Re-evaluation of acid-base prediction rules in patients with chronic respiratory acidosis

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RATIONALE: The prediction rules for the evaluation of the acid-base status in patients with chronic respiratory acidosis, derived primarily from an experimental canine model, suggest that complete compensation should not occur. This appears to contradict frequent observations of normal or near-normal pH levels in patients with chronic hypercapnia.

METHODS: Linear regression analysis was used to estimate the relationships between arterial pH, bicarbonate and partial pressure of carbon dioxide (PCO_2) from 18 separate arterial blood gas measurements in 18 clinically stable outpatients with chronic hypercapnic respiratory failure from chronic obstructive lung disease, and without clinical conditions or medications likely to cause a primary metabolic alkalosis.

RESULTS: The PCO_2 ranged from 45 mmHg to 77 mmHg, and pH ranged from 7.37 to 7.44. In only three of the arterial blood gas measurements were the pH values lower than 7.38. From the regression equations derived from these measurements, the pH decreased by 0.014 for each 10 mmHg increase in the PCO_2, and the bicarbonate level increased by 5.1 mmol/L. These values are quite different from a decrease in pH of 0.03 and an increase in bicarbonate of 3.5 mmol/L predicted using the rules derived from the canine model.

CONCLUSIONS: In patients with chronic stable hypercapnia, acid-base compensatory mechanisms appear to be more effective than would be predicted using the classic rules.

Key Words: *Acid-base equilibrium; Chronic obstructive pulmonary disease; Hypercapnia; Respiratory acidosis*

La réévaluation des règles de prédiction acidobasique chez les patients atteints d'une acidose respiratoire chronique

JUSTIFICATION : Les règles de prédiction pour l'évaluation de l'état acidobasique des patients atteints d'une acidose respiratoire chronique, principalement dérivées d'un modèle canin expérimental, laissent supposer l'impossibilité théorique d'une compensation complète. Ce constat semble être en contradiction avec les observations fréquentes de taux de pH normal ou quasi-normal chez les patients atteints d'hypercapnie chronique.

MÉTHODOLOGIE : Une analyse de régression linéaire a été utilisée pour évaluer le lien entre le pH artériel, le bicarbonate et la pression partielle du dioxyde de carbone (PCO_2) à partir de 18 gazométries artérielles distinctes prises chez 18 malades externes cliniquement stables atteints d'insuffisance respiratoire hypercapnique chronique causée par une bronchopneumopathie chronique obstructive ne souffrant pas de pathologie clinique ou ne prenant pas de médicaments susceptibles de causer une alcalose métabolique.

RÉSULTATS : Le PCO_2 variait entre 45 mmHg et 77 mmHg et le pH, entre 7,37 et 7,44. Seules trois gazométries artérielles s'associaient à un pH inférieur à 7,38. D'après les équations de régression dérivées de ces mesures, le pH diminuait de 0,014 pour 10 mmHg d'augmentation de PCO_2, et le taux de bicarbonate augmentait de 5,1 mmol/L. Ces valeurs diffèrent beaucoup de la diminution de pH de 0,03 et de l'augmentation de bicarbonate de 3,5 mmol/L prédites d'après les règles dérivées du modèle canin.

CONCLUSIONS : Chez les patients atteints d'hypercapnie chronique stable, les mécanismes acidobasiques compensatoires semblent plus efficaces qu'on le prédirait au moyen des règles classiques.

Hydrogen ion concentration is a critical determinant of many physiological functions (1). For this reason, the blood pH is very tightly regulated and normally ranges between 7.38 and 7.42 in humans and many other species (2). Many physiological systems are involved in this regulation, including the respiratory system and kidneys, as well as red blood cells, proteins and the bicarbonate buffering system within the blood.

The current prediction equations used to assess the acid-base status in patients with chronic respiratory acidosis were derived from experiments in dogs (3-5). In these experiments, large changes (greater than 20 mmHg) in the partial pressure of carbon dioxide (PCO_2) were induced and sustained for a maximum of seven days. However, this is not the typical rate of increase, nor duration, of hypercapnia in patients with slowly progressive diseases such as chronic obstructive pulmonary disease (COPD). In these patients, normal or near-normal pH values have been observed (6). These are often attributed to the presence of a metabolic alkalosis due to diuretics and/or corticosteroids, superimposed on the primary respiratory acidosis. In four earlier studies (7-10), the degree of acid-base compensation was greater in patients with chronic respiratory acidosis than that described in the canine experiments. However, the patients studied were hospitalized and clinical stability was not defined (10),

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or was defined as elevated PCO_2 that was stable for only three days (7-9). It is possible that, as in the dog experiments, the measurements were made before there was complete acid-base compensation.

The present study was performed to re-evaluate the relationships between the arterial pH, PCO_2 and bicarbonate levels in patients with chronic respiratory acidosis who were clinically stable for at least one month.

METHODS

Patients were considered eligible if they had arterial blood gas analyses performed as outpatients at the Montreal Chest Institute, Montreal, Quebec, had COPD or cystic fibrosis (CF) and were hypercapnic (arterial PCO_2 of 45 mmHg or higher). Patients were excluded if they had taken diuretics, oral steroids or angiotensin-converting enzyme inhibitors, or had renal failure in the month before the arterial blood gas sampling. This study was approved by the Ethics Committee of the Montreal Chest Institute.

Eligible patients were defined as clinically stable at the time of the arterial blood gas sampling if they met the following criteria: the arterial blood gas analysis was performed during a routinely scheduled outpatient visit; the blood gas analysis was done to assess need for home oxygen or rehabilitation; there were no new respiratory symptoms or change in medications for at least one month before and after the blood gas analysis; and they were considered stable by their primary physician.

Arterial blood gas results were also extracted from patients who were eligible but not clinically stable at the time, as defined above. These patients were defined as clinically unstable and their blood gas analyses were used as observations for comparison with the observations from clinically stable patients.

Data collection

Data abstracted retrospectively from the patients' charts included age, sex, comorbid diseases, medications, diagnosis, use of home oxygen, baseline pulmonary function tests and all results of outpatient arterial blood gas measurements. Clinical stability was assessed from the data collected by one of the investigators, without knowledge of the arterial blood gas results.

TABLE 1
Baseline characteristics of patients with chronic obstructive pulmonary disease (COPD) or cystic fibrosis (CF)

Number of subjects	18
Diagnosis (n)	
COPD	4
CF	14
Age in years (mean ± SD)	
COPD	64.6±8.3
CF	28±4.9
Sex – number of males (%)	11 (61%)
Number on long term oxygen therapy (%)	7 (49%)
Mean baseline forced expiratory volume in 1 s ± SD (L)	0.71±0.53

The arterial blood gas measurements were analyzed using a Bayer 800 series analyzer (Bayer, Canada). This instrument provides linear measurements for the PCO_2 in the range of 5 mmHg to 250 mmHg (machine specification). To ensure accuracy of the measurements, the machines are calibrated using three controls on a daily basis; the results of quality assessments over the study period are listed below.

Control 1 – Expected pH range: 7.13 to 7.17;
Measured (± SD): 7.147±0.003
Expected PCO_2 range: 68.3 to 81.1 mmHg
Measured (± SD): 72.5±1.1 mmHg

Control 2 – Expected pH range: 7.341 to 7.381
Measured (± SD): 7.36±0.002
Expected PCO_2 range: 36.5 to 46.5 mmHg
Measured (± SD): 40.7±0.2 mmHg

Control 3 – Expected pH range: 7.543 to 7.595
Measured (± SD): 7.569±0.002
Expected PCO_2 range: 20.6 to 24.6 mmHg
Measured (± SD): 23.6±0.3 mmHg

The within-run precision was within 2% at all levels. The bicarbonate levels were calculated from the arterial PCO_2 and pH using the Henderson-Hasselbalch equation.

Data analysis

To estimate the relationship between PCO_2 and arterial pH, bicarbonate and hydrogen ion concentrations by comparison with other studies, linear regression was performed using SAS (SAS Institute, USA).

RESULTS

Arterial blood gas analyses were performed on 18 eligible patients who were deemed to be clinically stable at the time of sampling. As shown in Table 1, four patients had CF and 14 had COPD. Although these two groups were very different in terms of age, their arterial blood gas results and acid-base compensations were very similar. Therefore, results from patients with these two diagnoses were combined in all tables and figures. The overall average pH was 7.40 and PCO_2 was 58 mmHg. The lowest observed pH was 7.37; a pH lower than 7.38 was measured in only three instances (17%) (Table 2).

The slope of the relationship between arterial PCO_2 and pH estimated from regression is shown in Figure 1. Similarly, the estimated relationship between arterial PCO_2 and bicarbonate is shown in Figure 2. As shown in Table 3, an increase of 10 mmHg in the PCO_2 was associated with a decrease of only 0.014 in the pH and an increase of 5.1 mmol/L in the bicarbonate level. Using the regression coefficients and intercept, in a stable patient with a PCO_2 of 55 mmHg, one could predict that the pH would be 7.40 with a bicarbonate level of 33 mmol/L.

There were 17 blood gas samples taken from 17 eligible patients who did not meet the criteria of clinical stability at the time of arterial blood gas sampling. A test performed to evaluate whether the two regression curves were statistically significantly different almost reached statistical significance (P=0.06). The estimated relationships between arterial pH, bicarbonate and PCO_2 in the unstable group were very similar to those obtained

TABLE 2
Characteristics and arterial blood gas values for stable hypercapnic patients

Patient	Diagnosis	Age (years)	pH	PCO_2 level (mmHg)	Bicarbonate level (mmol/L)
1	COPD	71	7.41	46	29
2	COPD	80	7.37	53	30
3	COPD	67	7.38	67	39
4	COPD	60	7.41	51	31
5	COPD	62	7.39	69	41
6	COPD	72	7.43	48	31
7	COPD	54	7.4	71	42
8	COPD	54	7.39	59	35
9	COPD	67	7.41	62	38
10	COPD	68	7.39	68	40
11	COPD	74	7.44	47	31
12	COPD	66	7.38	52	30
13	COPD	54	7.43	52	34
14	COPD	55	7.41	51	30
15	CF	27	7.42	47	30
16	CF	22	7.39	59	36
17	CF	28	7.37	77	45
18	CF	34	7.37	61	33
COPD patients (n=14)*		64.6±8.3	7.40±0.02	57±9.0	34±4.8
CF patients (n=4)*		27.8±4.9	7.39±0.02	61±12.3	36±6.5

**Values expressed as mean ± SD. CF Cystic fibrosis; COPD Chronic obstructive pulmonary disease; PCO_2 Partial pressure of carbon dioxide*

in the canine experiments and in studies of patients whose clinical stability was defined in an inpatient setting (Table 4).

DISCUSSION

In our study, 18 patients with chronic hypercapnic respiratory disease and without any possible metabolic alkalosis underwent arterial blood gases analyses when they had been without any change in respiratory symptoms or medications for at least one month. Despite having PCO_2 levels as high as 77 mmHg, all of the patients maintained their pH at 7.37 or greater, and more than 80% had a pH of 7.38 or greater. In patients with chronic hypercapnia, acid-base compensation appears more complete than previously believed.

The limitations of our study include the retrospective design, which can result in incomplete data or confounding, because blood gases are often taken to evaluate symptomatic illnesses (ie, when patients are not stable). Incomplete data was not a problem in the patients reviewed, who form part of a large, prospectively gathered patient database at the Montreal Chest Institute. As well, the indications for blood gas analysis were assessed for home oxygen or rehabilitation programs, both of which emphasize that patients should be stable at the time of the blood gas analysis. The major limitation was the small number of observations. However, statistically significant associations were nevertheless detected, which suggests that the relationships were strongly correlated, because they were detected even with limited power. The small numbers in the study resulted in wide CIs obtained around the estimates of the slope and intercept.

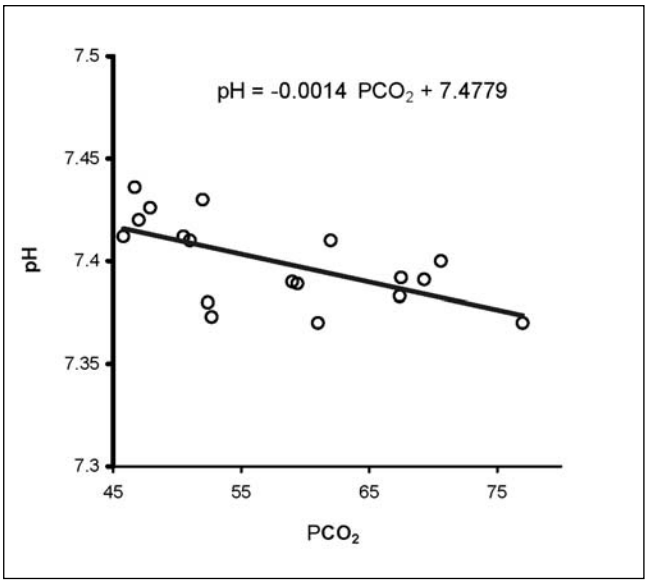

Figure 1) *Relationship between pH and partial pressure of carbon dioxide (PCO_2) in stable hypercapnic outpatients (estimates for slope regression in 18 patients, r^2= 0.39)*

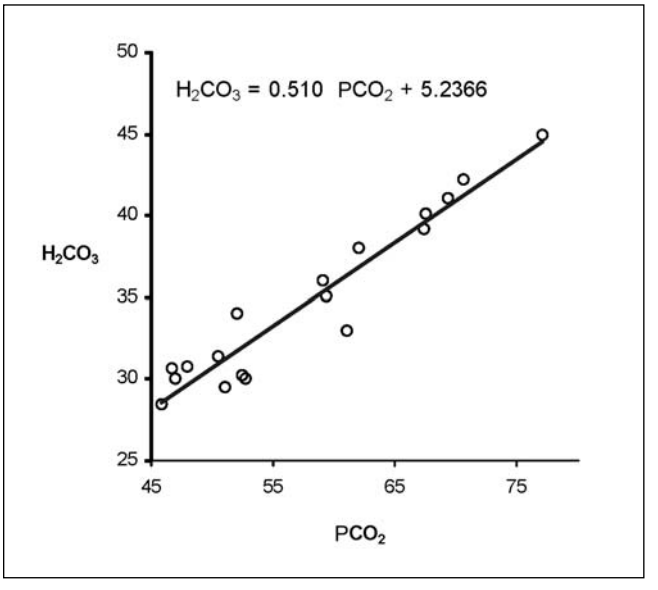

Figure 2) *Relationship between bicarbonate (HCO_3) and partial pressure of carbon dioxide (PCO_2) in stable hypercapnic outpatients (estimates for slope regression in 18 patients, r^2= 0.92)*

The major strength of our study is that patients were carefully defined as clinically stable for at least one month. As well, patients with disorders likely to cause a superimposed metabolic alkalosis were excluded. Therefore, the findings are of much greater relevance to clinical practice than those from an experimental dog model (3,4) or short term observations in hospitalized patients (7,10). These studies are likely to have underestimated the compensation that patients with chronic respiratory failure may achieve.

The rules for the expected compensation in the setting of acute and chronic respiratory acidosis, which are still applied

today (11,12), were developed in 1965 from experiments in dogs (3,4). In one of these canine studies (3), 10 dogs were exposed to normal atmosphere and then to successive concentrations of 7%, 11% and 17% carbon dioxide, each for five to seven days. A chronic state was defined as a sustained elevation in the arterial PCO_2 for four to five days. This definition was based on previous observations that after four to five days of exposure to a carbon dioxide concentration of 12%, the correction of the pH appeared to reach a plateau (5).

How applicable are the results of this experiment to patients with slowly progressive lung diseases? First, the experimental procedure of three episodes of acute hypercapnia, each maintained for less than one week, is very different from patients with chronic lung diseases, who develop hypercapnia over a period of years. Also, in the canine study, hypernatremia and significant bicarbonate losses were described in all of the dogs who survived the experiment; however, hypernatremia is not a usual finding in patients with hypercapnia from chronic respiratory failure.

As summarized in Table 3, the relationships between PCO_2, bicarbonate and pH found in the unstable patients in this study were more comparable to the classic dog experiments (3-5) and two studies in humans (10,13). In one of these human studies, 20 patients were evaluated after three days of stability while hospitalized for a respiratory decompensation (10). In the other study, 420 patients with chronic lung disease were evaluated, but chronicity of the respiratory acidosis, patient medications and other confounding factors were not described (13). In a third study among hospitalized hypercapnic patients whose PCO_2 levels varied less than 10% over three days (9), a normal arterial pH was seen in 87% of the patients with PCO_2 between 46 mmHg and 55 mmHg, compared with only 50% of patients with PCO_2 between 56 mmHg and 65 mmHg and 32% of patients with PCO_2 between 66 mmHg and 75 mmHg. The results among the stable patients in this study are most similar to the results of a study examining 247 arterial blood gas samples in 106 outpatients (8). In that study, although pH was not reported, for each increase of 10 mmHg in the PCO_2, the bicarbonate level increased by 5.3 mmol/L – very similar to the findings among stable patients in the present study. Ingram et al (14) studied patients with chronic hypercapnia who had acute changes in their PCO_2, with the aim of trying to define the relationship between the change in pH and increases in the PCO2 at different baseline PCO2 levels. The demographics of the patients in the steady state were not provided, but they reported the regression equation of the correlation between the steady state hydrogen ion concentration and PCO_2 in the patients studied. The correlation was very similar to the one found in the present study. In a recent report (15) examining the strong ion difference in patients with chronic hypercapnia, while not specifically examining the correlation of pH and PCO_2, the authors found that instead of a predicted pH of 7.355, they found a measured pH of 7.372 in a group of 12 patients with a mean PCO_2 of 54 mmHg.

There is a physiological concept that compensation should never be complete, because then the stimulus to compensate would be lost. This would mean that as the pH approaches normality, the kidney would no longer be stimulated to retain

TABLE 3
Regression equations for the relationships between partial pressure of carbon dioxide (PCO_2), pH and bicarbonate in 18 patients

Prediction of pH from PCO_2	
Number of observations	18
Intercept (95% CI)	7.48 (7.43 to 7.53)
Slope (95% CI)	–0.0014 (-0.0023 to -0.0005)
R^2	0.39
From equation: pH if PCO_2=55 mmHg	7.40
For ΔPCO_2 of 10 mmHg (eg, 55 to 65 mmHg), expected pH	7.38
T test slope P=0.006; Intercept P=0.0001; F test for ANOVA P=0.006	
Prediction of bicarbonate from PCO_2	
Number of observations	18
Intercept (95% CI)	5.23 (0.58 to 9.9)
Slope (95% CI)	0.51 (0.43 to 0.59)
R^2	0.92
From equation: bicarbonate (mmol/L) if PCO_2=55 mmHg	33
For ΔPCO_2 of 10 (eg, 55 to 65), expected bicarbonate (mmol/L)	38
T test slope P=0.0001; Intercept P=0.03; F test for ANOVA P=0.0001	

TABLE 4
Comparison from the present and earlier studies of regression equations of the relationship of chronic steady state partial pressure of carbon dioxide (PCO_2) to hydrogen ion concentration [H+], and predicted bicarbonate concentrations and pH at two levels of PCO_2

Reference	Hydrogen ion regression equation	Calculated bicarbonate (mmol/L) at a PCO_2 of 55 mmHg	65 mmHg	Calculated pH at a PCO_2 of 55 mmHg	65 mmHg
Subjects – Patients					
Present study (Stable)	*[H+] = 0.13 × chronic PCO_2 + 32.6*	*33*	*38*	*7.40*	*7.38*
Ingram et al (14)	[H+] = 0.12 × chronic PCO_2 + 33.8	33	38	7.39	7.38
Engel et al (9)	[H+] = 0.12 × chronic PCO_2 + 35.2	32	36	7.38	7.37
Van Ypersele de Strihou et al (13)	[H+] = 0.30 × chronic PCO_2 + 26.8	31	34	7.36	7.33
Brackett et al (10)	[H+] = 0.24 × chronic PCO_2 + 27.2	33	36	7.39	7.37
Present study (Unstable)	*[H+] = 0.27 × chronic PCO_2 + 26.5*	*33*	*35*	*7.39*	*7.36*
Subjects – Dogs					
Schwartz et al (3)	[H+] = 0.30 × chronic PCO_2 + 26.9	30	33	7.36	7.33
Goldstein et al (4)	[H+] = 0.27 × chronic PCO_2 + 33.0	28	31	7.32	7.30

bicarbonate and the pH would reach equilibrium below the normal range. However, in animal studies, the signal to compensate was not the low pH. Instead, the elevated PCO_2 directly stimulated the proximal tubule of the kidney to increase bicarbonate reabsorption (16-18). This implies that increased reabsorption of bicarbonate should continue as long as the PCO_2 remains elevated, raising interesting questions regarding feedback control of this compensatory response. Chronic adaptation is believed to be entirely due to renal adaptive processes, with increased net acid secretion, primarily in the form of ammonium, reduced reabsorption of chloride and increased reabsorption of bicarbonate ion (16,18). One study found changes in the gastrointestinal handling of chloride ion but little change in renal chloride excretion (19).

CONCLUSIONS

Although the mechanisms are not understood, renal compensatory mechanisms in chronic respiratory failure appear to be more complete than previously recognized. The clinical implication is important. In a patient with chronic hypercapnia, an arterial pH below the normal range should suggest the occurrence of worsening respiratory acidosis or new metabolic acidosis.

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