i An update to this article is included at the end

Respiratory Acidosis and Respiratory Alkalosis: Core Curriculum 2023

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The respiratory system plays an integral part in maintaining acid–base homeostasis. Normal ventilation participates in the maintenance of an open buffer system, allowing for excretion of CO_2 produced from the interaction of nonvolatile acids and bicarbonate. Quantitatively of much greater importance is the excretion of CO_2 derived from volatile acids produced from the complete oxidation of fat and carbohydrate. A primary increase in CO_2 tension of body fluids is the cause of respiratory acidosis and develops most commonly from one or more of the following: (1) disorders affecting gas exchange across the pulmonary capillary, (2) disorders of the chest wall and the respiratory muscles, and/or (3) inhibition of the medullary respiratory center. Respiratory alkalosis or primary hypocapnia is most commonly caused by disorders that increase alveolar ventilation and is defined by an arterial partial pressure of CO_2 <35 mm Hg with subsequent alkalization of body fluids. Both disorders can lead to life-threatening complications, making it of paramount importance for the clinician to have a thorough understanding of the cause and treatment of these acid–base disturbances.

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Am J Kidney Dis. 82(3):347-359. Published online June 21, 2023.

doi: 10.1053/j.ajkd.2023.02.004

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Arterial blood pH is normally maintained between 7.35 and 7.45 despite a continuous production of acid metabolites generated from metabolic processes within the body. The defense of arterial pH requires the coordinated actions of intracellular and extracellular buffers operating in conjunction with the lungs and kidney. This installment of *AJKD*'s Core Curriculum in Nephrology will focus on the respiratory regulatory mechanisms involved in acid–base homeostasis and the pathophysiologic disturbances that arise when this system operates abnormally.

Sources of Carbon Dioxide

There are 2 types of acids generated from metabolic processes in the body. Nonvolatile acids (ie, H^+) are primarily derived from the metabolism of sulfur-containing amino acids (cysteine and methionine) contained in the diet that generate sulfuric acid and phosphoproteins that generate phosphoric acid. Other sources of acid include metabolism of dietary cationic amino acids (lysine, arginine, and histidine) and a small daily production of organic acids such as acetic acid, lactic acid, and pyruvic acid. After accounting for the small amount of acid generated by the excretion of alkali into the stool, ingestion of a typical Western diet generates a daily net acid load of approximately 1 mmol of H^+ per kilogram of body weight. This amount varies depending on the makeup of the diet. Grains, eggs, cheese, and meats impart a higher acid load, whereas fruits and vegetables provide alkali.

Intracellular and extracellular buffers provide the most immediate defense against changes in pH following the addition of nonvolatile acid to the body. The HCO_3^-/CO_2 system is the most important buffer system because of the high concentration of the constituents and open nature of the system. Addition of acid converts HCO_3^- to CO_2 according to the reaction $HA + NaHCO_3 \leftrightarrow NaA + H_2O + CO_2$. While HCO_3^- is consumed, the CO_2 concentration is maintained at a constant level set by respiratory control. The net result is that the H^+ generated is no longer free and the change in pH is minimal. Were this system closed, the consumption of HCO_3^- would be accompanied by an immediate increase in CO_2, causing a precipitous decrease in systemic pH. The consumed HCO_3^- is ultimately regenerated when the acid has been excreted by the kidney.

Volatile acid (ie, H_2CO_3) is the second type of acid generated in the body. Each day, approximately 15,000 mmol of CO_2 is produced, largely from the complete oxidation of dietary carbohydrate and fats. The formation of H_2CO_3 from CO_2 and H_2O is catalyzed by the enzyme carbonic anhydrase according to the reaction $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$. The respiratory tract is responsible for the excretion of daily cellular CO_2 produced from the dehydration of carbonic acid during cellular metabolism. CO_2 excretion by the lungs maintains arterial CO_2 tension (ie,

partial pressure of CO_2 in the arterial blood [$PaCO_2$]) relatively constant between 35 and 45 mm Hg. Even during maximal exercise, when CO_2 production increases as much as 20-fold, the arterial CO_2 tension in body fluids is maintained in the normal range because of matching increases in minute ventilation and CO_2 excretion. Comparing the daily ratio of nonvolatile acid (70-100 mmol) to volatile acid (15,000 mmol) requiring excretion, it becomes apparent that cessation of pulmonary ventilation causes an almost immediate disruption in acid–base balance, resulting in fatal acidemia in less than 1 hour. By contrast, a similar degree of systemic acidity following loss of kidney function requires days to occur, with the length of time strongly influenced by diet.

CO_2 Transport

Question 1: Which one of the following is the primary mechanism by which CO_2 generated in tissues is transported to the lungs for excretion?

(a) Dissolved as a gas in plasma
(b) Carried by hemoglobin in red blood cells
(c) Transported as $HCO3^-$ in plasma

For the answer to this question, see the following text.

Given the large amount of volatile acid produced during cellular metabolism, it is important to understand how CO_2 is transported from tissues to the lungs for final excretion. The majority of CO_2 produced in tissues that enters the blood is converted to nongaseous forms for transport (Fig 1). The efficiency of this conversion is made apparent by considering the low partial CO_2 pressure (PCO_2) gradient (approximately 6 mm Hg) between tissues and the lung required for successful excretion of tissue-generated CO_2. The partial pressure gradient would need to be 10 times greater to ensure successful excretion of the daily CO_2 load if transport occurred solely by physically dissolved gas in the plasma. In fact, only approximately 10% of metabolically produced CO_2 is carried in the plasma dissolved in water, making choice (a) incorrect. The bulk of CO_2 produced in tissues enters red blood cells, where it undergoes hydration to form carbonic acid, a reaction catalyzed by carbonic anhydrase. Carbonic acid then ionizes into H^+ and HCO_3^-. The deoxygenated form of hemoglobin in tissues readily binds H^+, and the HCO_3^- exits the cell in exchange for Cl^- via the anion exchange band 3 protein found on the red cell membrane. The band 3 or anion exchanger 1 (AE1) is a member of the Solute Carrier 4 family of bicarbonate transporters (SLC4A1). Approximately 80% of tissue-generated CO_2 is transported to the lungs as HCO_3^- by way of this process, making choice (c) the correct answer. The remaining 10% of transport occurs by a fraction of CO_2 directly binding with certain amino acids on the hemoglobin molecule, forming carbamino compounds. Choice (b) is therefore incorrect.

The arrival of blood in the pulmonary capillaries leads to unloading of CO_2 as a result of the low CO_2 tension in the alveolar space. The reduction in PCO_2 creates local alkalinity favoring release of H^+ from hemoglobin. In addition, as hemoglobin becomes oxygenated, the pK value of the imidazole group of histidine decreases, providing an additional stimulus for H^+ release. H^+ titrates HCO_3^- in red blood cells, leading to formation of carbonic acid, which is rapidly dehydrated to CO_2 and H_2O catalytically by carbonic anhydrase. The decrease in intracellular HCO_3^- favors movement of HCO_3^- into the red blood cell in exchange for Cl^-, a reversal of the sequence occurring in tissues. The CO_2 generated from HCO_3^-,

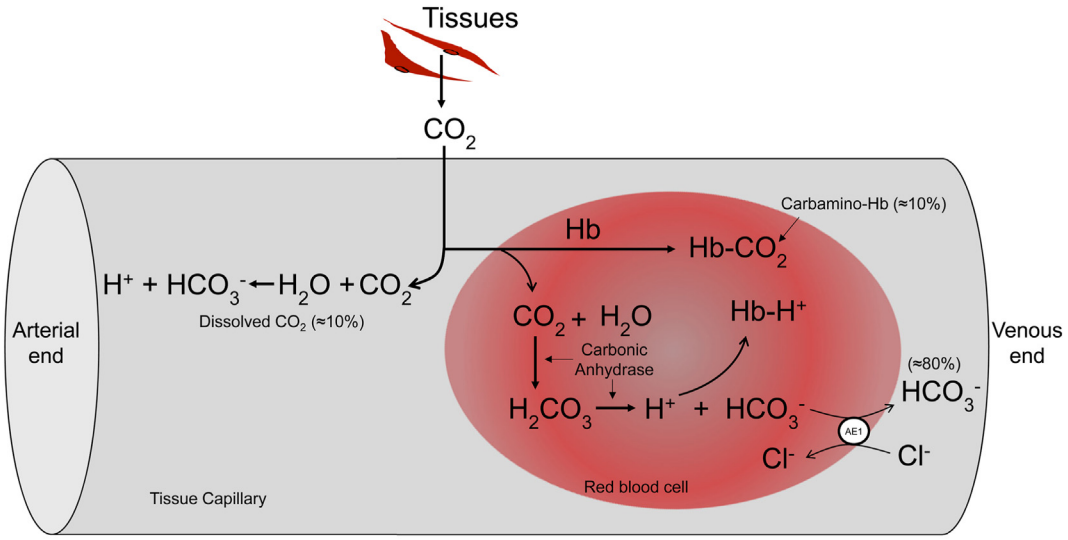

Figure 1. Mechanism of transport of CO_2 produced in peripheral tissues to the lung for excretion. See text for detailed discussion. Abbreviation: Hb, hemoglobin.

along with the small component from carbamino compounds, rapidly enters the alveolar compartment because the alveolar capillary membrane is highly permeable to CO_2. This equilibration occurs in a fraction of the transit time of red blood cells along the pulmonary capillaries.

Factors Determining the $PaCO_2$

The $PaCO_2$ is proportional to CO_2 production and inversely proportional to alveolar ventilation (V_A) according to the equation $PaCO_2 = K \times VCO_2/(V_A)$, where K is a proportionality constant and VCO_2 is CO_2 production. Under conditions of constant CO_2 production, increased V_A will reduce the $PaCO_2$, causing an increase in arterial pH. By contrast, increased CO_2 production in the setting of a fixed amount of V_A will increase the $PaCO_2$, causing acidemia.

Under normal circumstances, the central respiratory center in the medulla receives stimulatory signals from central chemoreceptors located on the ventral surface of the medulla oblongata and peripheral chemoreceptors in the carotid body, bifurcation of the carotid artery, and arch of the aorta. These chemoreceptors detect alterations in $PaCO_2$ and H^+ concentration. Changes in arterial oxygen tension are primarily sensed by peripheral chemoreceptors in the carotid bodies. As little as a 1–mm Hg increase in CO_2 tension is sufficient to initiate a stimulatory signal by medullary chemoreceptors. The sensitive nature of these chemoreceptors explains why hypercapnia is almost always due to ineffective V_A and not a result of increased metabolic CO_2 production. Input received by the respiratory centers in the brainstem adjust motor input to the respiratory muscles, altering respiratory rate as well as depth and duration of inspiration. Deviations in $PaCO_2$ and pH in a negative feedback loop are corrected through adjustments in tidal volume and respiratory rate, and arterial blood gases are stabilized.

A component of each breath is distributed to areas where gas exchange does not occur. These areas comprise the anatomic dead space and include the nose, trachea, and bronchi up to and including the terminal bronchioles. This volume is approximately 30% of the normal tidal volume of 500 mL, or 150 mL. The anatomic dead space remains relatively constant even though tidal volume varies. For this reason, a breathing pattern characterized by a low tidal volume will increase the percentage of anatomic dead space (eg, 300-mL tidal volume/150-mL dead space = 0.5) and predispose to hypercapnia if total ventilation is unchanged.

V_A refers to the component of total ventilation reaching the perfused alveoli and is therefore effective in elimination of CO_2. The efficiency of this process is determined by the relative matching of V_A and perfusion (V_A/Q) in individual units of gas exchange (Fig 2). At one extreme, the composition of gas leaving nonperfused alveoli is the same as inspired air and is therefore a component of dead space ventilation. At the other extreme, perfusion of nonventilated areas of lung prevents gas exchange from occurring and creates a shunt or venous admixture. At both extremes and with lesser degrees of mismatch in between,

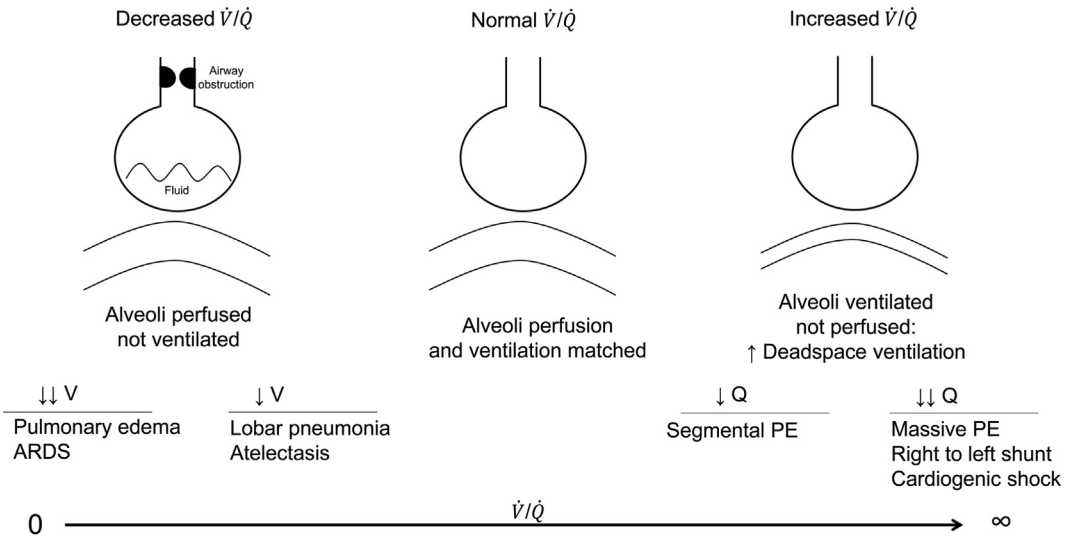

Figure 2. Spectrum of alveolar ventilation/perfusion (V_A/Q) mismatch. Exposure of alveolar gas to blood in the pulmonary capillaries is required for the normal exchange of O_2 and CO_2 in alveoli. Incomplete arterialization of systemic venous blood occurs when ventilation is reduced in excess of perfusion (ie, decreased V_A/Q). Obstruction of airflow and fluid accumulation in the alveoli are causes of such a mismatch. Complete absence of ventilation in the setting of preserved perfusion causes intrapulmonary shunting of systemic venous blood to the systemic arterial circulation. Ventilation in excess of perfusion does not contribute to gas exchange and is referred to as dead-space ventilation. As the V_A/Q mismatch increases, there is a greater amount of atmospheric gas, with negligible amounts of CO_2 returned to the atmosphere during exhalation. Pulmonary emboli and severely reduced cardiac output are causes of increased mismatch. Abbreviations: ARDS, acute respiratory distress syndrome; PE, pulmonary emboli.

gas-exchange efficiency is reduced, creating what is called alveolar dead space. Physiologic dead space is the sum of anatomic and alveolar dead space.

Increased alveolar dead space is the main cause of hypercapnia in patients with parenchymal lung disease affecting the gas-exchanging component of the lung (chronic obstructive pulmonary disease [COPD], pneumonia, and interstitial fibrosis) and pulmonary vascular disease. In early stages of these diseases, the increase in dead space stimulates minute ventilation (hence V_A), avoiding retention of CO_2, and patients manifest only hypoxemia. Hypercapnia ultimately develops when hyperventilation of remaining normal alveoli can no longer compensate for the increasing alveolar dead space in lung units with a worsening V_A/Q mismatch. Impairment of the compensatory response occurs earlier with superimposed muscle weakness, fatigue, or increases in airway resistance.

Additional Readings

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- Berger AJ, Mitchell RA, Severinghaus JW. Regulation of respiration (first of three parts). *N Engl J Med*. 1977;297(2):92-97. https://doi.org/10.1056/NEJM197707142970206 ★ESSENTIAL READING

Respiratory Acidosis

Case 1: *A 32-year-old woman with type 1 diabetes mellitus presents with lethargy. Five days before admission, she noted the acute onset of diarrhea and vomiting accompanied by polyuria and polydipsia. Physical examination on admission is noteworthy for blood pressures of 110/70 mm Hg (supine) and 90/60 mm Hg (sitting). The respiratory rate is 24 breaths per minute. Other than decreased arousability, the remainder of the examination is unremarkable. She received 3 L of normal saline solution and intravenous insulin in the first 4 hours in the emergency department. Laboratory data on admission and 12 hours later are as follows:*

	On Admission	12 h Later
Plasma glucose, mg/dL	760	280
Serum creatinine, mg/dL	2.2	1.8
Plasma electrolytes, mEq/L		
Na^+	138	144
K^+	4.2	1.4
Cl^-	103	112
HCO_3^-	6	14
Anion gap	29	18
Arterial blood gas		
pH	7.19	7.01
$PaCO_2$, mm Hg	10	42

Question 2: Which of the following best explains the worsening acidemia?

(a) Dilutional acidosis from administration of normal saline solution
(b) Decreased ventilation from respiratory muscle paralysis
(c) Lactic acidosis

For the answer to this question, see the following text.

Respiratory acidosis is an acid–base disturbance initiated by a primary increase in CO_2 tension of body fluids. The disorder should be distinguished from secondary hypercapnia, which is a compensation for primary metabolic alkalosis. Primary hypercapnia is indicated by $PaCO_2$ levels >45 mm Hg on blood gas analysis. However, low $PaCO_2$ levels (<45 mm Hg) can still indicate respiratory acidosis if V_A does not effectively counteract primary metabolic acidosis. A similar situation can occur in the setting of an acute and severe decrease in cardiac output. The combination of decreased pulmonary perfusion with relatively preserved pulmonary ventilation can potentially give rise to arterial eucapnia or even hypocapnia at the same time net retention of CO_2 in body fluids is reflected by venous hypercapnia.

The patient in case 1 presents with an increased anion gap metabolic acidosis secondary to diabetic ketoacidosis. The $PaCO_2$ of 10 mm Hg on admission is lower than the expected compensatory value of 17 mm Hg, indicating an additional component of respiratory alkalosis. Cell shift of K^+ induced by administration of insulin and improvement of metabolic acidosis unmasked the severe reduction in total body K^+, which accounts for the development of respiratory muscle paralysis and acute respiratory acidosis at 12 hours, making choice (b) the correct answer. Indirect loss of HCO_3^- in the urine, along with the Cl^- contained in normal saline solution, account for the development of a hyperchloremic acidosis; however, the improvement in plasma HCO_3^- concentration at 12 hours makes choices (a) and (c) incorrect.

Mechanisms of Hypercapnia

The approach to a patient with acute or chronic respiratory acidosis should focus on whether one or more of the following pathologic processes are present: increased CO_2 production, disturbances in pulmonary capillary gas exchange, abnormalities in chest wall and respiratory muscle function, and neurologic disorders affecting the medullary respiratory center (Box 1). In this section, we discuss the underlying mechanisms that give rise to these disorders.

Increased CO_2 Production

Physiologic and pathophysiologic conditions can lead to increased production of CO_2. Such conditions include fever, shivering, increased physical activity, hyperthyroidism, and prolonged status epilepticus. However, hypercapnia rarely results in these settings because of

Box 1. Differential Diagnosis of Acute and Chronic Respiratory Acidosis

I. Pulmonary capillary gas-exchange disorders
  A. Acute
    1. Exacerbation of underlying lung disease
    2. Adult respiratory distress syndrome
    3. Acute pulmonary edema
    4. Severe asthma or pneumonia
    5. Pneumothorax or hemothorax
    6. Aspiration of foreign body or vomitus
    7. Laryngospasm
  B. Chronic
    1. Chronic obstructive pulmonary disease
    2. Extreme obesity
II. Chest wall and respiratory muscle disorders
  A. Acute
    1. Muscle weakness: myasthenia gravis crisis, Guillain-Barré syndrome, severe hypokalemia or hypophosphatemia
  B. Chronic
    1. Muscle weakness: spinal cord injury, poliomyelitis, amyotrophic lateral sclerosis, multiple sclerosis, myxedema
    2. Kyphoscoliosis
    3. Extreme obesity, obstructive sleep apnea
III. Central nervous system respiratory center dysfunction
  A. Drugs: opiates, anesthetics, sedatives
  B. Administration of oxygen in chronic hypercapnia
  C. Central sleep apnea
  D. Extreme obesity (Pickwickian syndrome)
  E. Central nervous system lesions
  F. Metabolic alkalosis (although hypercapnia is an appropriate response to the increase in pH)
IV. Increased CO_2 production (rare and only occurs if ventilation is fixed)

increased ventilation driven by chemosensitive areas of the medulla responding to changes in interstitial pH brought about by increased levels of CO_2. Ventilatory reserve is sufficient in most patients to match any increase in CO_2 production and avoid the development of hypercapnia. By contrast, when ventilation is fixed, as in a patient receiving controlled ventilation, increased production can contribute to the genesis of respiratory acidosis.

High amounts of carbohydrates given to a patient undergoing mechanical ventilation can result in heightened CO_2 production, especially if glycogen supplies are full. Excess glucose calories result in lipogenesis, which markedly increases the respiratory quotient (RQ). This factor reflects cellular rates of CO_2 production relative to O_2 consumption decreasing toward 0.7 with greater amounts of fatty acid metabolism and increasing to greater than 1 when carbohydrate metabolism is dominant. The RQ of glucose is 1.0 and that of fat is 0.7, but the RQ of lipogenesis or fat production is approximately 8.0, accounting for the substantial increase in CO_2 production relative to oxygen consumption. Normal subjects avoid hypercapnia because of a corresponding increase in ventilation. By contrast, patients with a limited ventilatory status such as COPD or those with fixed minute ventilation due to weak respiratory muscles may not be able to increase ventilation appropriately. Development of hypercapnia in these patients can precipitate respiratory distress or acute respiratory failure and make weaning from mechanical ventilation more difficult.

Disturbances in Gas Exchange Across the Pulmonary Capillary

Disorders within this category cause hypercapnia due to an increase in dead-space ventilation resulting from ventilation/perfusion mismatching. This situation occurs when alveoli remain ventilated but are no longer perfused or when the amount of ventilation of lung regions is excessive with respect to their perfusion. In both instances, the V_A/Q is increased. When minute ventilation is kept constant, hypercapnia develops as the relative amount of dead space ventilation increases.

The mismatch in V_A/Q can be profoundly increased in areas of lung affected by a pulmonary embolism, and yet, in most circumstances, patients present with hypoxia and hypocapnia. The absence of hypercapnia despite the increase in dead-space ventilation is due to several reasons. First, minute ventilation increases in this setting as a result of stimulation of the respiratory center caused by activation of irritant and juxtacapillary sensors in the lung. Second, the predicted mismatch in V_A/Q from cessation of perfusion is attenuated as a result of bronchoconstriction in the affected area caused by the low partial pressure of alveolar CO_2. Third, nonaffected areas of the lung maintain a high capacity for CO_2 elimination given the linear relationship with no saturation point between the amounts of CO_2 carried by whole blood as a function of PCO_2. This characteristic differs from the sigmoidal relationship between O_2 content of whole blood and the prevailing partial O_2 pressure (PO_2), whereby blood becomes fully saturated with O_2 at the upper range of physiologic PO_2 levels (Fig 3). Failure of one of these mechanisms can precipitate hypercapnia. For example, patients with respiratory-center depression or those undergoing mechanical ventilation with the mode set on "controlled" will be unable to significantly increase minute ventilation. Lung disease affecting the nonembolized portions of the lung and low cardiac output states in which mixed venous PCO_2 is already increased are additional risk factors for the development of hypercapnia.

Mismatching between ventilation and perfusion is the main mechanism for the development of respiratory acidosis in patients with COPD. Destruction of capillaries, airflow obstruction leading to hyperinflation, and reduced lung compliance contribute to increases in dead-space ventilation. In early stages of the disease, increases in minute ventilation compensate for these pathologic changes, allowing eucapnia to be maintained.

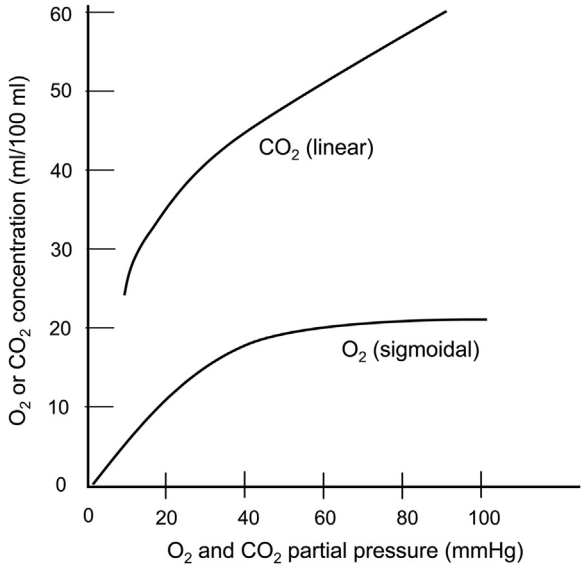

Figure 3. A comparison of the O_2 and CO_2 disassociation curves. An increase in alveolar ventilation/perfusion mismatch can range from a state in which perfusion is simply in excess of ventilation to one in which totally unventilated areas remain perfused. These settings primarily affect oxygenation without increasing the arterial partial CO_2 pressure. Increased ventilation of relatively preserved lung units compensates to normalize the arterial partial CO_2 pressure but not the arterial partial O_2 pressure. This distinction is accounted for by the relative straight-line relationship of the hemoglobin–CO_2 dissociation curve, which demonstrates no saturation for CO_2 and therefore allows averaging of capillary CO_2 from hyperventilated and hypoventilated areas. By contrast, the decreased hemoglobin–O_2 saturation in poorly ventilated areas cannot be compensated for by well-ventilated areas because hemoglobin–O_2 saturation has already reached near-maximum levels based on the sigmoidal characteristics of the oxygen-disassociation curve.

However, as the extent of disease progresses, the increase in ventilation can no longer compensate for the inefficiency in CO_2 excretion imposed by V_A/Q mismatching. When hypercapnia has become chronic, the breathing pattern tends to be shallow and rapid compared with that in normocapnic patients with COPD. As discussed previously, this pattern of low-tidal-volume breathing further increases anatomic dead space. Clinical decompensation can occur when airway resistance acutely increases as a result of bronchial spasm or edema, retention of secretions, or muscle fatigue due to the high workload required to maintain increased minute ventilation.

A blunted sensitivity to CO_2 develops in patients with advancing degrees of COPD, who become increasingly dependent on hypoxemia to drive ventilation. Administration of high flow rates of supplementary oxygen can lead to reductions in V_A and worsening hypercapnia as the hypoxemic drive to ventilation is removed. An even greater cause of hypercapnia in this setting is increased dead-space ventilation due to worsening V_A/Q mismatch. Hypoxia causes pulmonary vasoconstriction, redirecting blood flow from poorly ventilated to well ventilated areas of lung, resulting in a better match between ventilation and blood flow and reducing physiologic dead space. Hypoxic pulmonary vasoconstriction is removed with supplementary oxygen, causing an increase in dead-space ventilation, an effect most pronounced in patients with a low arterial partial O_2 pressure (PaO_2). A third mechanism to explain worsening hypercapnia is decreased affinity of hemoglobin for CO_2 following oxygenation, a phenomenon known as the Haldane effect. As oxygen displaces CO_2 from hemoglobin, the $PaCO_2$ increases as a result of increased amounts of CO_2 dissolved in blood. This effect is most pronounced between PaO_2s of 20 and 60 mm Hg, a range corresponding to the steep portion of the oxygen–hemoglobin disassociation curve.

Disorders of Respiratory Muscles and Chest Wall

Disorders of the respiratory muscles, including the diagram and inspiratory muscles of the chest wall, can lead to hypercapnia when the muscles fail to adequately propel air through the conducting airways. In these disorders, respiratory drive is inadequately translated into effective ventilation. Neurologic diseases like spinal cord injury, myasthenia gravis, Guillain-Barré syndrome, poliomyelitis, amyotrophic lateral sclerosis, and multiple sclerosis are causes of hypercapnia due to respiratory muscle weakness. Muscle weakness is a potential complication of poor nutritional states or body deficits in electrolytes such as severe hypokalemia or hypophosphatemia. Decreased muscle energy supply caused by low cardiac output, anemia, and decreased oxygen saturation may also play contributory roles.

Diminished chest wall compliance and impaired respiratory muscle mechanics lead to chronic hypercapnia in chest wall disorders such as ankylosing spondylitis, kyphoscoliosis, and pectus excavatum. Hyperinflation and increased lung resistance in COPD increases the workload and places inspiratory muscles at a decreased mechanical advantage to generate pressure. For example, flattening of the diaphragm increases its radius of curvature such that the pressure generated for any level of contraction is reduced according to Laplace's law. With severe flattening, contraction may actually cause lung deflation, resulting in inward movement of the lower rib cage during inspiration, a phenomenon referred to as Hoover sign.

Inhibition of the Medullary Respiratory Center

Anesthetic, sedative, and opiate agents decrease respiratory drive and can precipitate hypercapnia. Decreased respiratory drive in combination with altered chest wall and abdominal compliance contributes to CO_2 retention in obesity hypoventilation syndrome. Clinically important dampening of respiratory drive also occurs in encephalitis, brainstem disease, hypothermia, and severe hypothyroidism.

Clinical Manifestations of Respiratory Acidosis

Acute respiratory acidosis manifests with a variety of neurologic symptoms, the severity of which depends on the magnitude of hypercapnia and rapidity of development. The degree of hypoxemia also influences the clinical presentation, as all patients with hypercapnia will exhibit hypoxemia when breathing room air.

Hypercapnic encephalopathy is a clinical syndrome initially presenting with irritability, headache, mental cloudiness, apathy, confusion, anxiety, and restlessness and later progressing to asterixis, myoclonic jerks, transient psychosis, delirium, somnolence, and coma. Neurologic manifestations are accompanied by increased levels of brain glutamine and γ-aminobutyric acid and reductions in the levels of glutamate and aspartate. Increases in cerebral blood flow can cause papilledema and other manifestations of increased intracranial pressure, findings collectively referred to as pseudotumor cerebri. Cardiovascular manifestations of hypercapnia include decreased myocardial contractility, systemic vasodilation, and a blunting effect of endogenous and exogenous catecholamines at the level of the receptor. These effects can progress to cardiovascular instability, arrhythmias, and death.

Diagnosis

The diagnosis of primary respiratory acidosis is made based on the presence of acidemia and hypercapnia on arterial blood gas analysis. Differentiation between acute and chronic hypercapnia can be challenging. A detailed clinical history, physical examination, and determination of the underlying etiology is useful in making this distinction. Acute respiratory acidosis is typically more symptomatic than acute metabolic acidosis because CO_2 diffuses and equilibrates across the blood–brain barrier more rapidly than does HCO_3^-, resulting in a more rapid decrease in cerebrospinal fluid and cerebral interstitial pH.

Changes in plasma chemistries can aid in the diagnosis of respiratory acidosis. Primary hypercapnia elicits an immediate increase in plasma HCO_3^- of 1 mmol/L for every 10–mm Hg increase in PCO_2 through a variety of mechanisms. First, a decrease in pH leads to an increase in H^+ binding to albumin, causing a decrease in anion gap and a slight increase in plasma HCO_3^-. Second, some H^+ enters cells in exchange for Na^+ and K^+, leading to a small increase in extracellular HCO_3^- with corresponding small increases in plasma Na^+ and K^+. Third, CO_2 immediately enters red blood cells, where, in the presence of carbonic anhydrase, it is converted to H_2CO_3. The acid disassociates into H^+, which binds to hemoglobin, leaving HCO_3^- in the cytoplasm free to exit the cell in exchange for plasma Cl^-, a process termed the red cell HCO_3^-–Cl^- shift. The magnitude of this acute adaptation is influenced by the baseline plasma HCO_3^- concentration. Preexisting hypobicarbonatemia, whether from metabolic acidosis or chronic respiratory alkalosis, leads to a greater increase in plasma H^+ and HCO_3^- concentration following acute hypercapnia compared with higher baseline values, whether caused by metabolic alkalosis or chronic respiratory acidosis.

Sustained hypercapnia for longer than 24-48 hours leads to a greater increase in plasma HCO_3^- due to increasing kidney H^+ secretion in response to CO_2 retention. In chronic respiratory acidosis, the plasma HCO_3^- increases by 3.5 mEq for each 10–mm Hg increase in PCO_2. This response attenuates the severity of acidemia but does not fully correct the disorder. Chronic increases in CO_2 acidify proximal tubular cells, causing parallel increases in the rate of the luminal Na^+/H^+ antiporter and the basolateral Na^+-$(HCO_3^-)_3$ cotransporter. Effective arterial blood volume becomes slightly expanded as a result of kidney retention of $NaHCO_3$, leading to increased loss of NaCl in the urine in an attempt to restore euvolemia. The net effect is an increase in plasma HCO_3^- and decreased Cl^- concentration (Fig 4). Changes in plasma HCO_3^- concentrations outside of the expected levels of compensation suggest the presence of mixed respiratory and metabolic acid–base disorders.

Treatment of Acute and Chronic Respiratory Acidosis

Case 2: *A 58-year-old man with stable COPD is intubated secondary to respiratory failure precipitated by pneumonia. He exhibits a response to broad-spectrum antibiotics, and, on hospital day 10, he is successfully extubated, but he remains lethargic and not yet able to eat. Physical examination is noteworthy for a blood pressure of 108/72 mm Hg, no jugular venous distension, and no peripheral edema. Laboratory data obtained immediately before and 36 hours after extubation are as follows:*

	Before Extubation	36 h After Extubation
Arterial blood gas		
pH	7.43	7.52
$PaCO_2$	58	44
Serum electrolytes, mEq/L		
Na^+	138	140
K^+	4.9	4.1
Cl^-	93	94
HCO_3^-	36	36
Serum urea nitrogen, mg/dL	–	56
Serum creatinine, mg/dL	–	1.6

Question 3: Which one of the following is the most appropriate therapy to correct the increased plasma HCO_3^- at this time?

(a) Acetazolamide
(b) Normal saline solution (0.9% sodium chloride)
(c) 0.45% sodium chloride

For the answer to this question, see the following text.

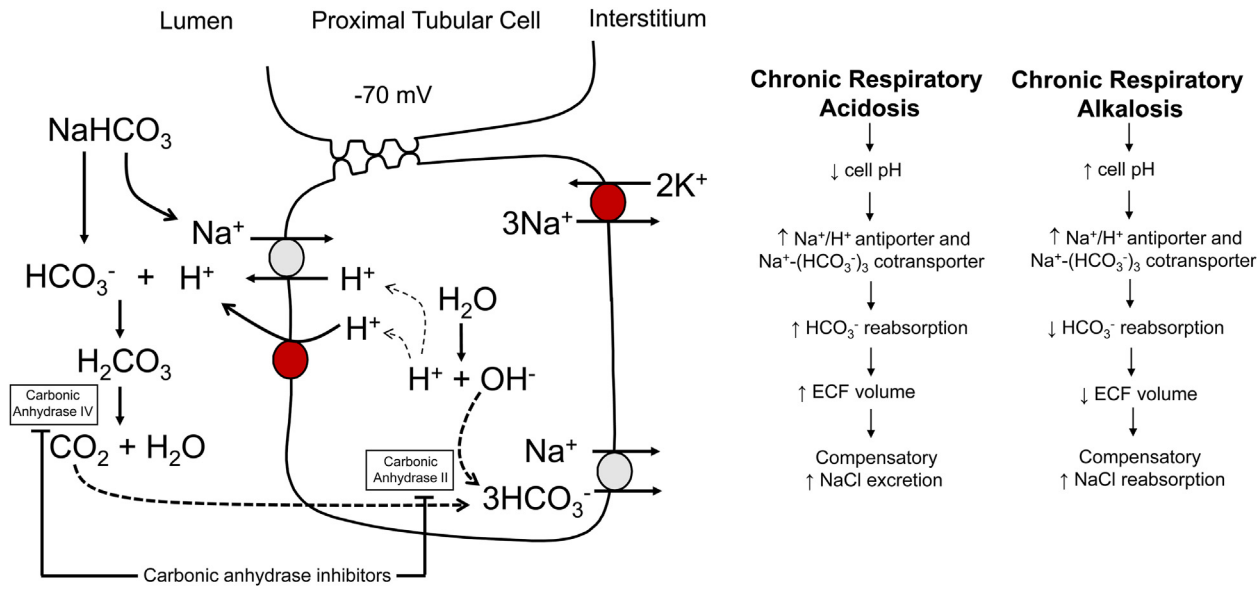

Figure 4. Mechanisms by which chronic respiratory acidosis and alkalosis alter proximal tubular HCO_3^- reabsorption. Increases or decreases in CO_2 concentration rapidly equilibrate across the cell membrane, leading to decreased or increased cell pH, respectively. The change in cell pH causes parallel changes in activity of the Na^+–H^+ exchanger on the apical membrane and Na^+–HCO_3^- cotransport on the basolateral membrane. In chronic respiratory acidosis, the compensatory increase in $NaHCO_3$ reabsorption combined with urinary loss of NaCl to maintain extracellular fluid volume is reflected by a decrease in plasma Cl^- concentration with respect to plasma Na^+ concentration. In chronic respiratory alkalosis, the compensatory loss of $NaHCO_3$ combined with kidney retention of NaCl to maintain euvolemia is reflected by an increase in plasma Cl^- concentration with respect to plasma Na^+ concentration. Abbreviation: ECF, extracellular fluid.

Recognition and prompt removal of the underlying cause is the initial step in treating acute respiratory acidosis. Efforts should focus on establishing and securing a patent airway to provide adequate oxygenation because hypoxemia poses the greatest risk to survival, not hypercapnia or acidemia. A high inspired oxygen tension should be provided to all patients because there is no evidence that this measure will further depress ventilation. Ensuring maximal PaO_2 levels is particularly urgent in those found apneic, in cardiac arrest, or unconscious from carbon monoxide poisoning. Prompt initiation of assisted ventilation is indicated in patients with coma, severe obtundation, extreme hypercapnia ($PaCO_2$ >80 mm Hg), or severe acidemia (blood pH <7.10).

There is no indication for administration of $NaHCO_3$ in acute respiratory acidosis as a simple acid–base disorder. Potential complications include increased CO_2 production with worsening hypercapnia secondary to the decomposition of HCO_3^-, impairment in alveolar gas exchange secondary to volume overload, and pH-mediated depression of respiration. Alkali therapy is useful when coexistent metabolic acidosis is present or when permissive hypercapnia is required. In this latter situation, administration of $NaHCO_3$ may allow the pH to be partially corrected in settings in which the PCO_2 cannot be rapidly corrected. Permissive hypercapnia is sometimes required in status asthmaticus, in which a lower ventilatory rate and peak inspiratory pressure are purposely prescribed to minimize barotrauma to the lung but at the expense of a persistently higher PCO_2.

In patients with chronic respiratory acidosis, the underlying disorder can rarely be corrected. The primary therapeutic goal in these patients is to ensure adequate oxygenation; however, unlike in acute respiratory acidosis, oxygen should be administered cautiously and lowering of $PaCO_2$ should proceed gradually.

As previously discussed, excessive oxygen administration can lead to CO_2 retention secondary to the removal of the hypoxemic drive for respiration, increase in dead-space ventilation due to worsening V_A/Q mismatch, and unloading of CO_2 by hemoglobin. In general, worsening hypercapnia can be avoided as long as the PaO_2 does not exceed 60 mm Hg. Oxygen flow rates of 2 L/min by nasal cannula deliver an inspired oxygen concentration of 23%-28% and improve PaO_2 values to levels of 50-60 mm Hg in many patients with chronic respiratory failure. Clinicians should also be careful in prescribing drugs, which might suppress the central ventilatory drive.

For the patient in case 2, the correct answer is administration of normal saline solution, choice (b). There is no evidence of volume overload, making choice (a) incorrect, or dehydration requiring free water replacement, making choice (c) incorrect.

Mechanical ventilation is sometimes required in patients with chronic respiratory acidosis who experience

worsening hypercapnia and hypoxia during an episode of acute worsening of pulmonary function. Care should be taken to lower the $PaCO_2$ slowly to minimize the risk of "overshoot" alkalemia due to the presence of high plasma HCO_3^-. Kidney excretion of HCO_3^- is blunted when $PaCO_2$ is reduced in the setting of a decreased effective arterial blood volume. This setting is common in sodium-avid states such as cirrhosis and congestive heart failure or following diuretic therapy and restricted intake of dietary salt. This conversion of chronic respiratory acidosis to metabolic alkalosis is called posthypercapnic metabolic alkalosis. Neurologic manifestations such as seizure and coma can be precipitated by high pH in the central nervous system.

Administration of parenteral Cl^--containing solutions and discontinuation of loop diuretic agents are effective in correcting the superimposed metabolic alkalosis. In patients with decompensated heart failure in whom this approach is not feasible, acetazolamide can be used to correct the alkalosis. This drug inhibits proximal HCO_3^- reabsorption by inhibiting luminal carbonic anhydrase. This effect creates an unfavorable concentration gradient for further H^+ secretion due to an increase in the concentration of luminal carbonic acid. The drug also inhibits intracellular carbonic anhydrase, thereby decreasing the supply of H^+ available for secretion (Fig 4). Both mechanisms decrease reabsorption of filtered HCO_3^- and allow for at least partial correction of the metabolic alkalosis. The magnitude of the bicarbonaturia is directly related to the plasma concentration. As the HCO_3^- concentration decreases, the clinical effectiveness of the drug decreases in a parallel fashion.

A complication of acetazolamide therapy in patients with lung disease is worsening of hypercapnia. Inhibition of carbonic anhydrase in red blood cells can prevent red cell uptake of CO_2 in peripheral tissues and can prevent CO_2 release in the lung. In patients with normal lungs, increased respiration prevents increases in the PCO_2 of arterial blood. However, patients with lung disease cannot respond adequately and are at risk for further increases in arterial PCO_2 and tissue PCO_2.

Additional Readings

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Respiratory Alkalosis

Respiratory alkalosis is one of the most common acid–base disturbances encountered in clinical practice. Primary hypocapnia is synonymous with respiratory alkalosis and refers to a $PaCO_2$ <35 mm Hg with subsequent alkalinization of body fluids. In patients with a primary metabolic alkalosis, a normal or even increased $PaCO_2$ indicates an element of respiratory alkalosis when the value remains below what is appropriate as a compensatory response. Secondary hypocapnia is a compensatory response to metabolic acidosis. If the reduction in $PaCO_2$ is greater than the expected compensatory response, a coexisting respiratory alkalosis may be present.

Mechanisms of Hypocapnia

The causes of respiratory alkalosis are listed in Box 2. In this section, we discuss the underlying mechanisms that give rise to these disorders. The balance between production and elimination of CO_2 determines the $PaCO_2$. Under most circumstances, CO_2 production is relatively stable and hypocapnia is the result of increased V_A enhancing elimination. Increased clearance of CO_2 can also occur through extracorporeal techniques such as cardiopulmonary bypass and extracorporeal membrane oxygenation. Of historical interest, acetate was the most common buffer used in dialysate for administration of hemodialysis before widely being replaced by bicarbonate. The absence of HCO_3^- in acetate dialysate favored movement of HCO_3^- from blood to dialysate during the procedure. Despite the loss of base, the pH of blood exiting the dialysis cartridge did not change

Box 2. Differential Diagnosis of Respiratory Alkalosis

I. Decreased CO_2 production (rare)
  A. Myxedema coma[a]
  B. Hypothermia
II. Hypoxemia
  A. Hypobaric hypoxia (increasing altitude)
  B. Pulmonary disease
  C. Methemoglobinemia (tissue hypoxia)
III. Cardiopulmonary disorders (in addition to hypoxia, stimulation of respiration emanating from receptors (nociceptive, stretch, juxtacapillary, chemo)
  A. Pneumonia
  B. Interstitial pneumonitis
  C. Fibrosis
  D. Pulmonary edema
  E. Pulmonary embolism
  F. Vascular disease
  G. Bronchial asthma
  H. Pneumothorax
  I. Congestive heart failure
IV. Central nervous system disorders
  A. Psychogenic or anxiety-induced hyperventilation syndrome
  B. Central nervous system infection
  C. Central nervous system tumors
V. Drugs
  A. Salicylates
  B. Methylxanthines
  C. β-Adrenergic agonist
  D. Progesterone[b]
  E. Quetiapine
VI. Miscellaneous
  A. Fever and sepsis
  B. Pain
  C. Alcohol withdrawal
  D. Pregnancy
  E. Hepatic failure

[a]Ventilation is usually fixed (ventilator) in this setting; myxedema coma can also be associated with respiratory acidosis.
[b]Increased circulating levels of progesterone account for development of respiratory alkalosis in normal pregnancy.

because of the simultaneous CO_2 diffusion from blood to dialysate. The procedure was complicated by hypoxemia because loss of soluble CO_2 signaled pulmonary hypoventilation in an attempt to maintain normal blood CO_2 concentration. Oxygenation of the blood prevents hypoxemia during extracorporeal membrane oxygenation and with the use of heart–lung machines despite the diffusive loss of CO_2 in these procedures.

Myxedema coma or hypothermia are conditions in which basal metabolic rate can be severely reduced, causing hypocapnic alkalosis from decreased CO_2 production. However, even in these circumstances, V_A needs to be fixed (ie, intubation with fixed ventilation) because the decrease in $PaCO_2$ normally elicits a reflexive decrease in ventilation due to inhibitory chemoreceptor input to the respiratory center.

Increased V_A and primary hypocapnia often develop from stimulatory input originating in the lung, carotid, and aortic chemoreceptors, brainstem chemoreceptors, and other centers of the brain. There is increased sensitivity to CO_2 in the brainstem in disease states such as chronic liver disease and sepsis, explaining why respiratory alkalosis is commonly present in these disorders. Unexplained respiratory alkalosis should prompt consideration of Gram-negative sepsis because circulating endotoxin exerts a direct stimulatory effect on central chemoreceptors. Pharmacologic agents, anxiety, and volition also augment this response (Box 2).

Case 3: *A 57-year-old man, completely acclimatized, reaches the summit of Mt Everest.*

Question 4: Which one of the following sets of laboratory data is most likely to be present?

	Option (a)	Option (b)	Option (c)
pH	7.45	7.35	7.53
PaO_2, mm Hg	40	32	25
$PaCO_2$, mm Hg	20	15	13
Plasma HCO_3^-, mEq/L	20	16	10
Plasma lactate, mg/dL	8	15	2
Arterial saturation, %	30	75	54
Hemoglobin, g/dL	14	22	19

For the answer to this question, see the following text.

Hypoxemia is a major stimulus to pulmonary ventilation, particularly as the PaO_2 decreases to 60 mm Hg. Increasing altitude leads to arterial hypoxemia due to a progressive decrease in barometric pressure and reduction in the inspired PO_2. The subsequent reduction in alveolar PO_2 and, ultimately, PaO_2 stimulates increased ventilation through signals originating in the peripheral chemoreceptors located primarily in the carotid and aortic bodies. Increases in the depth and rate of breathing serve to maintain arterial oxygen content but also cause respiratory alkalosis. The magnitude of this involuntary increase in ventilation can be enormous. V_A is increased approximately 5-fold at the summit of Mt Everest, such that the $PaCO_2$ is reduced to as low as 10 mm Hg. This adaptive increase in ventilation limits the decrease in PaO_2 to approximately 25-30 mm Hg even though the inspired PO_2 is only 29% of its sea-level value. Normally, the reduction in $PaCO_2$ would exert an inhibitory effect on respiration, causing $PaCO_2$ and pH to return to normal levels. However, at altitude, this inhibitory effect is overridden by central medullary chemoreceptors, allowing a robust hypoxic ventilatory response to be maintained. The persistent increase in ventilation is driven by desensitization of the carotid body to hypoxia following prolonged exposure to hypobaric hypoxia and loss of HCO_3^- and lowering of the pH in the cerebrospinal fluid. The correct answer to Question 4 is choice (c). Hypoxia leads to activation of hypoxia-inducible factor, which is responsible for increases in hemoglobin concentration. With acclimatization, the magnitude of activation is attenuated, accounting for low lactate levels despite the

Box 3. Laboratory and Clinical Manifestations of Respiratory Alkalosis

I. Laboratory
  A. Hypokalemia
  B. Hypophosphatemia
  C. Increased lactate production causing increased anion gap
    1. Leftward shift in O_2 disassociation curve causing tissue ischemia
    2. Stimulation of phosphofructokinase (rate-limiting enzyme glycolysis)
  D. Decreased ionized calcium (due to increased protein binding)
  E. Increased serum chloride and decreased serum bicarbonate concentration
II. Cardiovascular
  A. Coronary vasospasm with potential to precipitation angina
  B. Arrhythmias
III. Central nervous system
  A. Neuromuscular irritability, confusion, lightheadedness
  B. Seizure
IV. Pulmonary
  A. Increased airway resistance
  B. Decreased lung compliance
  C. Increased pulmonary capillary permeability

hypoxic environment, a phenomena referred to as the lactate paradox.

Respiratory alkalosis is frequent in patients with cardiopulmonary disease. Stimulatory effects on respiration can result from irritants via nociceptive receptors, pulmonary expansion and collapse via stretch receptors, and capillary congestion via juxtacapillary receptors. Tissue hypoperfusion and oxygen deprivation increase ventilation through activation of arterial chemoreceptors. A progressive widening of the arteriovenous difference in pH and PCO_2 can develop in patients with advanced circulatory failure or those undergoing cardiopulmonary resuscitation, such that arterial hypocapnia may coexist with venous or tissue hypercapnia, findings collectively referred to as pseudorespiratory alkalosis. This situation occurs when CO_2 excretion by the lungs is limited by severely reduced pulmonary blood flow, resulting in increased venous PCO_2. The increase in V_A/Q ratio causes a greater amount of CO_2 to be removed from blood that does traverse the pulmonary circulation, causing arterial eucapnia or frank hypocapnia. In both situations, the PaO_2 may be relatively preserved despite ongoing severe tissue O_2 deprivation.

Decreased hemoglobin concentration or a reduction in capacity to transport and unload oxygen at the tissue level can cause increased ventilation. This latter situation occurs in methemoglobinemia, in which oxidation of iron to the ferric state (Fe^{3+}) impairs the ability of hemoglobin to transport oxygen. Development of tissue hypoxia and cyanosis provides a stimulus for increased ventilation. Hypoxemia from hepatopulmonary syndrome, limited respiratory capacity due to ascites, and direct stimulatory effects of progesterone on respiratory drive account for the development of primary hypocapnia in patients with advanced liver disease. A mild degree of respiratory alkalosis is common in normal pregnancy and is due to increased circulating levels of progesterone. Toxic concentrations of salicylate exert a direct stimulatory effect on the respiratory center in the medulla, causing an increase in the rate and depth of respiration and the development of respiratory alkalosis. A high anion gap acidosis is commonly present as a result of increased ketogenesis and lactic acid production. Respiratory alkalosis commonly develops in patients with chronic alcohol use syndrome who are undergoing withdrawal. This acid–base disorder can be associated with precipitous decreases in plasma phosphate predisposing to rhabdomyolysis, hemolytic anemia, and tissue ischemia due to a leftward shift in the oxygen disassociation curve.

Clinical Manifestations

Respiratory alkalosis occurring as a simple disorder or as a component of a mixed disorder is common in critically ill patients. The signs and symptoms of respiratory alkalosis are most prominent when the disorder is acute in onset compared with chronic respiratory alkalosis. In addition to reducing the acidity of body fluids, acute hypocapnia causes a decrease in cerebral and coronary blood flow, a pH-induced leftward shift of the oxyhemoglobin dissociation curve, and decreased ionized calcium (Box 3). Clinical manifestations of these alterations include lightheadedness, palpitations, paresthesias of the extremities and circumoral area, carpopedal spasm, and seizures.

Although often treated as a benign condition, alkalosis may cause clinical tissue hypoxia in certain settings. In fact, the presence of the disorder portends a poor prognosis because there is a graded relationship between the severity of alkalemia and mortality in hospitalized intensive care unit patients. Alkalosis decreases tissue oxygen delivery through at least 2 mechanisms. First, increased pH leads to a leftward shift in the oxygen dissociation curve, decreasing the ability of hemoglobin to release oxygen in peripheral tissues. Second, primary hypocapnia leads to vasoconstriction and decreased perfusion of the brain, heart, and peripheral circulation. In vitro studies suggest that the increase in pH is the critical determinant of vascular smooth muscle tone because a comparable degree of alkalemia due to metabolic alkalosis causes a similar effect.

The vascular effects of acute hypocapnia can precipitate angina, ischemic electrocardiographic changes, and cardiac arrhythmias in patients with coronary artery disease. In this regard, coronary artery spasm documented by angiography and accompanied by ST-segment elevation and chest pain can develop in association with hyperventilation. Arrhythmias are more resistant to pharmacologic therapy in patients with alkalemia. In mechanically

ventilated patients, acute and severe hypocapnia reduces cardiac output and increases arteriolar vasoconstriction, causing tissue hypoperfusion, as evidenced by increased lactate production. In patients with a low $PaCO_2$, abrupt cessation of mechanical ventilation can lead to severe respiratory depression and critical hypoxia. Restoration of adequate ventilatory drive does not occur until the $PaCO_2$ increases sufficiently to again stimulate ventilation. This scenario accounts for the increased risk of cardiopulmonary arrest during recovery from general anesthesia.

The reduction in cerebral blood flow that occurs with acute hypocapnia has been used therapeutically to treat brain edema resulting from neurosurgical procedures, head trauma, meningitis, and encephalitis. However, reductions in tissue oxygen supply and increased cerebral oxygen demand are potential complications. Increased oxygen demand is secondary to increases in neuronal excitability, seizure activity, and anaerobic metabolism that occur following the induction of hypocapnia via hyperventilation. In addition, rapid correction of severe hypocapnia can potentially lead to reperfusion injury by causing vasodilation in ischemic areas. In this regard, prophylactic induction of hypocapnia is associated with worse outcomes in patients with traumatic brain injury and acute stroke. This procedure is particularly injurious to the brain in premature infants.

Diagnosis

Case 4: *A 68-year-old woman with heart failure presents with pneumonia and respiratory failure. Upon admission, she requires intubation and, in addition to receiving antibiotics, she is treated with a continuous infusion of furosemide secondary to anasarca. Laboratory data 5 days after hospital admission are as follows:*

	Value
Serum electrolytes, mEq/L	
Na^+	142
K^+	3.2
Cl^-	106
HCO_3^-	26
Arterial blood gas	
pH	7.58
$PaCO_2$	29
Serum creatinine, mg/dL	1.42
Serum urea nitrogen, mg/dL	54

Question 5: Which one of the following best describes the acid–base status of the patient?

(a) Respiratory alkalosis and metabolic alkalosis
(b) Respiratory alkalosis and metabolic acidosis
(c) Chronic respiratory alkalosis

For the answer to this question, see the following text.

History, physical examination, and laboratory data including a blood gas analysis are sufficient to diagnose respiratory alkalosis. Physical examination findings of hyperpnea or Kussmaul breathing can provide an initial clue as to the presence of a primary respiratory alkalosis or a compensatory respiratory response to a primary metabolic acidosis.

Respiratory alkalosis is accompanied by characteristic changes in plasma electrolyte composition. Red blood cell CO_2 tension decreases following an acute decrease in $PaCO_2$, causing albumin and other non-HCO_3^- buffers to release H^+ and reduce plasma HCO_3^- concentration. In red blood cells, the decrease in HCO_3^- concentration is due to H^+ released from hemoglobin. This effect creates a favorable gradient for movement of extracellular HCO_3^- into the cell in exchange for Cl^-, accounting for a small initial compensatory response in acute respiratory alkalosis. The magnitude of this rapid response (measured in minutes) is a decrease in plasma HCO_3^- concentration by 2 mEq/L for each 10–mm Hg decrease in $PaCO_2$.

In chronic respiratory alkalosis, the decrease in $PaCO_2$ decreases the reabsorptive capacity of the kidney proximal tubule, causing a transient HCO_3^- diuresis. Over the course of 2-3 days, a new steady state is achieved in which the plasma HCO_3^- concentration will have decreased by 5 mEq/L for each 10–mm Hg decrease in $PaCO_2$. Kidney loss of HCO_3^- in secondary hypocapnia due to a primary metabolic acidosis is small and does not overcome the direct effect of hypocapnia. For this reason, worsening acidemia in a patient with metabolic acidosis cannot be attributed to the kidney compensatory response to increased ventilation. In Question 5, the lack of a compensatory decrease in plasma HCO_3^- concentration in the setting of chronic respiratory alkalosis is due to diuretic-induced metabolic alkalosis. Choice (a) is the correct answer.

Chronic respiratory alkalosis leads to kidney retention of NaCl in an attempt to defend extracellular fluid volume due to urinary loss of $NaHCO_3$. Loss of HCO_3^- and retention of Cl^- is reflected in the basic metabolic profile demonstrating a plasma Cl^- concentration that is increased with respect to the plasma Na^+ concentration (Fig 4). In the absence of arterial blood gas, the findings of increased plasma Cl^- and decreased HCO_3^- concentration can be erroneously diagnosed as a hyperchloremic metabolic acidosis.

A 3-5–mEq/L increase in the serum anion gap is also a characteristic feature of chronic respiratory alkalosis. This increase is primarily due to a greater negative charge on serum albumin as H^+ is released in response to the high pH. Increased pH also stimulates the rate-limiting enzyme for glycolysis (phosphofructokinase), causing a mild increase in lactate production. Increased glycolysis accounts for development of hypophosphatemia in the setting of acute hyperventilation. In addition, intracellular shift in K^+ also occurs acutely, although this effect is trivial. Chronic hypocapnia is not associated with disturbances in plasma phosphate or potassium.

Treatment

Treatment of the underlying cause is the initial goal in patients with primary respiratory alkalosis. Administration of oxygen and returning to lower altitude can reverse respiratory alkalosis that develops secondary to hypoxemia or

altitude-related hypobaric hypoxia, respectively. The hyperventilation syndrome is a common disorder characterized by fear- or anxiety-related episodes of excessive ventilation. Reassurance, cognitive behavior therapy, and stress-reduction techniques are useful in these patients. Underlying mood or anxiety disorders may require pharmacologic treatment with anxiolytic and antidepressant agents or some combination of these techniques. Breathing into a paper bag creates a closed system, causing an increase in PCO_2 with each breath taken. However, this technique is not without risk because hypoxemia can develop in patients with underlying lung or cardiovascular disease.

Increasing the ventilator-circuit dead space or increasing the inspired CO_2 tension is an effective strategy to increase the $PaCO_2$ in mechanically ventilated patients. Sedation and muscle relaxants are sometimes used in this situation. Patients with coronary artery disease should be approached with a sense of urgency given the increased risk of arrhythmias. On the contrary, more caution is required in patients with brain injury because rapid increases in $PaCO_2$ can increase cerebral perfusion and potentially worsen intracranial pressure. A low dialysate HCO_3^- concentration is effective in minimizing the degree of alkalemia in patients receiving dialysis in whom an acute illness causes primary hypocapnia.

Unexplained respiratory alkalosis, particularly in association with an increased anion gap metabolic acidosis, should prompt consideration of salicylate poisoning. The acute form of toxicity is typically straightforward, as patients voluntarily report a recent ingestion or partially filled containers of salicylates are found with the patient. By contrast, chronic intoxication is more difficult to diagnose because intoxication is accidental in nature, often with no clear history of excess ingestion. The initial goal of therapy is to correct systemic acidemia if present and to alkalinize the urine pH. Hemodialysis is indicated at serum concentrations >80 mg/dL or in the setting of severe clinical toxicity.

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Article Information

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Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received November 29, 2022, in response to an invitation from the journal. Evaluated by 2 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form February 5, 2023. Dr Palmer, who serves on the Core Curriculum Advisory Board, was entirely recused from any involvement in the manuscript consideration process.

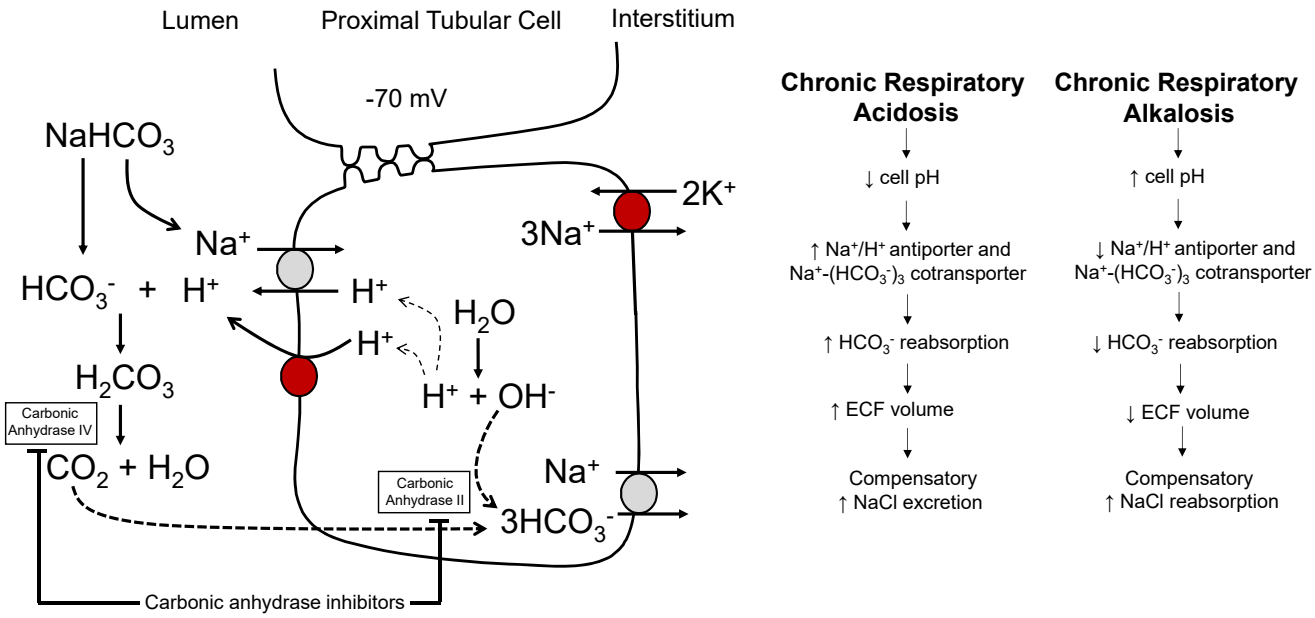
Update

American Journal of Kidney Diseases
Volume 83, Issue 1, January 2024, Page 126

DOI: https://doi.org/10.1053/j.ajkd.2023.10.005

Erratum Regarding "Respiratory Acidosis and Respiratory Alkalosis: Core Curriculum 2023" (*Am J Kidney Dis.* 2023;82(3):347-359)

In the Core Curriculum entitled "Respiratory Acidosis and Respiratory Alkalosis: Core Curriculum 2023" that appeared in the September 2023 issue of *AJKD*,[1] Figure 4 contained an error in the depiction of the mechanism of chronic respiratory alkalosis. In particular, an arrow indicating the change in Na^+/H^+ antiporter and $Na^+/3HCO_3^-$ cotransporter was in error: Na^+/H^+ antiporter and $Na^+/3HCO_3^-$ cotransporter should have been depicted as decreasing, not as increasing. The text describing the mechanism is correct as published. The correct version is supplied below.



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