Exaggerated compensatory response to acute respiratory alkalosis in panic disorder is induced by increased lactic acid production

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Abstract

Background. In acute respiratory alkalosis, the severity of alkalaeemia is ameliorated by a decrease in plasma $[\text{HCO}_3^-]$ of 0.2 mEq/L for each 1 mmHg decrease in PaCO₂. Although hyperventilation in panic disorder patients is frequently encountered in outpatients, the drop in plasma $[\text{HCO}_3^-]$ sometimes surpasses the expectation calculated from the above formula. The quantitative relationship between reduced PaCO₂ and plasma $[\text{HCO}_3^-]$ in acute respiratory alkalosis has not been studied in panic disorder patients. Our objective was to provide reference data for the compensatory metabolic changes in acute respiratory alkalosis in panic disorder patients.

Methods. In 34 panic disorder patients with hyperventilation attacks, we measured arterial pH, PaCO₂, plasma $[\text{HCO}_3^-]$ and lactate on arrival at the emergency room.

Results. For each decrease of 1 mmHg in PaCO₂, plasma $[\text{HCO}_3^-]$ decreased by 0.41 mEq/L. During hypocapnia, panic disorder patients exhibited larger increases in serum lactate levels (mean ± SD; 2.59 ± 1.50 mmol/L, range; 0.78–7.78 mmol/L) than previously reported in non-panic disorder patients. Our results suggest that the compensatory metabolic response to acute respiratory alkalosis is exaggerated by increased lactic acid production in panic disorder patients. Here, we call attention to the diagnosis of acid–base derangement by means of plasma $[\text{HCO}_3^-]$ and lactate concentration in panic disorder patients.

Conclusions. These results suggest that the compensatory metabolic response to acute respiratory alkalosis is exaggerated by increased lactic acid production in panic disorder patients. Here, we call attention to the diagnosis of acid–base derangement by means of plasma $[\text{HCO}_3^-]$ and lactate concentration in panic disorder patients.

Keywords: lactic acid; panic disorder; respiratory alkalosis

Introduction

Acid–base derangements are encountered frequently in clinical situations, and many have life-threatening implications. The co-existence of respiratory alkalosis and high anion gap acidosis is commonly observed in critically serious patients, such as those with sepsis, salicylate intoxication and coexistence of renal failure and hepatic failure. Treatment depends on correctly identifying the acid–base disorder and repairing the underlying causal process. The severity of alkalaeemia produced by a reduction in arterial carbon dioxide tension (PaCO₂) in normal humans is ameliorated by buffer and renal responses that diminish plasma bicarbonate concentrations ([HCO₃⁻]). In contrast, these adjustments are complicated when hypocapnia develops into metabolic acidoses. To determine whether adaptation is appropriate for a given disorder, it is essential to know the expected renal response. The Δplasma bicarbonate slope ($\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$) is generally considered to be 0.2 mEq/L/mmHg in acute respiratory alkalosis.

Respiratory alkalosis is the most common acid–base derangement among seriously ill patients, and can be observed in hypoxicemic conditions, sepsis, metabolic disorders, drug intoxication, inappropriate mechanical ventilation, some psychiatric conditions and central nervous system disorders. Although hyperventilation in panic disorder patients is frequently encountered in outpatients and induces marked alkalaeaemia, the quantitative relationship between reduced PaCO₂ and plasma $[\text{HCO}_3^-]$ in acute respiratory alkalosis has not been studied in panic disorder patients. Therefore, we undertook this study to provide reference data for the compensatory metabolic changes in acute respiratory alkalosis in panic disorder patients.

Materials and methods

Acid–base disturbances during acute respiratory alkalosis were studied in 34 panic disorder patients (6 males and 28 females) ranging in age from 15 to 63 years (mean: 35.4 years). All subjects were free of metabolic, endocrine, cardiovascular, respiratory and renal diseases, as determined by history, physical examination and laboratory data. All blood samples were drawn from the radial or femoral artery into heparinized syringes on arrival at the emergency room. Arterial lactate, Na, K, Cl, pH, PaCO₂, PaO₂, anion gap and
plasma $[\text{HCO}_3^-]$ were measured using the ABL System 625
(Radiometer Medical, Copenhagen, Denmark). Corrected
plasma $[\text{HCO}_3^-]$ was calculated by the following equation;
corrected $[\text{HCO}_3^-]$ (mEq/L) = $[\text{HCO}_3^-]$ (mEq/L) + the
increase in plasma lactate (mmol/L).

**Results**

We examined the arterial acid–base composition and lactate
levels in panic disorder patients on arrival at the emergency
room. As a result of hyperventilation, arterial PaCO$_2$ de-
creased significantly to a range of 10.6–37.1 mmHg (mean;
23.5 ± 6.7). In association with degree of hypocapnia, ar-
terial pH increased to a range of 7.42–7.70 (mean; 7.57 ±
0.07), and plasma $[\text{HCO}_3^-]$ decreased to a range of 12.7–
26.2 mEq/L (mean; 20.9 ± 3.2). Plasma sodium con-
centration remained virtually within the normal range (135–
145 mEq/L). Plasma potassium concentration decreased
significantly (2.6–3.8 mEq/L).

The $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slope was 0.41 mEq/L/mmHg
(Figure 1), which was significantly steeper and virtually
twice as large as the previously reported formula [3–5].
The anion gap concentration increased to the range of
11.6–22.9 mEq/L (mean; 17.1 ± 2.7), and serum lactate
levels also increased to the range of 0.78–7.78 mmol/L
(mean; 2.59 ± 1.50). Serum lactate was significantly cor-
related with PaCO$_2$ ($P < 0.001$, Figure 2). Of particular
interest is that patients with severe hypocapnia (PaCO$_2 <$
16 mmHg) showed significantly higher plasma lactate
concentrations (mean; 4.6 ± 1.6 mmol/L) than those
with mild hypocapnia (PaCO$_2 >$ 16 mmHg) (mean;
2.0 ± 0.8 mmol/L, $P < 0.001$). Furthermore, the cor-
corrected $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slope was 0.26 mEq/L/mmHg
(Figure 3).

**Discussion**

The present study demonstrated that the compensatory
responses to acute respiratory alkalosis were exagger-
ated in panic disorder patients. In previous studies, the
secondary response to acute hypocapnia has been found
to be 0.20 mEq/L/mmHg, both in normal humans and
in dogs [3–5,7]. When compared with these background
data, the $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slope (0.41 mEq/L/mmHg)
was significantly steeper. The unexpected drop in plasma
$[\text{HCO}_3^-]$ may be explained by increased serum lactate.
Serum lactate levels were significantly correlated with
PaCO$_2$, and lactate-corrected $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$
slope 0.26 mEq/L/mmHg.

Respiratory alkalosis is caused by a process that leads to
a rise in pH due to a decrease in PaCO$_2$, primarily from in-
creased ventilation. Buffering constitutes the first response
in respiratory alkalosis [8]. In order to return the pH to-
wards normal, within 10 min after the onset of respiratory
alkalosis, H$^+$ ions are released from body buffers and then
combine with $\text{HCO}_3^-$, resulting in an appropriate decrease
in plasma $[\text{HCO}_3^-]$. These H$^+$ ions are primarily derived
from the protein, phosphate and haemoglobin buffers in the
cells. The second adaptive response in respiratory alkalosis
is induced by a renal mechanism, which consists of decreas-
ing the re-absorption of filtered $\text{HCO}_3^-$ and reducing the
generation of $\text{HCO}_3^-$. The process of renal adaptation is
The mechanisms accounting for the observed reduction in plasma \([HCO_3^-]\) during acute hypocapnia must have been largely of extrarenal origin, involving increased organic acid production and alkaline titration of nonbicarbonate buffers. We observed significant increases in serum lactate and anion gap in panic disorder patients. The increase in plasma lactate levels was responsible for almost 40% of the decrease in plasma \([HCO_3^-]\) (\(\Delta\text{lactate} = -0.39 \times \Delta[HCO_3^-]\), Figure 4). While simple acute respiratory alkalosis results in an increase in plasma lactate levels of <1 mEq/L [3,5], the higher plasma lactate observed in panic disorder patients might have resulted from an alkalemia-induced increase in cellular lactic acid production. Respiratory alkalosis produces a transient left shift in the haemoglobin–oxygen dissociation curve in red blood cells, decreasing delivery of oxygen to the tissues and favouring anaerobic glycolysis. The lactate production increased approximately 15-fold as the pH of the medium was increased from 5.7 to 7.8 [9]. In this phenomenon, the phosphofructokinase (PFK) reaction is critical in the enhancement of glycolysis by a rise in pH [9]. Alkalosis, however, induces glycolysis by directly activating enzymatic proteins, including PFK, in the glycolytic pathway in all tissues. In addition, alkalosis increases the tissue concentrations of all the measurable citric acid cycle intermediates, such as pyruvic acid and lactic acid [9]. Thus, the increase in lactic acid production appears to arise from tissue hypoxia secondary to vasoconstriction and increased haemoglobin affinity for oxygen. However, ten climbers, who reached the summit without supplementary oxygen, showed the same blood lactate level for a given work rate at a high altitude as at sea level [10].

The present study demonstrated that the adaptive response to acute respiratory alkalosis is exaggerated in panic disorder patients. The \(\Delta[HCO_3^-]/\Delta PaCO_2\) slope was 0.41 mEq/L/mmHg in acute respiratory alkalosis in panic disorder patients, which is about twice as large as previously reported for hypocapnia in non-panic disorder subjects including mountaineers [3–5,7]. The mechanisms for exaggerated compensatory metabolic response to acute respiratory alkalosis and increased lactic acid production in panic disorder patients remain unknown. It has been reported that panic disorder patients display a significantly greater increase in plasma lactate in response to hyperventilation than non-panic disorder subjects [11–13]. Furthermore, proton magnetic resonance spectroscopy shows greater rises in brain lactate level in panic disorder patients in response to hyperventilation [14]. This exaggerated lactic acid response to respiratory alkalosis may play an important role in the significant decrease in plasma \([HCO_3^-]\).

It has been reported that some panic disorder patients have a chronic, subtle respiratory alkalosis and acutely increase respiration when stressed [15]. Therefore, acute or chronic respiratory alkalosis may be one of the mechanisms for the exaggerated lactic acid production. Madias et al. [2] demonstrated that dogs with chronic metabolic alkalosis exhibit a large fall in plasma \([HCO_3^-]\) \((\Delta[HCO_3^-]/\Delta PaCO_2\) slope: 0.43) during acute hypocapnia, and that the plasma lactate concentration increased from 2.4 to 4.4 mEq/L. These results were similar to our observations in panic disorder patients, suggesting that some panic disorder patients are in a steady state of chronic alkalosis at baseline.

We demonstrated that patients with severe hypocapnia show significantly higher plasma lactate concentrations than those with mild hypocapnia, and that the corrected \(\Delta[HCO_3^-]/\Delta PaCO_2\) slope was 0.26 mEq/L/mmHg, which fits the previously proposed formula in acute respiratory alkalosis. As the coexistence of respiratory alkalosis and high anion gap acidosis is commonly observed in critically serious patients, the exaggerated compensatory metabolic response to acute respiratory alkalosis in panic disorder patients may mislead the diagnosis and treatment in clinical setting. Therefore, we would like to propose a new formula to exclude the life-threatening diseases. Further studies are necessary to evaluate whether the lactate increase is a directly compensatory action against an exaggerated brain pH response in panic disorder patients or a byproduct of another process affected by acid–base perturbation. In conclusion, the increase in plasma lactate levels accounted for the striking decrease in plasma \([HCO_3^-]\) observed in panic disorder patients. Examination of the plasma lactate levels in panic disorder patients appears to be useful in identifying acid–base derangements. In addition, we would like to propose a new formula for acute respiratory alkalosis in panic disorder patients: \(\Delta[HCO_3^-]/\Delta PaCO_2\) slope of 0.41 mEq/L/mmHg and a lactate-corrected \(\Delta[HCO_3^-]/\Delta PaCO_2\) slope of 0.26 mEq/L/mmHg.

Conflict of interest statement. None declared.

References


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