concentrations of AG, AGc, albumin, lactate, urea, and creatinine were also in the normal range, but glucose concentration was mildly increased, reflecting the values of the 3 diabetic patients and the nonfasting state of all of the patients. Excluding an inverse correlation between steady-state values for plasma [Cl⁻] and PaCO₂ (data not shown), none of these variables was correlated with PaCO₂. The mean steady-state eGFR was 107.1 ± 23.3 ml/min per 1.73 m².

DISCUSSION

The results of our study allow estimation of the 95% prediction intervals for plasma [HCO₃⁻] and pH at different levels of PaCO₂ in steady-state chronic respiratory acidosis in humans. This reference range enables differentiation between simple chronic respiratory acidosis and hypercapnia coexisting with additional acid–base disorders.

Our study indicates that, in steady-state chronic respiratory acidosis, the $\Delta[HCO_3^-]/\Delta PaCO_2$ slope equals 0.48 mEq/l per mm Hg. This slope was derived from a prospective analysis of the relationship between plasma [HCO₃⁻] and PaCO₂ of outpatients with chronic lung disease and stable hypercapnic respiratory failure, who met a stringent criterion of steady-state chronic hypercapnia, and who did not have other disorders and were not taking medications that could affect their acid–base status. Also, the prevailing hypoxemia should not have influenced the acid–base status; hypoxemia (PaO₂ 45–55 mm Hg) does not alter appreciably the renal response to chronic hypercapnia in dogs or humans.^{19–21} Therefore, we believe that we captured the $\Delta[HCO_3^-]/\Delta PaCO_2$ relationship in uncomplicated chronic respiratory acidosis. The range of chronic hypercapnia that we studied extended up to 70 mm Hg. Thus, our $\Delta[HCO_3^-]/\Delta PaCO_2$ slope cannot be applied to greater degrees of hypercapnia. Observations in dogs and scant human data suggest that the

Table 2. Predicted values and their 95% prediction intervals (PI) for plasma $[\text{HCO}_3^-]$, pH, and $[\text{H}^+]$ at different levels of steady-state PaCO_2 in uncomplicated chronic respiratory acidosis

PaCO_2 mm Hg	$[\text{HCO}_3^-]$ mEq/l			pH			$[\text{H}^+]$ nEq/l		
	Predicted value	Lower 95% PI	Upper 95% PI	Predicted value	Lower 95% PI	Upper 95% PI	Predicted value	Lower 95% PI	Upper 95% PI
40	23.8	21.6	25.9	7.39	7.36	7.42	41.1	38.0	44.1
41	24.3	22.1	26.4	7.39	7.36	7.42	41.2	38.2	44.2
42	24.7	22.6	26.8	7.38	7.35	7.41	41.3	38.3	44.3
43	25.2	23.1	27.3	7.38	7.35	7.41	41.4	38.5	44.4
44	25.7	23.6	27.7	7.38	7.35	7.41	41.5	38.6	44.5
45	26.2	24.1	28.2	7.38	7.35	7.41	41.6	38.7	44.5
46	26.6	24.6	28.7	7.38	7.35	7.41	41.8	38.9	44.6
47	27.1	25.1	29.1	7.38	7.35	7.41	41.9	39.0	44.7
48	27.6	25.6	29.6	7.38	7.35	7.41	42.0	39.1	44.8
49	28.1	26.1	30.0	7.38	7.35	7.41	42.1	39.3	44.9
50	28.5	26.6	30.5	7.38	7.35	7.40	42.2	39.4	45.0
51	29.0	27.0	31.0	7.37	7.35	7.40	42.3	39.5	45.1
52	29.5	27.5	31.5	7.37	7.34	7.40	42.4	39.6	45.3
53	30.0	28.0	31.9	7.37	7.34	7.40	42.6	39.7	45.4
54	30.4	28.5	32.4	7.37	7.34	7.40	42.7	39.8	45.5
55	30.9	28.9	32.9	7.37	7.34	7.40	42.8	40.0	45.6
56	31.4	29.4	33.4	7.37	7.34	7.40	42.9	40.1	45.7
57	31.9	29.9	33.9	7.37	7.34	7.40	43.0	40.2	45.9
58	32.3	30.3	34.3	7.37	7.34	7.39	43.1	40.3	46.0
59	32.8	30.8	34.8	7.36	7.34	7.39	43.2	40.4	46.1
60	33.3	31.3	35.3	7.36	7.33	7.39	43.4	40.5	46.2
61	33.8	31.7	35.8	7.36	7.33	7.39	43.5	40.6	46.4
62	34.2	32.2	36.3	7.36	7.33	7.39	43.6	40.6	46.5
63	34.7	32.6	36.8	7.36	7.33	7.39	43.7	40.7	46.7
64	35.2	33.1	37.3	7.36	7.33	7.39	43.8	40.8	46.8
65	35.7	33.6	37.8	7.36	7.33	7.39	43.9	40.9	46.9
66	36.1	34.0	38.3	7.36	7.33	7.39	44.0	41.0	47.1
67	36.6	34.5	38.8	7.36	7.32	7.39	44.1	41.1	47.2
68	37.1	34.9	39.3	7.35	7.32	7.39	44.3	41.1	47.4
69	37.6	35.4	39.8	7.35	7.32	7.38	44.4	41.2	47.5
70	38.1	35.8	40.3	7.35	7.32	7.38	44.5	41.3	47.7

$\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slope flattens at levels of chronic hypercapnia exceeding 70 mm Hg.^{4,9,11}

Two retrospective analyses of data of hospitalized adult patients with hypercapnic respiratory failure conducted in the 1960s yielded $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slopes of 0.35 to 0.4 mEq/l per mm Hg.^{13,14} The first study analyzed data of 420 unselected patients (88% inpatients) referred for evaluation or treatment of chronic lung disease.¹³ No evidence for a steady state of PaCO_2 was sought; 65% of patients were under active treatment, including diuretics, and 9% of patients had moderate kidney insufficiency. The authors conceded that, in some patients, complicating acid–base disorders were likely superimposed on hypercapnia. The second analysis involved 20 inpatients with decompensated hypercapnic respiratory failure.¹⁴ Patients had no kidney disease or “overt diabetes mellitus.” After medical stabilization, each patient contributed 2 to 3 acid–base measurements over a period of steady-state chronic hypercapnia (3–14 days), with PaCO_2 varying by no more than ± 4 mm Hg from the average

PaCO_2 in a given patient. During the steady-state period, patients had no apparent complicating condition that could affect acid–base status, nor were they receiving diuretics or steroids.

A third retrospective study also from that era analyzed 28 periods of steady-state hypercapnia in 13 patients (18 months to 23 years of age) with cystic fibrosis hospitalized with acute respiratory decompensation.¹⁵ No patient had kidney disease. The steady-state period was defined by daily PaCO_2 values (at least 2 values per patient) that varied by no more than $\pm 10\%$ from the mean PaCO_2 of the period in a given patient. No patient had shock or vomiting, nor was any patient taking diuretics or steroids during the steady-state period. Acid–base data were averaged for each steady-state period and yielded a $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slope of 0.43 mEq/l per mm Hg. Patients contributed a variable number of steady-state periods to the analysis.

Contrasted with studies in hospitalized patients, a recent retrospective study of 18 outpatients with stable hypercapnic respiratory failure reported a substantially

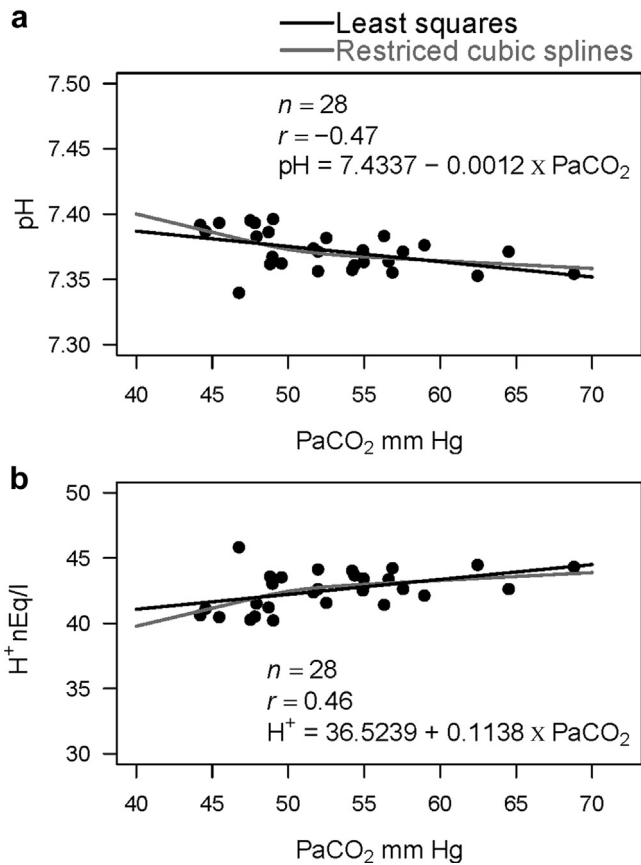


Figure 3. Steady-state relationship between plasma pH and PaCO₂ (a) and plasma H⁺ concentration and PaCO₂ (b) in study patients. Each point represents the average of the 2 determinations obtained in each patient. The value for the slope of each least-squares regression line is significantly different from 0 ($P < 0.01$). Using restricted cubic splines, there was no deviation from linearity for each of these relationships ($P > 0.5$ for both).

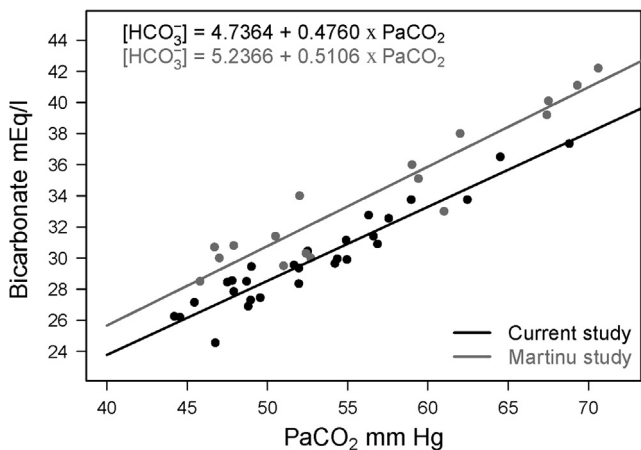


Figure 4. Comparison of the equality of the least-squares regression lines for plasma bicarbonate concentration and PaCO₂ between the current study and the Martinu *et al.* study.¹⁷ Each point of the current study (black circles) represents the average of the 2 determinations obtained in each patient. Each point of the Martinu *et al.* study (gray circles) represents the single determination obtained in each patient. Analysis of covariance revealed that the slopes of the 2 regressions were not significantly different ($P = 0.47$) but the x-axis intercepts were ($P < 0.01$).

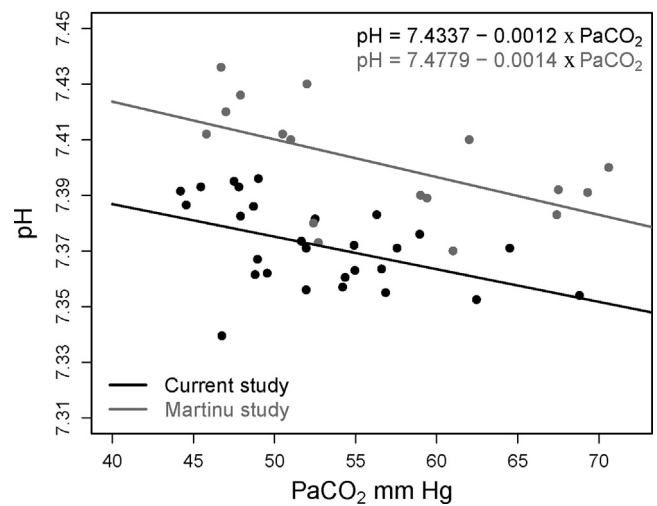


Figure 5. Comparison of the equality of the least-squares regression lines for plasma pH and PaCO₂ between the current study and the Martinu *et al.* study.¹⁷ Each point in the current study (black circles) represents the average of the 2 determinations obtained in each patient. Each point in the Martinu *et al.* study (gray circles) represents the single determination obtained in each patient. Analysis of covariance revealed that the slopes of the 2 regressions were not significantly different ($P = 0.76$) but the x-axis intercepts were ($P < 0.01$).

steeper $\Delta[HCO_3^-]/\Delta PaCO_2$ slope of 0.51 mEq/l per mm Hg.¹⁷ PaCO₂ ranged between 45 and 77 mm Hg. Patients had no kidney failure and had not taken diuretics, steroids, or angiotensin-converting enzyme inhibitors during the month prior to arterial blood sampling. However, only a single measurement was available for each patient, thereby offering no evidence for the presence of a steady state of chronic hypercapnia. Nonetheless, comparison of our plasma [HCO₃⁻] versus PaCO₂ regression equation with that of Martinu *et al.*¹⁷ showed that the intercepts, but not the slopes, were significantly different (Figure 4). Indeed, our regression equation predicts a plasma [HCO₃⁻] of 23.8 mEq/l at a PaCO₂ of 40 mm Hg, a value strikingly close to the mean normal value of 24 mEq/l for plasma [HCO₃⁻],²² whereas the corresponding value predicted by the Martinu *et al.* regression equation is 25.6 mEq/l. Similarly, predicted values for plasma [HCO₃⁻] at a PaCO₂ of 40 mm Hg in the 3 previous studies in hospitalized patients are in the range of 24.8 to 26.1 mEq/l.^{13–15} We can only speculate about potential explanations for such discrepancies in those studies. A measure of Cl⁻ deficiency might have prevented full correction of metabolic alkalosis (secondary to diuretics, steroids, or vomiting) in some patients. Hyperventilation at the time of arterial blood sampling in some patients might have distorted their plasma [HCO₃⁻] versus PaCO₂ relationship. Dietary differences (amount of animal protein, fruits, and vegetables) and blood sampling coinciding with the postprandial alkaline tide might have contributed.

Our findings call for discarding the currently held Δ $[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slope of 0.35 to 0.4 mEq/l per mm Hg for chronic hypercapnia^{3,16} and for its substitution with a slope of 0.5 mEq/l per mm Hg for clinical use, conveniently rounding up our actual slope of 0.476 mEq/l per mm Hg (Figure 2). Thus, we recommend use of the formula $[\text{HCO}_3^-] = 24 + [(\text{current PaCO}_2 - 40) \times 0.5]$, for calculating the predicted mean $[\text{HCO}_3^-]$ at a given steady-state PaCO_2 in chronic hypercapnia, with the 95% prediction intervals taken as ± 2 mEq/l around the predicted mean value. As an example, for a steady-state PaCO_2 of 60 mm Hg in a patient with chronic respiratory acidosis, the above formula will give a predicted mean $[\text{HCO}_3^-]$ of 34 mEq/l, with 95% prediction intervals of 32 and 36 mEq/l. These values are convenient approximations of the corresponding actual values of 33.3 mEq/l, and 31.3, and 35.3 mEq/l in Table 2.

Although plasma pH had a significant inverse relationship with PaCO_2 in our study, only 21% of our subjects had pH values of < 7.36 , the reported lower limit of normal.²² The predicted pH values in our study are marginally more acidemic than those in 2 previous studies in hospitalized patients^{14,15} and mildly more acidemic than the study of Martinu *et al.*¹⁷ (Figure 5). Substantially more acidemia is predicted by 1 of the previous studies in hospitalized patients¹³ and a study in dogs.¹¹ The limits of the 95% prediction intervals for plasma pH and $[\text{H}^+]$ during mild to moderate chronic hypercapnia presented in Table 2 indicate that systemic acidity varies between the mid-normal range and mild acidemia, highlighting a remarkably effective secondary response.

Our results bolster the experimental evidence that changes in systemic acidity do not drive the renal responses to increases or decreases in PaCO_2 .^{23–25} Nor are changes in intracellular pH, whether whole-body²⁶ or kidney-specific,^{27,28} prerequisite for these responses. Rather, the change in PaCO_2 itself appears to provide the signal that triggers the corresponding renal acidification response to chronic hypercapnia or chronic hypocapnia.^{23–26,29}

The renal response to chronic hypercapnia entails a transient increase in net acid excretion, largely as ammonium, which generates the characteristic hyperbicarbonatemia, and a persistent increase in bicarbonate reabsorption, which sustains the generated hyperbicarbonatemia.^{4,9–12,25} No systematic information exists on the impact of chronic kidney disease on the renal response to chronic hypercapnia. In a patient with hyporeninemic hypoaldosteronism, hyperkalemia, and an eGFR of ~ 20 ml/min per 1.73 m^2 , the secondary response to chronic hypercapnia was suppressed; however, correction of the hyperkalemia enabled an essentially normal secondary response,

likely by disinhibiting renal ammoniogenesis.³⁰ This report suggests that in the absence of hyperkalemia, only advanced chronic kidney disease would suppress the secondary response to chronic hypercapnia. Notably, our patients had preserved kidney function, and none featured hyperkalemia.

Adaptation to chronic hypercapnia in the dog requires 3 to 5 days to reach completion.^{4,9,11,12,25} Whether this temporal pattern applies to humans is unknown. Dogs were studied within an environmental chamber, each level of hypercapnia being introduced abruptly and then sustained for a period of 7 days or longer. In patients, chronic hypercapnia often reflects gradual deterioration in pulmonary function. Consequently, the secondary response might essentially keep pace with the slowly rising PaCO_2 without a perceptible delay.

Like previous studies in dogs and humans, our study demonstrates that chronic hypercapnia does not cause appreciable changes in plasma $[\text{Na}^+]$, $[\text{K}^+]$, lactate concentration, and anion gap.^{4,9} The renal adaptation to chronic hypercapnia entails chloruresis, which generates the characteristic hypochloremia (Table 1).^{4,9}

Our study has several strengths. It is the first prospective study to examine the secondary response to chronic hypercapnia in outpatients with chronic CO_2 retention. Our patients were in stable respiratory status, had sound hemodynamics and adequate kidney function, and did not have complicating conditions or take medications that could affect their acid–base status. Evidence for the presence of a steady state of chronic hypercapnia was provided. However, we were unable to recruit patients with chronic PaCO_2 level beyond 70 mm Hg.

In summary, our study describes the slope of the secondary response to chronic respiratory acidosis in humans. The results allow estimation of the prediction limits within which plasma $[\text{HCO}_3^-]$ and pH should fall with 95% confidence at a given level of steady-state PaCO_2 in chronic respiratory acidosis. This reference range enables the clinician to differentiate between simple chronic respiratory acidosis and hypercapnia coexisting with additional acid–base disorders.

DISCLOSURE

All the authors declared no competing interests.

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