

# Acid–Base Disorders

Mara Nitu, MD,\* Greg Montgomery, MD,<sup>†</sup> Howard Eigen, MD<sup>§</sup>

Author Disclosure  
Drs Nitu, Montgomery, and Eigen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

**Objectives** After completing this article, readers should be able to:

1. Understand the mechanisms for regulating acid–base physiology.
2. Know the differential diagnosis of metabolic acidosis associated with high anion gap and plan for initial management.
3. Know the differential diagnosis of normal anion gap metabolic acidosis.
4. Describe pulmonary compensatory changes in metabolic acidosis and alkalosis.
5. Understand how various diuretics can lead to acid–base imbalance.
6. Describe renal compensatory changes in respiratory acidosis and alkalosis.

## Case Study

A 16-year-old girl who has no significant previous medical history presents to the emergency department with a 4-day history of nausea, vomiting, fever, chills, diarrhea, leg cramps, abdominal pain, and headaches. She is finishing her menstrual period and arrives with a tampon in place, which she reports that she inserted yesterday. Her vital signs include a heart rate of 165 beats/min, respiratory rate of 28 breaths/min, blood pressure 65/30 mm Hg, and oxygen saturation of 100% on 4 L/min of oxygen. The most likely diagnosis for this patient is toxic shock syndrome, which was later confirmed with a positive antibody test.

The initial arterial blood gas (ABG) values are:

- pH, 7.24
- Partial pressure of oxygen (P<sub>O<sub>2</sub></sub>), 138 mm Hg
- Partial pressure of carbon dioxide (P<sub>CO<sub>2</sub></sub>), 19 mm Hg
- Bicarbonate (HCO<sub>3</sub><sup>-</sup>), 8 mEq/L (8 mmol/L)
- Base excess (BE), -18 mEq/L (18 mmol/L)

Such findings are suggestive of metabolic acidosis with respiratory compensation.

Further laboratory results are:

- Serum sodium (Na<sup>+</sup>), 133 mEq/L (133 mmol/L)
- Potassium (K<sup>+</sup>), 4.2 mEq/L (4.2 mmol/L)
- Chloride (Cl<sup>-</sup>), 109 mEq/L (109 mmol/L)
- HCO<sub>3</sub><sup>-</sup>, 12 mEq/L (12 mmol/L)
- Anion gap (AG), 12 mEq/L (12 mmol/L)
- Blood urea nitrogen (BUN), 49 mg/dL (17.5 mmol/L)
- Creatinine, 3.96 mg/dL (350 μmol/L)
- Calcium, 5.2 mg/dL (1.3 mmol/L)
- Albumin, 2.0 g/dL (20 g/L)

The apparently normal AG is misleading. After correcting the AG for hypoalbuminemia, the adjusted AG is 17 mEq/L (17 mmol/L).

Lactic acidemia due to shock, one of the likely causes for

## Abbreviations

<b>ABG:</b>	arterial blood gas
<b>AG:</b>	anion gap
<b>BE:</b>	base excess
<b>BUN:</b>	blood urea nitrogen
<b>Ca<sup>2+</sup>:</b>	calcium
<b>Cl<sup>-</sup>:</b>	chloride
<b>CNS:</b>	central nervous system
<b>DKA:</b>	diabetic ketoacidosis
<b>GI:</b>	gastrointestinal
<b>H<sup>+</sup>:</b>	hydrogen
<b>HCO<sub>3</sub><sup>-</sup>:</b>	bicarbonate
<b>K<sup>+</sup>:</b>	potassium
<b>Mg<sup>2+</sup>:</b>	magnesium
<b>Na<sup>+</sup>:</b>	sodium
<b>NH<sub>3</sub>:</b>	ammonia
<b>NH<sub>4</sub>:</b>	ammonium
<b>P<sub>CO<sub>2</sub></sub>:</b>	partial pressure of carbon dioxide
<b>P<sub>O<sub>2</sub></sub>:</b>	partial pressure of oxygen
<b>RTA:</b>	renal tubular acidosis

\*Associate Professor of Clinical Pediatrics, Section of Pediatric Pulmonology, Critical Care and Allergy; Medical Director, PICU/ Riley Hospital for Children; Medical Co-Director of Lifeline Transport Team, Indianapolis, IN.

<sup>†</sup>Assistant Professor of Clinical Pediatrics, Section of Pulmonology, Critical Care and Allergy; Medical Director, Pediatric Bronchoscopy Laboratory, James Whitcomb Riley Hospital for Children, Indianapolis, IN.

<sup>§</sup>Billie Lou Wood Professor of Pediatrics, Associate Chairman for Clinical Affairs; Director, Section of Pediatric Pulmonology, Critical Care and Allergy, James Whitcomb Riley Hospital for Children, Indianapolis, IN.

increased AG metabolic acidosis, is confirmed by a high serum lactate value of 6.9 mg/dL (0.8 mmol/L). One hour later, the ABG values are:

- pH, 7.06
- $P_{O_2}$ , 63 mm Hg
- $P_{CO_2}$ , 47 mm Hg
- $HCO_3^-$ , 13.2 mEq/L (13.2 mmol/L)
- BE, -16 mEq/L (16 mmol/L)

This ABG panel reveals metabolic acidosis without respiratory compensation due to developing respiratory failure.

## Introduction

The loss of acid-base balance is an expression of various conditions encountered frequently in clinical practice. Changes in hydrogen ion concentration can lead to unraveling of the protein tertiary structure, thereby causing enzyme dysfunction, enzyme loss, and cell death. Understanding the physiology behind various disturbances in acid-base balance is necessary for determining a correct diagnosis and management plan.

Maintaining acid-base homeostasis involves the lungs, kidneys, and a very complex system of buffers, all aiming to maintain the normal pH (7.35 to 7.45) of the arterial blood. Lowering the arterial pH below 7.35 is termed acidosis, and an increase of the arterial pH above 7.45 constitutes alkalosis.

Metabolic acidosis is associated with a low pH and low  $HCO_3^-$  concentration. Metabolic alkalosis is associated with a high pH and high  $HCO_3^-$  concentration. Respiratory acidosis is associated with a low pH and high  $PCO_2$ . Respiratory alkalosis is associated with a high pH and low  $PCO_2$  (Fig. 1).

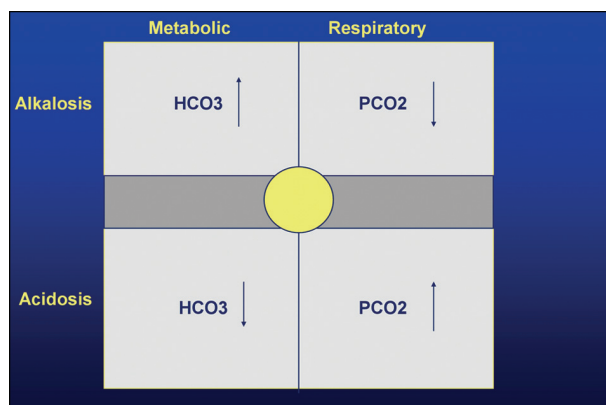


Figure 1. Acid-base changes in metabolic versus respiratory disorders.

Each acid-base disorder leads to countering respiratory or renal compensatory responses that attempt to normalize the pH. In metabolic acidosis, for example, ventilation is increased, resulting in a decrease in  $PCO_2$ , which tends to raise the pH toward normal. These compensatory attempts never overshoot correcting the pH (Figs. 2 and 3). The process of acid-base regulation involves the respiratory system (controls  $PCO_2$ ), kidneys (regulates plasma  $HCO_3^-$  by changes in acid excretion), and a very complex system of extracellular and intracellular buffers.

## The Respiratory System in Acid-Base Balance

The respiratory system contributes to acid-base balance via timely adjustments in alveolar minute ventilation that maintain systemic acid-base equilibrium in response to alterations in systemic pH and arterial  $PCO_2$ . Systemic pH is monitored by central chemoreceptors on the ventrolateral surface of the medulla oblongata and arterial  $PCO_2$  (as well as arterial  $PO_2$ ) by peripheral chemoreceptors located at the carotid and aortic bodies. These chemoreceptors act through central respiratory control centers in the pons and medulla to coordinate the respiratory muscle efforts of inhalation and exhalation, leading to adjustments in both components of minute ventilation: tidal volume and respiratory cycle frequency. Lung-mediated changes in arterial  $PCO_2$  can lead to rapid alteration in systemic hydrogen ions ( $H^+$ ) because  $CO_2$  is lipid-soluble and may readily cross cell membranes according to the following equation:  $H^+ + HCO_3^- \leftrightarrow H_2CO_3$  (carbonic acid)  $\leftrightarrow CO_2 + H_2O$  (water). Under normal physiologic conditions, this process allows for tight control of arterial  $PCO_2$  near 40 mm Hg.

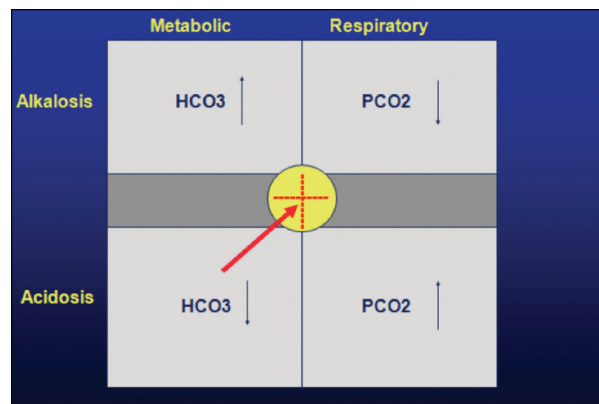


Figure 2. Primary metabolic acidosis with subsequent respiratory alkalosis compensation. The red arrow does not cross into the alkalosis range, reflecting the concept that overcompensation never occurs.

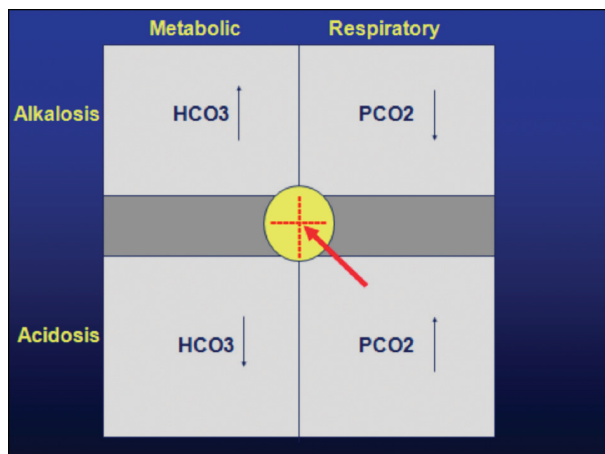


Figure 3. Primary respiratory acidosis with subsequent metabolic alkalosis compensation. The red arrow does not cross into the alkalosis range, reflecting the concept that overcompensation never occurs.

### The Kidneys in Acid-Base Balance

The kidney's role in acid-base balance consists of reabsorbing filtered  $\text{HCO}_3^-$  and excreting the daily acid load derived principally from the metabolism of sulfur-containing amino acids. Ninety percent of filtered  $\text{HCO}_3^-$  is reabsorbed in the proximal tubules, primarily by  $\text{Na}^+$ - $\text{H}^+$  exchange, and the remaining 10% is reabsorbed in the distal nephron, primarily via hydrogen secretion by a proton pump ( $\text{H}^+$ -ATPase). Under normal conditions, no  $\text{HCO}_3^-$  is present in the final urine.

The excretion of the daily  $\text{H}^+$  load occurs in the distal tubule. Once excreted in the urine, the  $\text{H}^+$  must be bound to a buffer to avoid excessive urine acidification and promote further excretion. The two primary buffers in the urine are ammonia ( $\text{NH}_3$ ), which is excreted and measured as ammonium ( $\text{NH}_4^+$ ) and phosphate (referred to and measured as titratable acidity). The kidneys synthesize and excrete  $\text{NH}_3$ , which combines with  $\text{H}^+$  excreted by the collecting duct cells to form  $\text{NH}_4^+$ :  $\text{H}^+ + \text{NH}_3 = \text{NH}_4^+$ .  $\text{NH}_3$  diffuses freely across membranes;  $\text{NH}_4^+$  does not. Failure to produce and excrete sufficient  $\text{NH}_4^+$ , therefore, leads to the development of metabolic acidosis.

### Extracellular and Intracellular Buffers in Acid-Base Balance

The most important buffer in the extracellular fluid is  $\text{HCO}_3^-$ , due both to its relatively high concentration and its ability to vary  $\text{PCO}_2$  via changes in alveolar ventilation. Chemoreceptor analysis of arterial pH and  $\text{PCO}_2$  allows for centrally mediated adjustments in minute ven-

tilation to maintain arterial  $\text{PCO}_2$ . The  $\text{HCO}_3^-$  interacts with  $\text{H}^+$ , as demonstrated in the following formula:  $\text{H}^+ + \text{HCO}_3^- \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{CO}_2 + \text{H}_2\text{O}$ . This reaction serves as the basis for the Henderson-Hasselbalch equation:  $\text{pH} = 6.1 + \log (\text{HCO}_3^- / 0.03 \times \text{PCO}_2)$ . Although this equation describes a patient's acid-base status, it does not provide insight into the mechanism of the acid-base disorder.

The Henderson-Hasselbalch equation lists  $\text{PCO}_2$  and  $\text{HCO}_3^-$  as independent predictors of acid-base balance, but in reality they are interdependent (as suggested by the chemical reaction  $\text{H}^+ + \text{HCO}_3^-$  described previously). Furthermore, the Henderson-Hasselbalch equation does not account for other important nonbicarbonate buffers present in the body, such as the primary intracellular buffers of proteins, organic and inorganic phosphates, and hemoglobin. In addition, bone is an important site for buffering of acid and base loads.

### Laboratory Assessment of Acid-Base Balance

Acid-base balance is assessed by blood gas analysis and serum measurement of several important electrolytes, leading to the calculation of the AG. Blood gas analyzers measure the pH and the  $\text{PCO}_2$  directly. The  $\text{HCO}_3^-$  value is calculated from the Henderson-Hasselbalch equation. The BE value also is calculated as the amount of base/acid that should be added to a sample of whole blood in vitro to restore the pH to 7.40 while the  $\text{PCO}_2$  is held at 40 mm Hg. The  $\text{PCO}_2$  not only points to the type of disorder (respiratory or metabolic) but also corresponds to the magnitude of the disorder.

The AG method was developed to include other nonbicarbonate buffers in the analysis. Based on the principle of electroneutrality, the sum of the positive charges should equal the sum of the negative charges as follows:  $\text{Na}^+ + \text{K}^+ + \text{Mg}^{2+}$  (magnesium) +  $\text{Ca}^{2+}$  (calcium) +  $\text{H}^+ = \text{Cl}^- + \text{HCO}_3^- + \text{protein}^- + \text{PO}_4^{3-}$  (phosphate) +  $\text{OH}^- + \text{SO}_4^{2-}$  (sulfate) +  $\text{CO}_3^{2-}$  + conjugate base<sup>-</sup>. Sodium, chloride, and  $\text{HCO}_3^-$  are measured easily in the serum. Therefore, the AG is calculated by the formula  $\text{AG} = \{\text{Na}^+\} - \{\text{Cl}^- + \text{HCO}_3^-\}$ . A normal AG is  $12 \pm 2$  mEq/L (12 mmol/L). Some clinicians and some published reports include potassium as a measured cation in the calculation of AG, which raises the normal value by 4 mEq/L (4 mmol/L).

The AG is defined as the difference between the unmeasured plasma anions and the unmeasured plasma cations. Clinically, an elevated AG is believed to reflect an increase of unmeasured anions and, therefore, a metabolic acidosis. This concept is explained by the fact that unmeasured cations ( $\text{Mg}^{2+} + \text{Ca}^{2+} + \text{H}^+$ ) are more

tightly controlled and the unmeasured anions have a greater tendency to fluctuate. Theoretically, the AG also can increase following a decrease in serum  $K^+$ ,  $Ca^{2+}$ , or  $Mg^{2+}$ , but the normal concentration of these cations is so low that a reduction does not have a significant clinical impact on the AG.

In general, these principles hold true for the previously healthy individual who develops an acute illness. However, for the critically ill host whose plasma protein concentrations are greatly reduced, the low protein values hide an associated increase in unmeasured anions. Without the correction for hypoalbuminemia, it is possible to overlook a true high AG acidosis, mistakenly assuming it to be a normal AG acidosis.

According to the Figge formula, each 1-g/dL reduction in the serum albumin concentration is expected to reduce the AG by 2.5 mEq/L:

$$\text{Adjusted AG} = \text{observed AG} + (2.5 \times [\text{normal albumin} - \text{observed albumin}])$$

## Metabolic Acid-Base Disturbance

### Metabolic Acidosis

Metabolic acidosis is defined as an acid-base imbalance that leads to anion excess (low  $HCO_3^-$  concentration) and subsequently to an arterial pH below 7.35. Several mechanisms can lead to metabolic acidosis: excess acid production, increased acid intake, decreased renal acid excretion, increased  $HCO_3^-$  loss from the gastrointestinal (GI) tract, and excess  $HCO_3^-$  excretion in the kidney.

For a patient who has intact respiratory function, developing metabolic acidosis leads to respiratory compensation by hyperventilation. Each 1-mEq/L reduction in plasma  $HCO_3^-$  concentration prompts a 1.2-mm Hg compensatory fall in the  $PCO_2$ . Clinically, the patient's respiratory rate increases within the first hour of the onset of metabolic acidosis, and respiratory compensation is achieved within 24 hours. Failure of the respiratory system to compensate for metabolic acidosis is an ominous sign that should trigger careful evaluation of the patient's mental status and cardiorespiratory function.

Calculating the AG is a very useful initial step in diagnosing various causes of metabolic acidosis.

### Metabolic Acidosis With Normal Anion Gap

Metabolic acidosis with normal AG reflects an imbalance of the *measured* plasma anions and cations. According to the formula:  $AG = Na^+ - (Cl^- + HCO_3^-)$ , metabolic acidosis with normal AG can be explained by excessive loss of  $HCO_3^-$  (in the stool or in the urine) or by inability to excrete hydrogen ions. Table 1 lists the most

## Table 1. Causes of Normal Anion Gap Metabolic Acidosis

### Disorders of the Gastrointestinal (GI) Tract Leading To Excessive Bicarbonate Loss

- Diarrhea: the leading cause of normal anion gap metabolic acidosis in children
- Surgical procedures that lead to an anastomosis of the ureter with the GI tract, such as ureteroenterostomy/ ureterosigmoidostomy, due to bicarbonate loss in the intestine
- Pancreatic fistula

### Iatrogenic Hyperchloremic Metabolic Acidosis

- Result of excessive fluid resuscitation with 0.9% sodium chloride or excessive use of 3% sodium chloride to correct hyponatremia

### Renal Loss of Bicarbonate

- Renal tubular acidosis type II (proximal)
- Iatrogenic: carbonic anhydrase inhibitor (acetazolamide)
- Hyperparathyroidism
- Medications

- Acidifying agents: sodium chloride, potassium chloride, enteral supplements
- Magnesium chloride
- Cholestyramine
- Spironolactone

### Hypoaldosteronism

frequent conditions leading to normal AG metabolic acidosis.

Of particular note is renal tubular acidosis (RTA), a complex set of disorders of the kidney that can lead to normal AG metabolic acidosis. One disorder is the inability to excrete the daily acid load (type 1 RTA), leading to progressive  $H^+$  ion retention and low plasma  $HCO_3^-$  concentration ( $<10$  mEq/L [ $10$  mmol/L]). Another disorder arises from the inability to reabsorb  $HCO_3^-$  normally in the proximal tubule (proximal RTA or type 2 RTA).  $HCO_3^-$  is lost in the urine despite some reabsorption in the distal nephron, leading to metabolic acidosis and alkaline urine.

Normal AG metabolic acidosis caused by excessive  $HCO_3^-$  losses may be corrected by slow infusion of sodium bicarbonate-containing intravenous fluids.

### Elevated Anion Gap Metabolic Acidosis

Elevated AG metabolic acidosis results from an excess of *unmeasured* anions. Various conditions that cause an

accumulation of unmeasured anions, leading to high AG metabolic acidosis, are listed in Table 2.

When faced with an elevated AG metabolic acidosis, calculating the osmotic gap may help determine the underlying condition. Similar to the AG, the osmotic gap is the difference between the measured serum osmolality and the calculated value. The calculated serum osmolality is:  $2 \times [\text{Na}^+] + \text{glucose}/18 + \text{BUN}/2.8$ . A normal osmotic gap should be  $12 \pm 2$  mOsm/L. A high osmotic gap is a sign of an excess of an unmeasured osmotic active substance such as ethylene glycol (antifreeze), methanol (wood alcohol), or paraldehyde.

### Ketoacidosis

Ketoacidosis describes accumulation of ketone bodies (beta-hydroxybutyrate and acetoacetic acid) following excessive intracellular use of lipids as a metabolic substrate. This metabolic shift occurs during starvation or fasting or as a reflection of a lack of appropriate metabolic substrate for energy production (during specific diets where carbohydrates are replaced with lipids). Hyperketotic diets sometimes are employed for intractable epilepsy in an effort to decrease the seizure threshold.

Diabetic ketoacidosis (DKA) results from a decrease in insulin production that leads to an inability to transport glucose into the cell. The cell shifts to lipid metabolism, despite the surrounding hyperglycemia (also described as “starvation in the middle of the plenty”). The diagnosis of DKA is confirmed by the findings of hyperglycemia, a high AG acidosis, ketonuria, and ketonemia.

**Table 2. Causes of Elevated Anion Gap Metabolic Acidosis**

#### Ketoacidosis

- Starvation or fasting
- Diabetic ketoacidosis

#### Lactic Acidosis

- Tissue hypoxia
- Excessive muscular activity
- Inborn errors of metabolism

#### Ingestions

- Methanol
- Ethylene glycol
- Salicylates
- Paraldehyde

#### Renal Failure

- Uremia

The earliest symptoms of DKA are related to hyperglycemia. Older children and adolescents typically present with polyuria (due to the glucose-induced osmotic diuresis), polydipsia (due to the increased urinary losses), fatigue, and weight loss. Hypovolemia may be severe if urinary losses are not replaced, with the presentation of very dry mucous membranes and prolonged capillary refill time. As a result of worsening metabolic acidosis, the patient develops hyperventilation and deep (Kussmaul) respirations, representing respiratory compensation for metabolic acidosis. Hyperpnea develops from an increase in minute volume (rate  $\times$  tidal volume) or from increased tidal volume alone without an increase in respiratory rate. When DKA is being managed, the patient's chest excursion and respiratory rate should be observed carefully to determine if hyperpnea is present. In infants, hyperpnea may be manifested only by tachypnea.

Without prompt medical attention, DKA can progress to cerebral edema and cardiorespiratory arrest. Neurologic findings, ranging from drowsiness, lethargy, and obtundation to coma, are related to the severity of hyperosmolality or to the degree of acidosis. Treatment of DKA includes sensitive correction of the underlying insulin, volume, and electrolyte deficiencies.

### Lactic Acidosis

Lactic acidosis, another cause of an elevated AG, occurs when cells shift to anaerobic pathways for energy production as a result of tissue hypoxia due to inappropriate tissue perfusion, inappropriate oxygen supply, or mitochondrial dysfunction (as seen in inborn errors of metabolism or ingestion of drugs or toxins). The clinical presentation may involve seizures or symptoms consistent with the initial disorder that led to lactic acidosis, such as cyanosis, signs and symptoms suggestive of tissue hypoperfusion, and hypotension. As lactic acidosis worsens, further hemodynamic compromise occurs. Management should be targeted to restoring adequate tissue perfusion and oxygen supply by treating the underlying cause of the lactic acidosis.

### Inborn Errors of Metabolism

Several inborn errors of metabolism can present with high AG metabolic acidosis. Based on the affected metabolic pathway, the increased AG is caused by a different chemical substance: urea cycle defects present with hyperammonemia; or inborn errors of amino acids, carbohydrate, or organic acid metabolism present either with ketoacidosis, lactic acidosis (as in Krebs cycle defects), or increased organic acids production. Symptoms often are nonspecific and include poor feeding, failure to thrive, seizures, and vomiting.

Managing inborn errors of metabolism involves identifying the defective or deficient enzyme and limiting the intake of the metabolic substrate that requires the use of that particular enzyme. In selected cases, dialysis may be the appropriate tool for removing the excess anion.

### Ingestions

Ingestions of various chemical substances are another cause of metabolic acidosis with an elevated AG. Salicylate overdose is well known to cause increased AG metabolic acidosis by interfering with cellular metabolism (uncoupling of oxidative phosphorylation). Early symptoms of salicylate overdose include tinnitus, fever, vertigo, nausea, vomiting, and diarrhea. More severe intoxication can cause altered mental status, coma, non-cardiac pulmonary edema, and death. Most patients show signs of intoxication when the plasma salicylate concentration exceeds 40 mg/dL. Treatment of salicylate ingestion involves promoting alkaline diuresis to enhance renal salicylate excretion. In severe cases, dialysis may be required (generally considered when plasma salicylate concentrations exceed 80 mg/dL in acute intoxication and 60 mg/dL in chronic ingestions).

Toluene inhalation also can lead to metabolic acidosis with an increased AG. In patients who experience toluene ingestion (glue sniffing), the overproduced hippurate is both filtered and secreted by the kidneys, leading to rapid elimination in the urine. As a result, the AG may be near-normal or normal at the time of presentation and the patient might be diagnosed mistakenly as having a normal AG acidosis.

Ethylene glycol (antifreeze), methanol, and paraldehyde ingestion lead to an increased AG metabolic acidosis and an increased osmotic gap. Both the AG and the acidosis due to methanol and ethylene glycol ingestions result from metabolism of the parent compound. Neither may be seen in patients early in the course of ingestion or when there is concurrent ingestion of ethanol. Ethanol combines competitively with alcohol dehydrogenase, thereby slowing the metabolism of methanol or ethylene glycol to their toxic metabolites and slowing the appearance of both the acidosis and the high AG. This effect explains why ethanol administration is used in the medical management of methanol and ethylene glycol ingestions, along with fomepizole (alcohol dehydrogenase inhibitor). Management of ethylene glycol and methanol toxicity also involves hemodialysis, which removes both the ingested substance and the metabolic byproducts from the serum.

Massive ingestions of creams containing propylene glycol (eg, silver sulfadiazine) also can lead to increased AG metabolic acidosis.

### Renal Failure

Renal failure causes an increased AG metabolic acidosis due to the failure to excrete  $H^+$ . Normally, elimination of the serum acid load is achieved by urinary excretion of  $H^+$ , both as titratable acidity and as  $NH_4^+$ . Titratable acid is a term used to describe acids such as phosphoric acid and sulfuric acid present in the urine. The term explicitly excludes  $NH_4^+$  as a source of acid and is part of the calculation for net acid excretion. The term titratable acid was chosen based on the chemical reaction of titration (neutralization) of those acids in reaction with sodium hydroxide.

As the number of functioning nephrons declines in chronic kidney disease and the glomerular filtration rate decreases to below 25% of normal, the patient develops progressive high AG metabolic acidosis (hyperchloremia may occur transiently in the initial phases of renal failure). In addition to the decrease in  $NH_4^+$  excretion, decreased titratable acidity (primarily as phosphate) may play a role in the pathogenesis of metabolic acidosis in patients who experience advanced kidney disease. Of course, dialysis often is employed to correct the severe fluid and electrolyte imbalances generated by renal failure.

### Management of Metabolic Acidosis

Regardless of the cause, acidemia, if untreated, can lead to significant adverse consequences (Table 3).

Use of  $HCO_3^-$  therapy to adjust the pH for patients who have metabolic acidosis is controversial. Slow infusion of sodium bicarbonate-containing intravenous fluids can be used in cases of normal AG metabolic acidosis to replenish excessive  $HCO_3^-$  losses (eg, as a result of excessive diarrhea). However, infusing sodium bicarbonate-containing fluids for increased AG metabolic acidosis has questionable benefit and should not be used clinically.

As discussed,  $HCO_3^-$  combines with  $H^+$ , leading to  $H_2CO_3$  that subsequently dissociates to  $CO_2$  and  $H_2O$ . Infusing  $HCO_3^-$  decreases serum pH and raises  $CO_2$  and  $H_2O$ . Neither the cell membranes nor the blood-brain barrier is very permeable to  $HCO_3^-$ ;  $CO_2$  diffuses freely to the intracellular space, where it combines with  $H_2O$ , leading to  $H_2CO_3$  and worsening of the intracellular pH. Administering intravenous sodium bicarbonate to a patient who has an increased AG metabolic acidosis can lead to a false sense of security because the underlying problem is hidden by an artificially improved serum pH.

**Table 3. Consequences of Metabolic Acidosis**

#### Cerebral

- Inhibition of metabolism
- Cerebral edema
- Obtundation and coma

#### Cardiovascular

- Decreased cardiac contractility
- Decreased cardiovascular responsiveness to catecholamine
- Decreased threshold for arrhythmias
- Reduction of cardiac output, blood pressure, and end-organ perfusion
- Pulmonary vasoconstriction

#### Respiratory

- Hyperventilation as a result of respiratory compensation
- Decreased respiratory muscle strength
- Increased work of breathing

#### Hematologic

- Oxyhemoglobin dissociation curve shifts to the right (the oxygen is more easily released at the tissue level due to a lower pH)

#### Metabolic

- Inhibition of anaerobic glycolysis
- Insulin resistance
- Decreased adenosine triphosphate synthesis
- Hyperkalemia
- Increased protein degradation

Sodium bicarbonate once held a prominent position in the management of cardiac arrest. Reversing the acidosis caused by global hypoperfusion made physiologic sense because severe acidemia may worsen tissue perfusion by decreasing cardiac contractility. However, the most effective means of correcting the acidosis in cardiac arrest is to restore adequate oxygenation, ventilation, and tissue perfusion. Because most pediatric cardiac arrests are due to respiratory failure, support of ventilation through early intubation is the primary treatment, followed by support of the circulation with fluids and inotropic agents. Currently, the American Heart Association recommends that sodium bicarbonate administration be considered only in children who suffer prolonged cardiac arrest and documented severe metabolic acidosis and who fail to respond to oxygenation, ventilation, intravenous fluids, and chest compressions combined with epinephrine in recommended doses.

## Metabolic Alkalosis

Metabolic alkalosis is defined as an acid-base imbalance leading to increased plasma  $\text{HCO}_3^-$  and an arterial pH above 7.45. Several mechanisms can lead to the elevation in the plasma  $\text{HCO}_3^-$ : excessive hydrogen loss, functional addition of new  $\text{HCO}_3^-$ , and volume contraction around a relatively constant amount of extracellular  $\text{HCO}_3^-$  (called a “contraction alkalosis”). The kidneys are extremely efficient in eliminating excess  $\text{HCO}_3^-$  in the urine. A confounding factor is required for serum  $\text{HCO}_3^-$  to accumulate, such as impaired renal function,  $\text{K}^+$  depletion, or volume depletion.

In general, a patient compensates for a metabolic alkalosis by decreasing ventilation. Respiratory compensation by hypoventilation raises  $\text{Pco}_2$  by 0.7 mm Hg for every 1 mEq/L (1 mmol/L) of serum  $\text{HCO}_3^-$  increase.

Excessive  $\text{H}^+$  losses can occur either in the urine or GI tract and lead to  $\text{HCO}_3^-$  accumulation as the result of the following reactions:



Increased loss of gastric content, which has high concentrations of hydrogen chloride, as a result of persistent vomiting (eg, self-induced, pyloric stenosis) or high nasogastric tube drainage leads to metabolic alkalosis. If fluid losses continue unreplaced, dehydration and lactic acidosis ultimately develop. Of note, infants of mothers who have bulimia have metabolic alkalosis at birth.

High  $\text{H}^+$  loss in the urine can occur in the distal nephron. Increased secretion of aldosterone stimulates the secretory H-ATPase pump, increasing  $\text{Na}^+$  reabsorption, thereby making the lumen more electronegative and causing more  $\text{H}^+$  and  $\text{K}^+$  excretion, which results in concurrent metabolic alkalosis and hypokalemia. Patients who have primary mineralocorticoid excess present with hypokalemia and hypertension. In contrast, secondary hyperaldosteronism due to congestive heart failure or cirrhosis usually does not present with metabolic alkalosis or hypokalemia because the above-mentioned mechanism is blunted by decreased distal nephron  $\text{Na}^+$  delivery. Iatrogenic metabolic alkalosis along with volume contraction can occur in patients treated with loop or thiazide diuretics, which cause  $\text{Cl}^-$  depletion and increased delivery of  $\text{Na}^+$  to the collecting duct, which enhances  $\text{K}^+$  and  $\text{H}^+$  secretion.

Bartter and Gitelman syndromes present with metabolic alkalosis and hypokalemia due to a genetic defect in the transporters in the loop of Henle and distal tubule,

respectively, the same locations as those inhibited by loop and thiazide diuretics.

In addition to  $H^+$  loss, metabolic alkalosis also can be induced by the shift of  $H^+$  into the cells.

As discussed previously, hypokalemia is a frequent finding in patients who have metabolic alkalosis. Hypokalemia by itself causes intracellular acidosis and increased serum alkalosis by the following mechanism: intracellular  $K^+$  shifts into the serum to replete the extracellular stores, and to maintain electroneutrality,  $H^+$  enters the cells. Hydrogen movement into the cells lowers the intracellular pH and leaves unbuffered excess  $HCO_3^-$  in the serum. The intracellular acidosis in renal tubular cells promotes  $H^+$  secretion and, therefore,  $HCO_3^-$  reabsorption.

Metabolic alkalosis due to functional addition of “new”  $HCO_3^-$  can occur by several mechanisms: decreased renal excretion of  $HCO_3^-$ , posthypercapnic alkalosis, or excessive intake or administration of alkali.

#### Decreased Renal Bicarbonate Excretion

Renal failure can lead to metabolic alkalosis because the kidneys fail to excrete excess  $HCO_3^-$ .

#### Posthypercapnic Alkalosis

Chronic respiratory acidosis (retention of  $CO_2$ ) leads to a compensatory increase in hydrogen secretion and an ensuing increase in the plasma  $HCO_3^-$  concentration to correct the pH. When the  $PCO_2$  is decreased rapidly by mechanical ventilation of a patient who has chronic respiratory acidosis, the ensuing metabolic alkalosis is slow to disappear. Because  $Cl^-$  loss often is present in posthypercapnic alkalosis, repleting the  $Cl^-$  deficit may be essential to correct the alkalosis.

Furthermore, the acute fall in  $PCO_2$  in a person who has chronic respiratory acidosis raises the cerebral intracellular pH acutely, a change that can induce serious neurologic abnormalities and death because  $CO_2$  can diffuse freely across the blood-brain barrier out of the intracellular space, leading to severe alkalosis. Accordingly, the  $PCO_2$  must be reduced gradually in mechanically ventilated patients who present initially with chronic hypercapnia.

#### Excessive Intake or Administration of Alkali

Alkali administration does not induce metabolic alkalosis in healthy people because the healthy kidney can excrete  $HCO_3^-$  rapidly in the urine. However, metabolic alkalosis can occur if very large quantities of  $HCO_3^-$  are administered acutely or if the ability to excrete  $HCO_3^-$  is impaired. The administration of large quantities of citrate is known to lead to metabolic alkalosis. Examples

of large administrations of citrate are infusion of more than 8 units of banked blood or fresh frozen plasma or administration of citrate as an anticoagulant during dialysis.

#### Contraction Alkalosis

Contraction alkalosis occurs when relatively large volumes of  $HCO_3^-$ -free fluid are lost, a situation frequently seen with administration of intravenous loop diuretics. Contraction alkalosis also may occur in other disorders in which a high- $Cl^-$ , low- $HCO_3^-$  solution is lost, such as sweat losses in cystic fibrosis, loss of gastric secretions in patients who have achlorhydria, and fluid loss from frequent stooling by patients who have congenital chloridorrhea, a rare congenital secretory diarrhea.

Regardless of the cause, alkalosis, if untreated, can lead to significant adverse consequences (Table 4).

#### Management of Metabolic Alkalosis

Three general principles apply to the therapy of metabolic alkalosis: correct true volume depletion, correct  $K^+$  depletion, and correct  $Cl^-$  depletion (in  $Cl^-$ -responsive metabolic alkalosis). For patients who have true volume

Table 4. Consequences of Untreated Alkalosis

##### Cerebral

- Cerebral vasoconstriction with reduction of cerebral blood flow
- Tetany, seizures, lethargy, delirium, and stupor

##### Cardiovascular

- Vasoconstriction of the small arterioles, including coronary arteries
- Decreased threshold for arrhythmias

##### Respiratory

- Compensatory hypoventilation with possible subsequent hypoxemia and hypercarbia (respiratory failure)

##### Hematologic

- Oxyhemoglobin dissociation curve shifts to the left (the oxygen is bound more tightly to the oxyhemoglobin)

##### Metabolic and Electrolyte Imbalances

- Stimulation of anaerobic glycolysis
- Hypokalemia
- Decreased plasma ionized calcium
- Hypomagnesemia and hypophosphatemia



depletion, fluid administration of normal saline replaces the  $\text{Cl}^-$  and free water deficits. Potassium chloride administration for patients who have concurrent hypokalemia is an important component of treatment. This agent becomes particularly helpful in patients who are edematous due to heart failure or cirrhosis and cannot receive sodium chloride because an infusion can increase the degree of edema. Another method for treating metabolic alkalosis in an edematous patient is to administer acetazolamide, a carbonic anhydrase inhibitor, which causes a mild increase in production of urine that has high  $\text{HCO}_3^-$  content, thus reacidifying the blood.

Correcting metabolic alkalosis (usually diuretic-induced) may be particularly important for intubated patients who have chronic respiratory acidosis. The higher pH caused by the metabolic alkalosis subsequently impairs the respiratory drive and leads to hypoventilation that exacerbates hypoxemia, delaying weaning and extubation. In these patients, metabolic alkalosis usually is corrected by enteral supplements of potassium chloride or sodium chloride. Very rarely, in the intensive care unit setting, the metabolic alkalosis can be so severe that it impairs weaning from mechanical ventilation. In these circumstances, intravenous infusion of hydrogen chloride can correct the alkalosis.

Measuring the urinary  $\text{Cl}^-$  is the preferred method for assessing the renal response to  $\text{Cl}^-$  therapy. For patients experiencing  $\text{Cl}^-$  depletion (urinary  $\text{Cl}^- < 10$  mEq/L [ $10$  mmol/L]) (eg, GI losses, diuretic therapy, and sweat losses in cystic fibrosis), every attempt should be made to correct hypochloremia. Conditions that cause metabolic alkalosis due to high aldosterone concentrations are unresponsive to  $\text{Cl}^-$  and are associated with high urine  $\text{Cl}^-$  concentrations.

Minimizing continuing acid and chloride losses by excessive nasogastric fluid drainage with a histamine<sub>2</sub> blocker or proton pump inhibitor also may be helpful.

### Respiratory Acid-Base Disturbances

As noted, chemoreceptor analysis of arterial pH and  $\text{PCO}_2$  allows for centrally mediated adjustments in minute ventilation to maintain arterial  $\text{PCO}_2$  near 40 mm Hg. Primary respiratory disturbances in acid-base equilibrium may result from different pathologic scenarios. Arterial  $\text{PCO}_2$  rises abnormally (respiratory acidosis) if systemic  $\text{CO}_2$  production exceeds the ventilatory capacity or when efficient ventilation is inhibited by intrinsic or acquired conditions. Conversely, arterial  $\text{PCO}_2$  decreases abnormally (respiratory alkalosis) in response to physiologic disorders that result in excessive ventilation. Both respiratory acidosis and alkalosis may appear in association

with other metabolic acid-base disturbances, often making accurate diagnosis and treatment of the underlying disease difficult to achieve.

### Respiratory Acidosis

Respiratory acidosis occurs when arterial  $\text{PCO}_2$  increases and arterial pH decreases due to a reduction in alveolar minute ventilation or, less commonly, an excessive increase in  $\text{CO}_2$  production. Acute respiratory acidosis occurs with an acute elevation in  $\text{PCO}_2$  as a result of sudden limitation or failure of the respiratory system. Chronic respiratory acidosis is due to more indolent increases in  $\text{PCO}_2$  as a consequence of systemic disease over the course of several days. Reduction in minute ventilation can result from depression of central nervous system (CNS) respiratory drive, anatomic obstruction of the respiratory tract, or intrinsic or acquired impairments of normal thoracic excursion (Table 5).

#### Table 5. Common Causes of Respiratory Acidosis in Children

##### Central Nervous System Depression

- Medication effects
  - Sedative: benzodiazepines, barbiturates
  - Analgesic: narcotics
  - Anesthetic agents: propofol
- Central nervous system disorders
  - Head trauma
  - Infection
  - Tumor
  - Congenital central hypoventilation

##### Impairments of Thoracic Excursion or Ventilatory Efficiency

- Chest wall/lung disorders
  - Asphyxiating thoracic dystrophy
  - Progressive thoracic scoliosis
  - Thoracic trauma
  - Acute lung injury/pneumonia
  - Pneumothorax/parapneumonic effusion
  - Severe obesity
- Nerve/muscle disorders
  - Congenital myopathies
  - Spinal cord injury
  - Toxin exposure: organophosphates, botulism
  - Guillain-Barré syndrome

##### Respiratory Tract Obstruction

- Upper airway obstruction
  - Adenotonsillar hypertrophy
- Status asthmaticus

The body's compensatory changes in response to acute respiratory acidosis initially are limited to buffering via systemically available cellular  $\text{HCO}_3^-$  stores. Because of this limitation, serum  $\text{HCO}_3^-$  concentrations rise acutely by only 1 mEq/L (1 mmol/L) for every 10-mm Hg elevation in arterial  $\text{PCO}_2$ . In response to chronic respiratory acidosis, the kidney retains  $\text{HCO}_3^-$  and secretes acid, an alteration in function that takes several (3 to 5) days to have a noticeable physiologic effect. Eventually, in chronic respiratory acidosis, serum  $\text{HCO}_3^-$  concentrations ultimately rise by approximately 3.5 mEq/L (3.5 mmol/L) for every 10-mm Hg elevation in arterial  $\text{PCO}_2$ .

Respiratory acidosis can affect both the CNS and cardiovascular system adversely. CNS effects include increased cerebral blood flow and increased intracranial pressure, which can present clinically as disorientation, acute confusion, headache, and mental obtundation. Cardiovascular effects include peripheral vasodilation and tachycardia. Severe hypoventilation leads to higher arterial  $\text{PCO}_2$  and more severe hypoxemia. Hypoxemia may be partially compensated by improved tissue extraction of oxygen via an acute acidosis-mediated rightward shift in the oxyhemoglobin dissociation curve and release of oxygen to the tissues. However, as respiratory acidosis persists, a reduction in red blood cell 2,3 diphosphoglycerate (an organophosphate created in erythrocytes during glycolysis) results in a shift of the curve to the left and an increase of hemoglobin affinity for oxygen.

### Management of Respiratory Acidosis

Treatment of respiratory acidosis usually focuses on correcting the primary disturbance. Immediate discontinuation of medications that suppress central respiratory drive or administration of appropriate reversal agents should be considered. Noninvasive ventilation or intubation with mechanical ventilation may be necessary to achieve adequate alveolar ventilation and appropriate reduction in arterial  $\text{PCO}_2$ . As arterial  $\text{PCO}_2$  is corrected, individuals who experience excessive  $\text{Cl}^-$  depletion may subsequently suffer poor renal clearance of  $\text{HCO}_3^-$ , leading to a concomitant state of metabolic alkalosis.

### Respiratory Alkalosis

Respiratory alkalosis occurs when there is reduction in arterial  $\text{PCO}_2$  and elevation in arterial pH due to excessive alveolar ventilation. Causes of excessive alveolar ventilation include medication toxicity, CNS disease, intrinsic lung diseases, and hypoxia (Table 6).

Compensatory changes in response to respiratory alkalosis involve renal excretion of  $\text{HCO}_3^-$ . As in respira-

## Table 6. Common Causes of Respiratory Alkalosis in Children

### Medication Toxicity

- Salicylate overdose
- Central nervous system stimulants
  - Xanthines (eg, caffeine)
  - Analeptics (eg, doxapram)

### Central Nervous System Disorders

- Central nervous system tumor
- Head injury/stroke
- Hyperventilation syndrome: stress/anxiety

### Respiratory Disorders

- Pneumonia
- Status asthmaticus
- Pulmonary edema
- Excessive mechanical or noninvasive ventilation
- Hypoxia/high altitude

tory acidosis, renal compensation improves as the disorder persists. Serum  $\text{HCO}_3^-$  concentrations decline by 2 mEq/L (2 mmol/L) for every 10-mm Hg decrease in arterial  $\text{PCO}_2$  in acute respiratory alkalosis. In chronic respiratory alkalosis, serum  $\text{HCO}_3^-$  concentrations decline by 4 mEq/L (4 mmol/L) for every 10-mm Hg decrease in arterial  $\text{PCO}_2$ .

### Adverse Effects of Respiratory Alkalosis

Adverse systemic effects of respiratory alkalosis include CNS and cardiovascular disturbances. Respiratory alkalosis often provokes increased neuromuscular irritability, manifested as paresthesias or carpopedal spasms. In addition, cerebral blood vessels vasoconstrict acutely and impede adequate cerebral blood flow. Myocardial contractility may be diminished and cardiac arrhythmias may occur. The oxyhemoglobin dissociation curve shifts to the left in response to acute respiratory alkalosis, impairing peripheral oxygen delivery.

### Management of Respiratory Alkalosis

Treatment of respiratory alkalosis centers on correcting the underlying systemic cause or disorder. Close assessment of oxygenation status and correction of hypoxemia via oxygen administration is paramount. Acute hyperventilation syndrome often is treated simply by having the patient breathe into a paper bag. To prevent high altitude-associated respiratory alkalosis, slow ascent to allow for acclimatization is recommended; administra-

## Summary

- A wide array of conditions ultimately can lead to acid-base imbalance, and interpretation of acid-base disorders always involves a mix of art, knowledge, and clinical experience.
- Solving the puzzle of acid-base disorders begins with accurate diagnosis, a process requiring two tasks. First, acid-base variables in the blood must be reliably measured to determine the effect of multiple ions and buffers. Second, the data must be interpreted in relation to human disease to define the patient's acid-base status.
- History, physical examination, and additional laboratory testing and imaging help the clinician to identify the specific cause of the acid-base disturbance and to undertake appropriate intervention.

tion of acetazolamide before ascent should be considered. The only cure for acute mountain sickness, once it has developed, is either acclimatization or descent. However, symptoms of acute mountain sickness can be reduced with acetazolamide and pain medications for headaches.

## Suggested Reading

- Brandis K. *Acid-Base Physiology*. Accessed March 2011 at: <http://www.anaesthesiamcq.com/AcidBaseBook/ABindex.php>
- Carrillo-Lopez H, Chavez A, Jarillo A, Olivar V. Acid-base disorders. In: Fuhrman B, Zimmerman J, eds. *Pediatric Critical Care*. 3rd ed. Philadelphia, PA: Mosby Elsevier; 2005:958–989
- Grogono AW. *Acid-Base Tutorial*. 2010. Accessed March 2011 at: <http://www.acid-base.com>
- Kraut JA, Madias NE. Approach to patients with acid-base disorders. *Respiratory Care*. 2001;46:392–403

## PIR Quiz

Quiz also available online at: <http://www.pedsinreview.aappublications.org>.

9. Which of the following statements *best* describes the roles of the different nephron segments in maintaining acid-base balance?
- The proximal and distal tubules are equally responsible for acid excretion.
  - The proximal tubule is the primary segment responsible for bicarbonate reabsorption and acid excretion.
  - The distal tubule is the primary segment responsible for bicarbonate reabsorption and acid excretion.
  - The proximal tubule is the primary segment responsible for bicarbonate reabsorption, and the distal nephron principally promotes acid excretion.
  - The proximal tubule and loop of Henle are primarily responsible for both bicarbonate reabsorption and acid excretion.

10. Which of the following constellation of choices *best* describes sequelae of metabolic acidosis?

	Cardiac Output	Respiratory Rate	Oxyhemoglobin Dissociation Curve Shift	Adenosine Triphosphate Synthesis
A.	Increased	Decreased	To the left	Increased
B.	Decreased	Increased	To the right	Decreased
C.	Increased	Increased	To the left	Increased
D.	Increased	Decreased	To the right	Increased
E.	Decreased	Decreased	To the right	Decreased

11. Among the following, the *most* common mechanism leading to metabolic alkalosis is:

- A. Chronic diarrhea.
- B. Secondary hypoaldosteronism.
- C. Hypokalemia.
- D. Hypoventilation.
- E. Primary hyperaldosteronism.

12. The *most* common sequelae of early acute respiratory acidosis are:

	Intracranial Pressure	Heart Rate	Oxyhemoglobin Dissociation Curve Shift	Renal Bicarbonate Reabsorption
A.	Increased	Decreased	To the right	Increased
B.	Decreased	Increased	To the right	Decreased
C.	Increased	Increased	To the left	Increased
D.	Increased	Increased	To the right	Increased
E.	Decreased	Decreased	To the left	Decreased

13. The *most* accurate statement about respiratory alkalosis is that:

- A. Cardiac arrhythmias are never observed.
- B. It occurs when there is a reduction in  $P_{CO_2}$ .
- C. It results in decreased renal excretion of alkali.
- D. It results in vasodilation of cerebral blood vessels.
- E. Oxygen delivery is generally unaffected.