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 alkalaemia is ameliorated by a decrease in plasma [HCO3−] 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 [HCO3−] sometimes surpasses the expectation calculated from the above formula. The quantitative relationship between reduced PaCO2 and plasma [HCO3−] 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 [HCO3−] and lactate on arrival at the emergency room.

Results. For each decrease of 1 mmHg in PaCO2, plasma [HCO3−] decreased by 0.41 mEq/L. During hypnotic, 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 objective was to provide reference data for the compensatory metabolic changes in acute respiratory alkalosis 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 derangements by means of plasma [HCO3−] 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 [1]. Treatment depends on correctly identifying the acid–base disorder and repairing the underlying causal process. The severity of alkalaemia 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−]) [2]. In contrast, these adjustments are complicated when hypocapnia develops into metabolic acidosis. To determine whether adaptation is appropriate for a given disorder, it is essential to know the expected renal response. The Δplasma bicarbonate slope (Δ[HCO3−]/ΔPaCO2) is generally considered to be 0.2 mEq/L/mmHg in acute respiratory alkalosis [3–5].

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 [6]. Although hyperventilation in panic disorder patients is frequently encountered in outpatients and induces marked alkalaemia, the quantitative relationship between reduced PaCO2 and plasma [HCO3−] 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 \(\text{PaCO}_2\) decreased significantly to a range of 10.6–37.1 mmHg (mean; 23.5 ± 6.7). In association with degree of hypocapnia, arterial 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 concentration 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 correlated with \(\text{PaCO}_2\) \((P < 0.001, \text{Figure 2})\). Of particular interest is that patients with severe hypocapnia (\(\text{PaCO}_2 < 16 \text{ mmHg}\)) showed significantly higher plasma lactate concentrations (mean; 4.6 ± 1.6 mmol/L) than those with mild hypocapnia (\(\text{PaCO}_2 > 16 \text{ mmHg}\)) (mean; 2.0 ± 0.8 mmol/L, \(P < 0.001\)). Furthermore, the 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 exaggerated 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 \(\text{PaCO}_2\), 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 \(\text{PaCO}_2\), primarily from increased ventilation. Buffering constitutes the first response in respiratory alkalosis \([8]\). In order to return the pH towards normal, within 10 min after the onset of respiratory alkalosis, \(\text{H}^+\) ions are released from body buffers and then combine with \([\text{HCO}_3^-]\), resulting in an appropriate decrease in plasma \([\text{HCO}_3^-]\). These \(\text{H}^+\) 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 decreasing the re-absorption of filtered \([\text{HCO}_3^-]\) and reducing the generation of \([\text{HCO}_3^-]\). The process of renal adaptation is
response to acute respiratory alkalosis is exaggerated in
who reached the summit without supplementary oxygen,
haemoglobin affinity for oxygen. However, ten climbers,
sue hypoxia secondary to vasoconstriction and increased
diates, such as pyruvic acid and lactic acid [9]. Thus, the
concentrations of all the measurable citric acid cycle interme-
tissues. In addition, alkalosis increases the tissue con-
matic proteins, including PFK, in the glycolytic pathway in
however, induces glycolysis by directly activating enzy-
enhancement of glycolysis by a rise in pH [9]. Alkalosis,
the phosphofructokinase (PFK) reaction is critical in the
was increased from 5.7 to 7.8 [9]. In this phenomenon,
creased approximately 15-fold as the pH of the medium
crease in plasma lactate in response to hyperventilation than
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 [HCO3−].
It has been reported that some panic disorder patients
have a chronic, subtle respiratory alkalosis and acutely in-
crease 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 ex-
hibit a large fall in plasma [HCO3−] (Δ[HCO3−]/ΔPaCO2
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 dis-
order 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
Δ[HCO3−]/ΔPaCO2 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 in-
crease is a directly compensatory action against an ex-
aggerated brain pH response in panic disorder patients
or a byproduct of another process affected by acid–base
perturbation. In conclusion, the increase in plasma lac-
tate levels accounted for the striking decrease in plasma
[HCO3−] observed in panic disorder patients. Examina-
tion of the plasma lactate levels in panic disorder patients
appears to be useful in identifying acid–base derange-
ments. In addition, we would like to propose a new for-
ma for acute respiratory alkalosis in panic disorder pa-
tients: a Δ[HCO3−]/ΔPaCO2 slope of 0.41 mEq/L/mmHg
and a lactate-corrected Δ[HCO3−]/ΔPaCO2 slope of
0.26 mEq/L/mmHg.

Conflict of interest statement. None declared.

References
1. Cohen JJ, Kassirer JP. Acid-base metabolism. In: Maxwell MH, Klee-
man CR (eds). Clinical Disorders of Fluid and Electrolyte Metabolism.
2. Madias NE, Cohen JJ, Adrogue HJ. Influence of acute and chronic
respiratory alkalosis on preexisting chronic metabolic alkalosis.
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