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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 ($[HCO_3^-]$) per mm Hg change in arterial carbon dioxide tension ($PaCO_2$), remains uncertain. Retrospective observations yielded $\Delta[HCO_3^-]/\Delta PaCO_2$ 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 gasses 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 (± SD) steady-state plasma acid–base values were as follows: $PaCO_2$, 52.8 ± 6.0 mm Hg; $[HCO_3^-]$, 29.9 ± 3.0 mEq/l, and pH, 7.37 ± 0.02. Least-squares regression for steady-state $[HCO_3^-]$ 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 $[HCO_3^-]$ 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 $\Delta[HCO_3^-]/\Delta PaCO_2$ slope equals 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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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 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 $[HCO_3^-]$ that originates from titration of nonbicarbonate buffers.[4–7] Observations in normal dogs and humans within an environmental chamber revealed a $\Delta[HCO_3^-]/\Delta PaCO_2$ 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 [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 $\Delta[HCO_3^-]/\Delta PaCO_2$ slope of 0.3 mEq/l per mm Hg obtains.[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 $\Delta[HCO_3^-]/\Delta PaCO_2$ 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 $\Delta[HCO_3^-]/\Delta PaCO_2$ 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 $\Delta[HCO_3^-]/\Delta PaCO_2$ 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 m^2), 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 gasses 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 m^2) on both measurements. The study protocol and informed consent were approved by the Institutional Review Board.

Laboratory Measurements

Arterial blood gasses (pH, $PaCO_2$, and oxygen tension, PaO_2) were measured anaerobically with an ABL800 FLEX automatic analyzer (Radiometer, Copenhagen, Denmark). Plasma [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 $[Na^+] - ([Cl^-] + [HCO_3^-])$. Corrected AG (AGc) was calculated as AG + 2.5 × (4.4 − 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 ± SD and categorical variables as frequency count (percentage). We used simple linear regression to model the relationship between the following response variables, plasma [HCO_3^-], pH, and [H^+], and $PaCO_2$ as the predictor variable. Using the linear regression model for plasma [HCO_3^-] and $PaCO_2$, we calculated the predicted [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

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