Respiratory alkalosis is the most frequent acid-base disturbance encountered in clinical practice. This is particularly true in critically ill patients, for whom the degree of hypocapnia directly correlates with adverse outcomes. Although this acid-base disturbance often is considered benign, evidence suggests that the alkalemia of primary hypocapnia can cause clinically significant decreases in tissue oxygen delivery. Mild respiratory alkalosis often serves as a marker of an underlying disease and may not require therapeutic intervention. In contrast, severe respiratory alkalosis should be approached with a sense of urgency and be aggressively corrected.


INDEX WORDS: Respiratory alkalosis; hyperventilation; alkalemia; hypocapnia.

INTRODUCTION

Respiratory alkalosis is a common acid-base disturbance. Although often considered benign by many clinicians, it can be associated with a significant increase in mortality. Therefore, recognition of its presence, elucidation of its cause, and initiation of therapy is important to ensure a good clinical outcome.

The level of arterial carbon dioxide tension (PaCO₂) normally is maintained at 35-45 mm Hg (at sea level). The terms hypocapnia and hypercapnia refer to decreases and increases less than and more than the normal value, respectively, and can be primary or secondary. Primary hypocapnia refers to a reduction in carbon dioxide tension with subsequent alkalization of body fluids and is synonymous with respiratory alkalosis.

PaCO₂ is <35 mm Hg in patients with a simple respiratory alkalosis. In patients with a primary metabolic alkalosis, an element of respiratory alkalosis may still be present when PaCO₂ is normal or increased, but still lower than the value considered appropriate as a compensatory response. Respiratory alkalosis should be distinguished from secondary hypocapnia, the latter condition being a compensatory response to metabolic acidosis. In this setting, if the decrease in PaCO₂ is greater than expected, coexisting respiratory alkalosis may be present.

CASE REPORT

Clinical History and Initial Laboratory Data

A 34-year-old man with recently diagnosed HIV (human immunodeficiency virus) infection presents with increasing shortness of breath. He was initiated on highly active retroviral therapy, and daily trimethoprim-sulfamethoxazole and weekly azithromycin were prescribed for antibiotic prophylaxis. Two weeks prior to admission, trimethoprim-sulfamethoxazole was replaced with daily dapsone secondary to development of a rash. Over the last 5 days, he noted the gradual onset of dyspnea on exertion that has progressively increased in severity. Physical examination shows blood pressure of 110/70 mm Hg, pulse rate of 104 beats/min, and respiratory rate of 22 breaths/min. His lips are a dark grayish-brown. The lungs are clear to auscultation. Laboratory examination shows the following values: serum sodium, 138 mEq/L (138 mmol/L); potassium, 4.2 mEq/L (4.2 mmol/L); chloride, 108 mEq/L (108 mmol/L); bicarbonate, 18 mEq/L (18 mmol/L); creatinine, 0.8 mg/dL (70.7 μmol/L); and estimated glomerular filtration rate, 135 mL/min/1.73 m² (2.25 mL/s/1.73 m²), calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation. The blood sample is brown.

Additional Investigations

Pulse oximetry on room air is 88%. An arterial blood gas on room air shows pH of 7.47, PaCO₂ of 28 mm Hg, PaO₂ of 110 mm Hg, and calculated oxygen saturation >95%. Methemoglobin concentration is 28% of total hemoglobin level, which was 13.4 g/dL (134 g/L).

Diagnosis

Respiratory alkalosis secondary to dapsone-induced methemoglobinemia.

Clinical Follow-up

The patient was treated with methylene blue (2 mg/kg given intravenously over 5 minutes), and 30 minutes later, pulse oximetry increased to 98% and methemoglobin level decreased to 6.4%.
Primarily by an involuntary increase in ventilation. Arterial oxygen content in this setting is achieved primarily in the carotid and aortic bodies, causing an increase in the depth and rate of breathing. The underlying mechanism when the basal metabolic rate is severely decreased, as in a patient with severe hypothyroidism or hypothermia. However, even in these circumstances, alveolar ventilation needs to be fixed (intubation with fixed ventilation) because the decrease in PaCO2 would reflexively decrease ventilation due to inhibitory chemoreceptor input to the respiratory center.

Increased ventilatory drive can be the result of input from a variety of anatomic sites, resulting in pulmonary hyperventilation and primary hypocapnia. Stimulatory input often originates in the lung, carotid, and aortic chemoreceptors; brainstem chemoreceptors; and other centers of the brain. In the setting of liver disease and sepsis, the response to carbon dioxide of the brain stem chemoreceptors is augmented. Pharmacologic agents, volition, and anxiety, among other influences, also may facilitate this response.

A key stimulus to pulmonary ventilation is hypoxemia. A healthy individual ascending to high altitude is illustrative of this effect. As altitude increases, barometric pressure decreases progressively, accompanied by a progressive decrease in Po2. Maintenance of arterial oxygen content in this setting is achieved primarily by an involuntary increase in ventilation. Arterial hypoxemia stimulates peripheral chemoreceptors primarily in the carotid and aortic bodies, causing an increase in the depth and rate of breathing. The reduction in alveolar Po2 and therefore PaO2 stimulates increased ventilation, thus causing respiratory alkalosis. At sea level, a decrease in PaCO2 normally would exert an inhibitory effect on respiration, causing PaCO2 and pH to return to normal levels. However, at altitude with hypoxia-driven hyperventilation, this inhibitory effect is overridden by central medullary chemoreceptors such that high levels of ventilation are maintained. The persistent increase in ventilation is partly dependent on the exit of bicarbonate from the cerebrospinal fluid, with subsequent lowering of pH, which in turn stimulates ventilation. Ventilation also is driven by sensitization of the carotid body to hypoxia during prolonged exposure to high altitude (Table 1).

In patients with cardiopulmonary disease, increased ventilation can be the result of input from nociceptive receptors (irritants), stretch receptors (pulmonary expansion and collapse), and juxtacapillary (J) receptors (capillary congestion; Box 1). Tissue hypoperfusion stimulates alveolar ventilation as a result of oxygen deprivation. In the setting of severe circulatory failure, arterial hypocapnia and alkalemia may coexist with venous and tissue hypercapnia and hypoxemia. In patients with cardiopulmonary disease, increased ventilation can be the result of input from nociceptive receptors (irritants), stretch receptors (pulmonary expansion and collapse), and juxtacapillary (J) receptors (capillary congestion; Box 1). Tissue hypoperfusion stimulates alveolar ventilation as a result of oxygen deprivation. In the setting of severe circulatory failure, arterial hypocapnia and alkalemia may coexist with venous and tissue hypercapnia and hypoxemia.

**Table 1. Arterial Blood Gas Measurements and Calculated Values of Gas Exchange in 4 Climbers at a High Elevation**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.53</td>
</tr>
<tr>
<td>PaO2 (mm Hg)</td>
<td>24.6</td>
</tr>
<tr>
<td>PacO2 (mm Hg)</td>
<td>13.3</td>
</tr>
<tr>
<td>HCO3 (mEq/L)</td>
<td>10.8</td>
</tr>
<tr>
<td>Lactate (mg/dL)</td>
<td>19.8</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>54</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>19.3</td>
</tr>
</tbody>
</table>

*Note: Measurements obtained from 4 climbers at 8,400 m during descent from the summit of Mt Everest. At the summit of Mt Everest, alveolar ventilation is increased approximately 5-fold. Conversion factors for units: lactate in mg/dL to mmol/L, ×0.111; Hb in g/dL to g/L, ×10. No conversion necessary for bicarbonate in mEq/L and mmol/L.*

*Abbreviations: Hb, hemoglobin; HCO3, bicarbonate; SaO2, arterial saturation.*

**DISCUSSION**

Respiratory alkalosis develops when alveolar ventilation is increased relative to carbon dioxide production. Under most circumstances, carbon dioxide production is relatively stable, such that hypocapnia usually is the result of increased carbon dioxide elimination. Decreased carbon dioxide production can be the underlying mechanism when the basal metabolic rate is severely decreased, as in a patient with severe hypothyroidism or hypothermia. However, even in these circumstances, alveolar ventilation needs to be fixed (intubation with fixed ventilation) because the decrease in PaCO2 would reflexively decrease ventilation due to inhibitory chemoreceptor input to the respiratory center.

Increased ventilatory drive can be the result of input from a variety of anatomic sites, resulting in pulmonary hyperventilation and primary hypocapnia. Stimulatory input often originates in the lung, carotid, and aortic chemoreceptors; brainstem chemoreceptors; and other centers of the brain. In the setting of liver disease and sepsis, the response to carbon dioxide of the brain stem chemoreceptors is augmented. Pharmacologic agents, volition, and anxiety, among other influences, also may facilitate this response.

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In patients with cardiopulmonary disease, increased ventilation can be the result of input from nociceptive receptors (irritants), stretch receptors (pulmonary expansion and collapse), and juxtacapillary (J) receptors (capillary congestion; Box 1). Tissue hypoperfusion stimulates alveolar ventilation as a result of oxygen deprivation. In the setting of severe circulatory failure, arterial hypocapnia and alkalemia may coexist with venous and tissue hypercapnia and hypoxemia.
acidemia. This situation arises when pulmonary perfusion and carbon dioxide delivery to the lungs are severely reduced, but alveolar ventilation is relatively well preserved. Large differences between arterial and mixed venous pH and PCO₂ are clues to this hemodynamic condition.

Increased ventilation can result from abnormalities in hemoglobin concentration or its capacity to transport and unload oxygen at the tissue level, as illustrated in the case report. Dapsone is metabolized in the liver to a hydroxylamine intermediate. This metabolite oxidizes the iron in hemoglobin from its ferrous (Fe²⁺) to its ferric (Fe³⁺) state. Ferric iron (Fe³⁺) binds oxygen ineffectively, while the remaining ferrous iron (Fe²⁺) binds oxygen with enhanced affinity. The combined effect of poor oxygen binding and decreased oxygen release leads to tissue hypoxia and cyanosis, providing a stimulus for increased ventilation. Methemoglobinemia should be suspected in patients who appear cyanotic but have PaO₂ sufficiently high that hemoglobin should be fully saturated. In addition, the oxygen saturation calculated from blood gas analysis is higher than the value obtained by pulse oximetry, giving rise to a saturation gap. Methylene blue reduces the iron in hemoglobin to its normal oxygen-carrying state. Methemoglobinemia has been the subject of a recent comprehensive review.

Primary hypocapnia is a frequent finding in patients with chronic liver disease. Massive ascites limiting respiratory excursion, hypoxemia due to hepatopulmonary syndrome, and direct effects of increased progesterone levels are causative factors. Systemic infection is a major cause of respiratory alkalosis. Bacterial toxins from Gram-negative organisms have a direct stimulatory effect on central chemoreceptors, accounting at least in part for the hyperventilation commonly observed in patients with sepsis. For this reason, Gram-negative bacteremia should be excluded in hospitalized patients with unexplained respiratory alkalosis. Primary hypocapnia is a frequent finding in patients with salicylate intoxication. High progesterone levels are the primary cause of increased respiration in normal pregnancy.

The use of acetate as the buffer in dialysate is a cause of decreased PaCO₂. Because the acetate dialysate lacks bicarbonate, there is diffusion of bicarbonate from blood to dialysate. However, the pH of blood exiting the dialysis cartridge does not decrease because carbon dioxide also diffuses from blood to dialysate. In response to the diffusive loss of soluble carbon dioxide and with the aim of maintaining normal blood carbon dioxide concentration, pulmonary hypoventilation occurs, which results in hypoxemia. Diffusive loss of carbon dioxide also occurs during extracorporeal membrane oxygenation and with heart-lung machines; however, simultaneous oxygenation of the blood prevents hypoxemia from developing with these procedures.

Acute-onset respiratory alkalosis can cause light-headedness, palpitations, and paresthesias of the extremities and circumoral area. Alterations implicated in the clinical manifestations of this acid-base disorder include a decrease in cerebral blood flow, reduced acidity of body fluids, a pH-induced leftward shift of the oxyhemoglobin dissociation curve, and decreased ionized calcium (Box 1). In certain situations, alkalemia can be a significant contributor to morbidity and mortality. In patients with pH >7.48, a direct connection has been observed between increasing blood pH and hospital mortality.

Alkalosis can decrease tissue oxygen delivery through at least 2 mechanisms. First, by the Bohr effect, increased pH causes the oxygen dissociation curve of hemoglobin to shift, decreasing hemoglobin’s ability to release oxygen in peripheral tissues. Accordingly, even when there are no changes in blood flow, alkalemia can bring about a noticeable decrease in the delivery of oxygen to tissues. Second, increased pH associated with primary hypocapnia leads to vasoconstriction and decreased perfusion of the brain, heart, and peripheral circulation. Whether changes in pH resulting from metabolic alkalosis have the same effect is not clear; however, in vitro studies have shown that pH is the critical determinant of vascular smooth muscle tone regardless of whether pH is altered by changes in carbon dioxide or bicarbonate concentration.

Although often treated as a benign condition, in certain settings alkalosis may cause clinical tissue hypoxia. Acute hypocapnia can precipitate ischemic electrocardiographic changes, cardiac arrhythmias, and angina in patients with coronary artery disease. In patients with an underlying predisposition, hyperventilation can precipitate angiographically documented coronary artery spasm accompanied by ST-segment elevation and chest pain. Cardiac arrhythmias may be less responsive to pharmacologic therapy in the setting of alkalosis. Acute and severe hypocapnia in mechanically ventilated patients has been associated with reductions in cardiac output and arteriolar vasoconstriction. These hemodynamic changes can be a cause of tissue hypoperfusion, as evidenced by increased lactate production.

Acute hypocapnia decreases cerebral blood flow and has been used as a strategy to treat brain edema resulting from neurosurgical procedures, head trauma, meningitis, and encephalitis. However, the utility of this strategy has been called into question because the benefit of hypocapnia’s effect on intracranial pressure...
may be offset by the resulting reduction in oxygen supply. In addition, hypocapnia elevates cerebral oxygen demand by increasing seizure activity, neuronal excitability, and anaerobic metabolism. A quick correction of severe hypocapnia causes vasodilation and can be the first clue to the presence of a primary metabolic mechanism in the setting of a primary metabolic acidosis.

Respiratory alkalosis is accompanied by characteristic changes in plasma electrolyte composition. An acute decrease in PaCO2 causes plasma and red blood cell carbon dioxide tensions to decrease. In response, albumin and other nonbicarbonate buffers release hydrogen ion to decrease plasma bicarbonate concentration. Within red blood cells, the decrease in carbon dioxide causes hemoglobin to release hydrogen ion, and red blood cell bicarbonate concentration also decreases. Plasma bicarbonate will enter the red blood cell in exchange for chloride. This bicarbonate-chloride shift accounts for the small initial compensatory response in acute respiratory alkalosis in which bicarbonate concentration decreases by 2 mEq/L for every 10-mm Hg decrease in PaCO2 and is completed within a matter of minutes.

In chronic respiratory alkalosis, renal bicarbonate reabsorptive capacity decreases and there is a transient bicarbonate diuresis. This process takes 2-3 days to fully manifest. When a new steady state is achieved, bicarbonate concentration will have decreased by 5 mEq/L for each 10-mm Hg decrease in PaCO2. In order to defend extracellular fluid volume in the setting of increased urinary loss of sodium bicarbonate, the kidney retains sodium chloride. These changes are reflected in serum electrolyte levels of patients with chronic respiratory alkalosis in which chloride level typically is increased with respect to serum sodium concentration. In the absence of an arterial blood gas, the findings of increased serum chloride and decreased bicarbonate levels can be diagnosed erroneously as hyperchloremic metabolic acidosis.

Another characteristic finding is an increase of 3-5 mEq/L in serum anion gap. The increased gap primarily is due to the greater negative charge on serum albumin. Although small in magnitude, plasma lactate level may be increased due to increased production as a result of a stimulatory effect of high pH on phosphofructokinase, the rate-limiting step in the glycolytic pathway. Increased glycolysis also is the likely mechanism for cellular uptake of phosphate and hypophosphatemia, another manifestation of acute hyperventilation. Acute respiratory alkalosis also is associated with a trivial decrease in serum potassium level due to intracellular shift. However, disturbances in serum potassium and phosphate levels are not features of chronic hypcapnia.

The diagnosis of respiratory alkalosis is made by evaluating the patient’s history, performing a physical examination, and obtaining laboratory data, including blood gas analysis (Box 2). Hyperpnea or Kussmaul breathing can be detected on physical examination and can be the first clue to the presence of a primary respiratory alkalosis or compensatory respiratory mechanism in the setting of a primary metabolic acidosis.

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The treatment of primary respiratory alkalosis begins with addressing the underlying cause when possible (Box 3). Administration of oxygen to those with hypoxemia or returning the patient to lower altitudes can reverse the respiratory alkalosis that arises in these settings. Reassurance should be provided to the patient with anxiety-hyperventilation syndrome. Breathing into a paper bag creates a closed system such that PCO2 will increase each time the patient takes a breath. This technique can lead to improvement in symptoms as the hypcapnia slowly corrects.

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**Box 2. Manifestations of Respiratory Alkalosis**

- Laboratory
  - Hypokalemia
  - Hypophosphatemia
  - Increased anion gap
  - Decreased ionized calcium (due to increased protein binding)
  - Increased serum chloride and decreased serum bicarbonate concentration
- Cardiovascular
  - Coronary vasospasm with potential to precipitation angina
  - Arrhythmias
- Central nervous system
  - Neuromuscular irritability, confusion, lightheadedness
  - Seizure
- Pulmonary
  - Increased airway resistance
  - Decreased lung compliance
  - Increased pulmonary capillary permeability

**Box 3. Treatment of Respiratory Alkalosis**

- Correct underlying cause
- Hypoxemia
  - Supplemental oxygen
  - Return to lower altitude
- Mechanical ventilation
  - Increase dead space in ventilatory circuit
  - Sedation and/or use of paralytic agent
- Psychogenic hyperventilation
  - Rebreathe into closed system (paper bag)
  - Antianxiety medications, sedatives, when indicated
- Salicylate toxicity
  - Urinary alkalinization
  - Hemodialysis with severe clinical toxicity or level >800 mg/L

*Note: Conversion factor for units: salicylate in mg/L to mmol/L, \( \times 0.00724 \).*
creased ventilation decreases PaCO₂ and the result is respiratory center. When an overdose occurs, in- 
perfusion. 
worsen intracranial pressure by increasing cerebral 
cautious because increasing PaCO₂ potentially can 
alkalosis can be associated with arrhythmias, particu-
lation to treatment is warranted because respiratory 
strategy to increase PaCO₂. Sedation and muscle relax-
inspired carbon dioxide tension can be used as a 
dead space of the ventilator circuit or increasing 
tive measures fail to correct the problem.

On occasion, sedatives may be needed when conserva-
tive measures fail to correct the problem. 
In mechanically ventilated patients, increasing the 
deep space of the ventilator circuit or increasing 
inspired carbon dioxide tension can be used as a 
strategy to increase PaCO₂. Sedation and muscle relax-
ants also can be used in this situation. Prompt atten-
tion to treatment is warranted because respiratory 
alkalosis can be associated with arrhythmias, particu-
arly in patients with underlying coronary disease. In 
patients with brain injury, one needs to be more 
cautious because increasing PaCO₂ potentially can 
worsen intracranial pressure by increasing cerebral 
perfusion.

Aspirin (acetylsalicylic acid) directly stimulates the 
respiratory center. When an overdose occurs, 
increased ventilation decreases PaCO₂ and the result is respiratory alkalosis. Often there also is a component of anion gap metabolic acidosis resulting from the increased production of lactate and ketoads. The first step in therapy is to resolve systemic acidemia if present and alkalinize the urine pH.\(^\text{18}\) Correcting systemic acidemia facilitates formation of the ionized fraction of salicylic acid, thereby lessening accumulation in the central nervous system. Likewise, an alkaline urine pH favors increased urinary excretion because the tubule poorly reabsorbs the ionized fraction of the drug. If serum concentrations of salicylate are >800 mg/L (>5.8 mmol/L) or there is severe clinical toxicity, hemodialysis is recommended to expedite removal of the drug from the body.

To summarize, respiratory alkalosis is a common acid-base disturbance that often serves as a signal to the presence of an underlying condition requiring specific therapy. Severe respiratory alkalosis should be approached with a sense of urgency and aggressively corrected. Key take home points are listed in Box 4, and for a fuller discussion, also see.\(^\text{19}\)

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**REFERENCES**