Chapter

21 ACID-BASE BALANCE AND BLOOD GAS ANALYSIS

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The concentrations of hydrogen and bicarbonate ions in plasma must be precisely regulated to optimize enzyme activity, oxygen transport, and rates of chemical reactions within cells. Each day approximately 15,000 mmol of carbon dioxide (which can generate carbonic acid as it combines with water) and 50 to 100 mEq of nonvolatile acid (mostly sulfuric acid) are produced and must be eliminated safely. The body is able to maintain this intricate acid-base balance by utilizing buffers, pulmonary excretion of carbon dioxide, and renal elimination of acid. This chapter will define concepts important for understanding acids and bases, discuss clinical measurements of blood gases and their interpretation, and present a diagnostic approach to common acid-base disturbances.

DEFINITIONS

Acids and Bases

Bronsted and Lowry defined an acid as a molecule that can act as a proton (H^+) donor and a base as a molecule that can act as a proton acceptor. In physiologic solutions, a strong acid is a substance that readily and irreversibly gives up an H^+, and a strong base avidly binds H^+. In contrast, biologic molecules are either weak acids or bases, which reversibly donate H^+ or reversibly bind H^+.

Acidemia and Acidosis

A blood pH less than 7.35 is called *acidemia* and a pH greater than 7.45 is called *alkalemia*, regardless of the mechanism. The underlying process that lowers the pH is called an *acidosis*, and the process that raises the pH is known as an *alkalosis*. A patient can have a mixed disorder with both an acidosis and an alkalosis concurrently, but can only be either acidemic or alkalemic. The last two terms are mutually exclusive.

Base Excess

Base excess (BE) is usually defined as the amount of strong acid (hydrochloric acid for BE greater than zero) or strong base (sodium hydroxide for BE less than zero) required to return 1 L of whole blood exposed in vitro to a P_{CO_2} of 40 mm Hg to a pH of 7.4.[1] Instead of an actual titration, the blood gas machine calculates the BE with algorithms utilizing plasma pH, blood P_{CO_2}, and hemoglobin concentration. The number is supposed to refer to the nonrespiratory or metabolic component of an acid-base disturbance. A BE less than zero (also called a *base deficit*) suggests the presence of a metabolic acidosis, and a value greater than zero suggests the presence of a metabolic alkalosis. In vitro, the number has been accurate, but in the living organism, because ions do cross beyond vascular and cellular boundaries, a primary acute change in P_{aCO_2} sometimes can cause the BE to move in the opposite direction, despite an unchanged metabolic acid-base status.[2] In clinical practice, the BE is often used as a surrogate measure for lactic acidosis, which is one measurement to help determine adequacy of intravascular volume resuscitation.

REGULATION OF THE HYDROGEN ION CONCENTRATION

At 37° C, the normal hydrogen ion concentration in arterial blood and extracellular fluid is 35 to 45 nmol/L, which is equivalent to an arterial pH of 7.45 to 7.35, respectively. The normal plasma bicarbonate ion concentration is 24 ± 2 mEq/L. The intracellular hydrogen ion concentration is approximately 160 nmol/L, which is equivalent to a pH of 6.8.

Physiologic changes to acid-base disturbances are corrected by three systems—buffers, ventilation, and renal response. The buffer systems provide an immediate chemical response. The ventilatory response occurs in minutes whenever possible, and, lastly, the renal response can slowly provide nearly complete restoration of the pH, but it can take days.

Buffer Systems

A buffer is defined as a substance within a solution that can prevent extreme changes in pH. A buffer system is composed of a base molecule and its weak conjugate acid. The base molecules of the buffer system bind excess hydrogen ions, and the weak acid protonates excess base molecules. The *dissociation ionization constant* (pKa) indicates the strength of an acid and is derived from the classic Henderson-Hasselbalch equation (Fig. 21.1). The pKa is the pH at which an acid is 50% protonated and 50% deprotonated. Hydrochloric acid, a strong acid, has a pKa of –7, whereas carbonic acid, a weak acid, has a pKa of 6. The most important buffer systems in blood, in order of importance, are the (1) bicarbonate buffer system (H_2CO_3/HCO_3^-), (2) hemoglobin buffer system (HbH/Hb), (3) other protein buffer systems (PrH/Pr$^-$), (4) phosphate buffer system ($H_2PO_4^-/HPO_4^{2-}$), and (5) ammonia buffer system (NH_3/NH_4^+).

$$pH = pK_a + \log_{10}\frac{[Base]}{[Conjugate\ acid]}$$

Fig. 21.1 Henderson-Hasselbalch equation. *[Base]*, Concentration of base; *[Conjugate acid]*, concentration of conjugate acid.

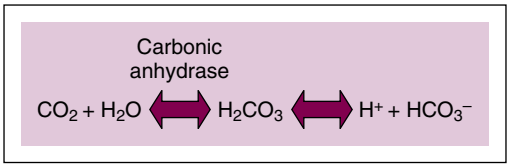

Fig. 21.2 Hydration of carbon dioxide results in carbonic acid, which dissociates into bicarbonate and hydrogen ions.

Bicarbonate Buffer System

Carbon dioxide, generated through aerobic metabolism, slowly combines with water to form carbonic acid, which spontaneously and rapidly deprotonates to form bicarbonate (Fig. 21.2). In this system, the base molecule is bicarbonate, and its weak conjugate acid is carbonic acid. Less than 1% of the dissolved carbon dioxide undergoes this reaction because it is so slow. However, the enzyme carbonic anhydrase, present in the endothelium, erythrocytes, and kidneys, catalyzes this reaction to accelerate the formation of carbonic acid and make this the most important buffering system in the human body when combined with renal control of bicarbonate and pulmonary control of carbon dioxide.

Hemoglobin Buffer System

The hemoglobin protein is the second most important buffering system because of multiple histidine residues. Histidine is an effective buffer from pH 5.7 to 7.7 (pKa 6.8) because it contains multiple protonatable sites on the imidazole side chains. Buffering by hemoglobin depends on the bicarbonate system to facilitate the movement of carbon dioxide intracellularly. Carbon dioxide freely diffuses into erythrocytes, where carbonic anhydrase resides. There, carbon dioxide combines with water to form carbonic acid, which rapidly deprotonates. The generated protons are bound by hemoglobin. The bicarbonate anions are exchanged electroneutrally back into plasma with extracellular chloride (chloride or Hamburger shift) (Fig. 21.3). At the lungs, the reverse process occurs. Chloride ions move out of the red blood cells as bicarbonate enters for conversion back to carbon dioxide. The carbon

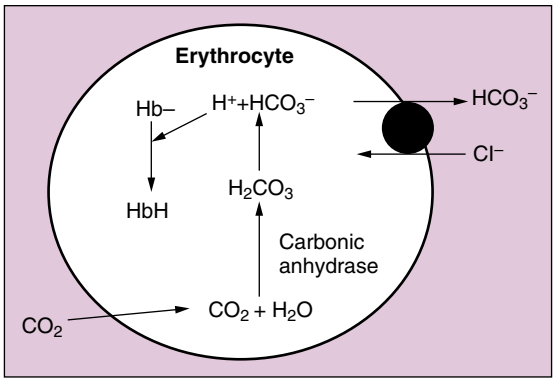

Fig. 21.3 Hemoglobin buffering system: Carbon dioxide freely diffuses into erythrocytes, where it combines with water to form carbonic acid, which rapidly deprotonates. The protons generated are bound up by hemoglobin. The bicarbonate anions are exchanged back into plasma with chloride.

dioxide is released back into plasma and is eliminated by the lungs. This process allows a large fraction of extrapulmonary carbon dioxide to be transported back to the lungs as plasma bicarbonate.

Oxygenated and deoxygenated hemoglobin have different affinities for hydrogen ions and carbon dioxide. Deoxyhemoglobin takes up more hydrogen ions, which shifts the carbon dioxide/bicarbonate equilibrium to produce more bicarbonate and facilitates removal of carbon dioxide from peripheral tissues for release into the lungs. Oxyhemoglobin favors the release of hydrogen ions and shifts the equilibrium to more carbon dioxide formation. At physiologic pH, a small amount of carbon dioxide is also carried as carbaminohemoglobin. Deoxyhemoglobin has a greater affinity (3.5 times) for carbon dioxide, so venous blood carries more carbon dioxide than arterial blood. These two mechanisms combine to account for the difference in carbon dioxide content of arterial versus venous plasma (25.6 mmol/L vs. 27.7 mmol/L, respectively) (Haldane effect).

Ventilatory Response

Central chemoreceptors lie on the anterolateral surface of the medulla and respond to changes in cerebrospinal fluid pH. Carbon dioxide diffuses across the blood-brain barrier to elevate cerebrospinal fluid (CSF) hydrogen ion concentration, which activates the chemoreceptors and increases alveolar ventilation. The relationship between $Paco_2$ and minute ventilation is almost linear except at very high arterial $Paco_2$, when carbon dioxide narcosis develops, and at very low arterial $Paco_2$, when the apneic threshold is reached. There is a very wide variation in individual $Paco_2$/ventilation response curves, but minute ventilation generally increases 1 to 4 L/min for every 1 mm Hg increase in $Paco_2$. During general anesthesia, spontaneous ventilation will cease when the $Paco_2$ decreases to less than the apneic threshold, whereas in the awake patient, cortical influences prevent apnea, so the apneic threshold is not ordinarily observed.

Peripheral chemoreceptors are located at the bifurcation of the common carotid arteries and surrounding the aortic arch. The carotid bodies are the principal peripheral chemoreceptors and are sensitive to changes in Pao_2, $Paco_2$, pH, and arterial perfusion pressure. They communicate with the central respiratory centers via the glossopharyngeal nerves. Unlike the central chemoreceptors, which are more sensitive to hydrogen ions, the carotid bodies are most sensitive to Pao_2. Bilateral carotid endarterectomies abolish the peripheral chemoreceptor response, and these patients have almost no hypoxic ventilatory drive (also see Chapter 25).

The stimulus from central and peripheral chemoreceptors to either increase or decrease alveolar ventilation diminishes as the pH approaches 7.4 such that complete correction or overcorrection is not possible. The pulmonary response to metabolic alkalosis is usually less than the response to metabolic acidosis. The reason is because progressive hypoventilation results in hypoxemia when breathing room air. Hypoxemia activates oxygen-sensitive chemoreceptors and limits the compensatory decrease in minute ventilation. Because of this, the $Paco_2$ usually does not rise above 55 mm Hg in response to metabolic alkalosis for patients not receiving oxygen supplementation.

Renal Response

Renal effects are slower in onset and may not be maximal for up to 5 days. The response occurs via three mechanisms: (1) reabsorption of the filtered HCO_3^-, (2) excretion of titratable acids, and (3) ammonia (Fig. 21.4).[3] Carbon dioxide combines with water in the renal tubular cell. With the help of carbonic anhydrase, the bicarbonate produced enters the bloodstream while the hydrogen ion is exchanged with sodium and is released into the renal tubule. There, H^+ combines with filtered bicarbonate and dissociates into carbon dioxide and water with help from carbonic anhydrase located in the luminal brush border, and the carbon dioxide diffuses back into the renal tubular cell. The proximal tubule reabsorbs 80% to 90% of the bicarbonate this way, while the distal tubule takes care of the remaining 10% to 20%. Once the bicarbonate is reclaimed, further hydrogen ions can combine with HPO_4^{2-} to form $H_2PO_4^-$, which is eliminated in the urine. The last important urinary buffer is ammonia. Ammonia is formed from deamination of glutamine, an amino acid. The ammonia passively crosses the cell membrane to enter the tubular fluid. In the tubular fluid, it combines with hydrogen ion to form NH_4^+, which is trapped within the tubule and excreted in the urine. All of these

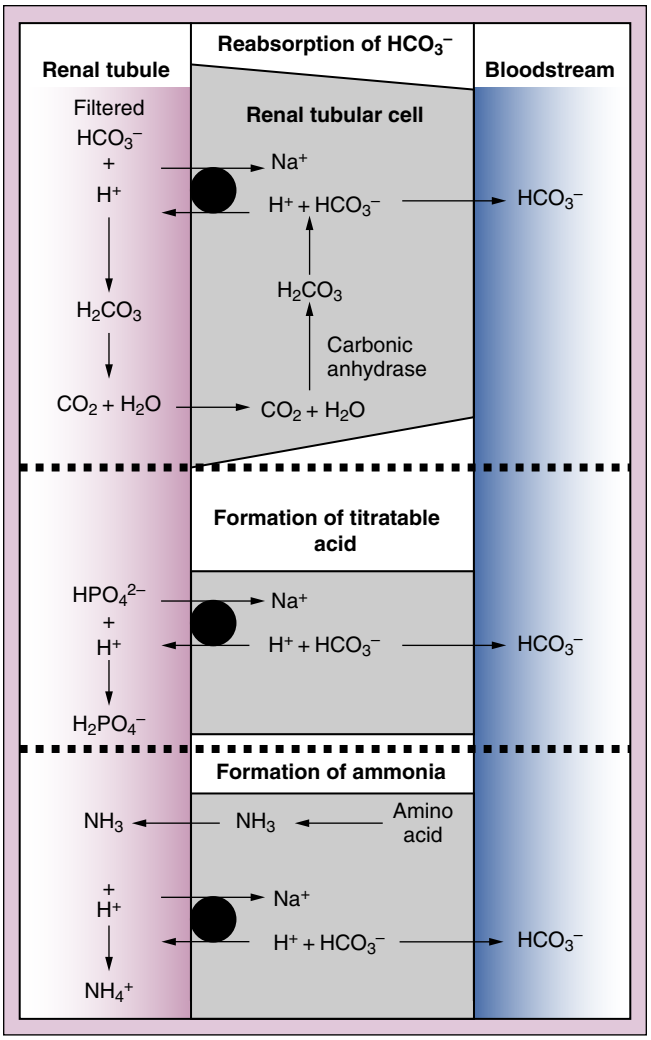

Fig. 21.4 Three mechanisms of renal compensation during acidosis to sequester hydrogen ions and reabsorb bicarbonate: (1) reabsorption of the filtered HCO_3^-, (2) excretion of titratable acids, and (3) production of ammonia.

steps allow for generation and return of bicarbonate into the bloodstream. The large amount of bicarbonate filtered by the kidneys allows for rapid excretion if necessary for compensation during alkalosis. The kidneys are highly effective in protecting the body against alkalosis except in association with sodium deficiency or mineralocorticoid excess.

ANALYSIS OF ARTERIAL BLOOD GASES

The ability to measure arterial blood gas (ABG) and venous blood gas has revolutionized patient care during anesthesia and in the intensive care unit. Although pulse oximetry and capnography can be monitored continuously, analysis of ABGs has increased our diagnostic ability and the accuracy of our measurements.

Blood Gas and pH Electrodes

pH Electrode

The pH electrode is a silver/silver chloride electrode encased in a special pH-sensitive glass that contains a buffer solution with a known pH. The electrode is placed in a blood sample and measures changes in voltage. The potential difference generated across the glass and a reference electrode is proportional to the difference in hydrogen ion concentration. Both electrodes must be kept at 37° C and calibrated with buffer solutions of known pH.

Oxygen Electrode

The O_2 electrode is known as the Clark or polarographic electrode.[4] It has a silver/silver chloride reference electrode that is immersed in a potassium chloride solution. Electrons are formed by the oxidation reaction of the silver with the chloride ions of the potassium chloride electrolyte solution. The electrons are then free to combine with O_2 molecules at the platinum cathode. The platinum surface is covered with an oxygen-permeable membrane (polyethylene), on the other side of which is placed the unknown sample. Current flow is increased if oxygen concentration is higher and more electrons are taken up. The current is directly proportional to the Po_2.

Carbon Dioxide Electrode

The carbon dioxide sensor was first described by Stow in 1957 and then modified by Bradley and Severinghaus.[5] The carbon dioxide electrode is a pH electrode immersed in a sodium bicarbonate solution and is separated from the blood specimen by a Teflon semipermeable membrane. The carbon dioxide in the sample diffuses into the sodium bicarbonate solution producing hydrogen ions and bicarbonate. The measured pH in the bathing solution is altered in direct proportion to the logarithm of the Pco_2.

Sampling

Arterial blood is most often obtained percutaneously from the radial, brachial, or femoral artery. In certain clinically stable situations, peripheral venous blood may serve as an approximation and save an arterial puncture. Venous pH is only 0.03 to 0.04 less than arterial values. Venous blood cannot be used for estimation of oxygenation because venous Po_2 (Pvo_2) is significantly less than Pao_2. Also, depending on the site of the venous blood draw, differences in tissue metabolic activity may alter Pvo_2. The correlation between arterial and venous blood gas measurements varies with the hemodynamic stability of the patient. Periodic correlations of arterial and venous measurements should be performed especially when venous measurements are used for serial monitoring in critically ill patients.[6]

A heparinized, bubble-free, fresh blood sample is required for blood gas analysis. In the past, liquid heparin was aspirated into a syringe and then expelled. This small amount of heparin remaining in the syringe was enough to anticoagulate the sample. Excessive amounts of anticoagulant in the sampling syringe could falsely dilute the measured Po_2, Pco_2, and ionized calcium. Commercially prepared syringes with preweighed lyophilized electrolyte-balanced heparin are used in most hospitals now. Air bubbles should be removed because equilibration of oxygen and carbon dioxide in the blood with the corresponding partial pressures in the air bubble could influence the measured results. A delay in analysis can lead to oxygen consumption and carbon dioxide generation by the metabolically active white blood cells. Usually this error is small and can be reduced by placing the sample on ice. In some leukemia patients with a markedly increased white blood cell count, this error can be large and lead to a falsely low Po_2 even though the patient's oxygenation is acceptable. This phenomenon is often referred to as *leukocyte larceny* and has also been described with extreme thrombocytosis (platelet larceny).[7]

Temperature Correction

Decreases in temperature decrease the partial pressure of a gas in solution, even though the total gas content does not change. Both Pco_2 and Po_2 decrease during hypothermia, but serum bicarbonate is unchanged. This leads to an increase in pH if the blood could be measured at the patient's temperature. A blood gas with a pH of 7.4 and Pco_2 of 40 mm Hg at 37° C will have a pH of 7.58 and a Pco_2 of 23 mm Hg at 25° C.[8] Unfortunately, all blood gas samples are measured at 37° C, which raises the issue of how to best manage the ABG measurement in hypothermic patients. This has led to two schools of thought: alpha stat and pH stat.

Alpha Stat

Alpha refers to the protonation state of the imidazole side chain of histidine. The pKa of histidine changes with temperature so that its protonation state is relatively constant regardless of temperature. The term *alpha stat* developed because as the patient's pH was allowed to drift with temperature, the protonation state of the histidine residues remained *static*. This concept arose from the observation that *cold-blooded* poikilothermic animals functioned well over a wide range of body temperatures, yet they relied on a similar complement of enzymes as *warm-blooded* homeothermic animals. During cardiopulmonary bypass, an anesthesia provider using alpha stat would manage the patient based on an ABG measured at 37° C and strive to keep that pH at 7.4, but the patient's true pH would be higher. No extra adjustments would be made for the patient's hypothermia.

pH Stat

pH stat is different from alpha stat in that it requires keeping a patient's pH static at 7.4 based on the core temperature (similar to that of a hibernating, homeothermic animal). During cardiopulmonary bypass, an anesthesia provider using pH stat would manage the patient based on an ABG that is corrected for the patient's temperature. With hypothermia, this usually means adding carbon dioxide so that the patient's temperature-correct (hypothermic) blood gas has a pH of 7.4. The lower pH and higher Pco_2 maintained during pH stat may improve cerebrovascular perfusion during hypothermia; however, there is still debate about which method provides better outcomes.[9]

Oxygenation

The same physical properties exist for oxygen and hypothermia as for carbon dioxide. Decreases in temperature decrease the partial pressure of a gas in solution, so temperature correction of Po_2 remains relatively important for assessing oxygenation at the extremes of temperature. To be exact, the change in Po_2 with respect to temperature depends on the degree that hemoglobin is saturated with oxygen, but as a guideline, the Po_2 is decreased approximately 6% for every 1° C that the patient's body temperature is below 37° C. Po_2 is increased approximately 6% for every 1° C that the body temperature exceeds 37° C.

DIFFERENTIAL DIAGNOSIS OF ACID-BASE DISTURBANCES

Acid-base disturbances are categorized as respiratory or metabolic acidosis (pH less than 7.35) or alkalosis (pH more than 7.45). These disorders are further stratified into acute versus chronic based on their duration, which is gauged clinically by the patient's compensatory responses.[10] It must be kept in mind that a patient may have a mixed acid-base disorder. The approach to managing acid-base disorders should first involve searching for the causes, rather than an immediate attempt to normalize the pH. Sometimes the treatment may be more detrimental than the original acid-base problem.

Adverse Responses to Acidemia and Alkalemia

Adverse responses can be associated with severe acidemia or alkalemia. Consequences of severe acidosis can occur regardless of whether the acidosis is of respiratory, metabolic, or mixed origin. Acidemia usually leads to decreased myocardial contractility and release of catecholamines. With mild acidosis, the release of catecholamines mitigates the myocardial depression. Permissive hypercapnia, which is used as a protective lung ventilation strategy for acute respiratory distress syndrome (ARDS) patients, has been quite well tolerated. No significant impact on systemic vascular resistance, pulmonary vascular resistance, cardiac output, or systemic oxygen delivery has been seen.[11] With severe acidemia (pH < 7.2), myocardial responsiveness to catecholamines decreases, so myocardial depression and hypotension predominates (Fig. 21.5). Respiratory acidosis may produce more rapid and profound myocardial dysfunction than metabolic acidosis because of the rapid entry of carbon dioxide into the cardiac cell. In the brain, this rapid increase in carbon dioxide can lead to confusion, loss of consciousness, and seizures. This is probably due to an abrupt decrease of intracellular pH, because chronic increases in carbon dioxide as high as 150 mm Hg are typically well tolerated.

Severe alkalemia (pH > 7.6) can lead to decreased cerebral and coronary blood flow as a result of arteriolar vasoconstriction. The consequences of severe alkalosis are also more prominent with respiratory than with metabolic causes because of the rapid movement of carbon dioxide across cell membranes.[12] Acute hyperventilation can produce confusion, myoclonus, depressed consciousness, and seizures.

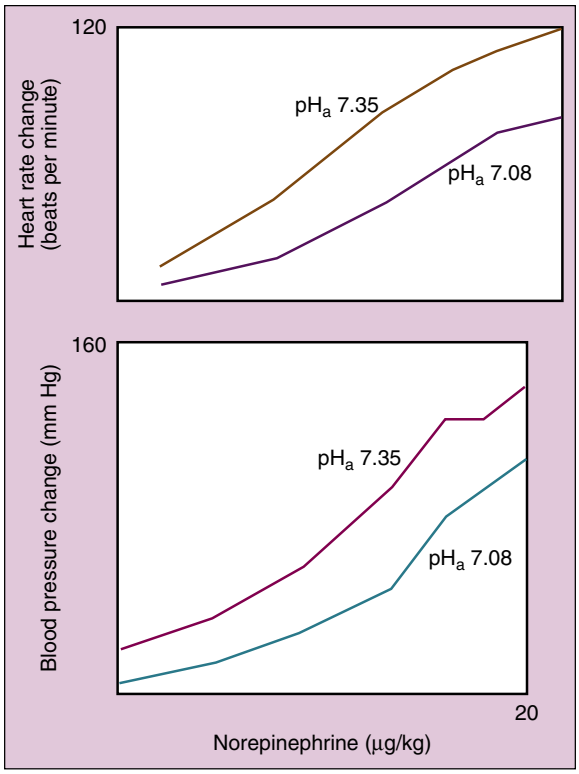

Fig. 21.5 Diminished hemodynamic response to intravenously administered norepinephrine in a canine model of lactic acidosis. pHa = arterial pH. (From Ford GD, Cline WH, Fleming WW. Influence of lactic acidosis on cardiovascular response to sympathomimetic amines. *Am J Physiol.* 1968;215(5):1123-1129, used with permission.)

Respiratory Acidosis

Respiratory acidosis occurs when alveolar minute ventilation is inadequate relative to carbon dioxide production (Box 21.1). It can occur with a normal or increased minute ventilation if carbon dioxide production is increased from sepsis or overfeeding or if there is decreased carbon dioxide elimination from ARDS or obstructive lung disease. Decreased carbon dioxide elimination from a decreased minute ventilation can occur with volatile or intravenous anesthetics (see Chapter 8), neuromuscular blocking drugs (see Chapter 11), or neuromuscular disease. Increased rebreathing or absorption, found with exhausted soda lime, an incompetent one-way valve, or laparoscopic surgery can cause respiratory acidosis.

Box 21.1 Causes of Respiratory Acidosis

- Increased CO_2 production
  - Malignant hyperthermia
  - Hyperthyroidism
  - Sepsis
  - Overfeeding
- Decreased CO_2 elimination
  - Intrinsic pulmonary disease (pneumonia, ARDS, fibrosis, edema)
  - Upper airway obstruction (laryngospasm, foreign body, OSA)
  - Lower airway obstruction (asthma, COPD)
  - Chest wall restriction (obesity, scoliosis, burns)
  - CNS depression (anesthetics, opioids, CNS lesions)
  - Decreased skeletal muscle strength (residual effects of neuromuscular blocking drugs, myopathy, neuropathy)
- Increased CO_2 rebreathing or absorption
  - Exhausted soda lime
  - Incompetent one-way valve in breathing circuit
  - Laparoscopic surgery

ARDS, Acute respiratory distress syndrome; *CNS*, central nervous system; *CO_2*, carbon dioxide; *COPD*, chronic obstructive pulmonary disease; *OSA*, obstructive sleep apnea.

Compensatory Responses and Treatment

Over the course of hours to days, the kidneys compensate for the respiratory acidosis by increased hydrogen ion secretion and bicarbonate reabsorption. After a few days, the P_{CO_2} will remain increased, but the pH will be near normal, which is the hallmark of a chronic respiratory acidosis. Respiratory acidosis with a pH less than 7.2 indicates the need for tracheal intubation or increased ventilatory support. In patients with chronic respiratory acidosis, the key is to avoid hyperventilation. The alkalosis from excessive ventilation and relative hypocapnia can result in central nervous system (CNS) irritability and cardiac ischemia. Also, the kidneys will now start to lose bicarbonate. The increased bicarbonate has allowed the patient to maintain a normal pH with a relatively smaller alveolar minute ventilation. Losing the bicarbonate will increase the work of breathing when ventilatory support is decreased, making it difficult to wean from the ventilator.

Respiratory Alkalosis

Respiratory alkalosis occurs when alveolar minute ventilation is increased relative to carbon dioxide production. The increased alveolar minute ventilation can be related to a variety of causes (Box 21.2). P_{aCO_2} is diminished relative to bicarbonate levels, resulting in a pH more than 7.45. The decreased P_{aCO_2} and increased pH trigger the peripheral and central chemoreceptors to decrease the stimulus to breathe. During prolonged respiratory alkalosis, active transport of bicarbonate ions out of CSF causes the central chemoreceptors to reset to a lower P_{aCO_2} level.

Box 21.2 Causes of Respiratory Alkalosis

- Increased minute ventilation
  - Hypoxia (high altitude, low F_{IO_2}, severe anemia)
  - Iatrogenic (mechanical ventilation)
  - Anxiety and pain
  - CNS disease (tumor, infection, trauma)
  - Fever, sepsis
  - Drugs (salicylates, progesterone, doxapram)
  - Liver disease
  - Pregnancy
  - Restrictive lung disease
  - Pulmonary embolism

CNS, Central nervous system; *F_{IO_2}*, fractional concentration of inspired oxygen.

Box 21.3 Causes of Metabolic Acidosis

Anion Gap Acidosis

- Methanol, ethylene glycol
- Uremia
- Lactic acidosis = CHF, sepsis, cyanide toxicity
- Ethanol
- Paraldehyde
- Aspirin, INH
- Ketones = starvation, diabetic ketoacidosis

Nongap Acidosis

- Excessive chloride administration
- GI losses—diarrhea, ileostomy, neobladder, pancreatic fistula
- Renal losses—RTA
- Drugs—acetazolamide

CHF, Congestive heart failure; *GI*, gastrointestinal; *INH*, isoniazid; *RTA*, renal tubular acidosis.

Compensatory Responses and Treatment

Respiratory alkalosis is compensated for by decreased reabsorption of bicarbonate ions from the renal tubules and increased urinary excretion of bicarbonate. Treatment of respiratory alkalosis is directed at correcting the underlying disorder. Mild alkalemia usually does not require treatment. In rare cases, severe acute respiratory alkalosis (pH > 7.6) may require sedation. During general anesthesia, acute respiratory alkalosis is easily remedied by decreasing total minute ventilation.

Metabolic Acidosis

Metabolic acidosis is present when accumulation of any acid in the body other than carbon dioxide results in a pH lower than 7.35 (Box 21.3). A compensatory increase in ventilatory elimination of carbon dioxide starts within minutes after the development of metabolic acidosis to provide a near normal pH. Some patients, however, may not be able to sustain the increased minute ventilation and require tracheal intubation and mechanical ventilation.

$$\text{Anion gap} = [Na^+] - ([Cl^-] + [HCO_3^-])$$

Fig. 21.6 Calculation of the anion gap: the difference between the cations and the anions equals the concentration of unmeasured anions in serum.

Anion Gap

The best way to categorize the differential diagnosis for a metabolic acidosis is to divide these causes into those that cause or do not cause an anion gap. The anion gap is the difference between measured cations (sodium) and measured anions (chloride and bicarbonate) and represents the concentration of anions in serum that are unaccounted for in this equation (Fig. 21.6). A normal anion gap value is 8 to 12 mEq/L and is mostly composed of anionic serum albumin.[13] A patient with a low serum albumin concentration will likely have a narrower anion gap value (each 1.0 g/dL decrease or increase in serum albumin less or more than 4.4 g/dL decreases or increases the actual concentration of unmeasured anions by approximately 2.5 mEq/L). An increase in the anion gap occurs when the anion replacing bicarbonate is not one that is routinely measured. The most common unmeasured anions are lactic acid and keto acids. Metabolic acidosis with a normal anion gap occurs when chloride replaces the lost bicarbonate such as with a bicarbonate-wasting process in the kidneys (renal tubular acidosis) or gastrointestinal tract (diarrhea). Aggressive fluid resuscitation with normal saline (>30 mL/kg/h) will induce a nongap metabolic acidosis secondary to excessive chloride administration, which impairs bicarbonate reabsorption in the kidneys.[14]

Strong Ion Difference

A second way to categorize metabolic acidoses is the strong ion difference (SID) introduced by Peter Stewart in the 1980s.[15] His major tenet is that although serum bicarbonate and BE can be used to determine the extent of a clinical acid-base disorder, they do not help determine the mechanism of the abnormality. Instead, he proposed that the independent variables responsible for changes in acid-base balance are the SID (the difference between the completely dissociated cations and anions in plasma) (Fig. 21.7), the plasma concentration of nonvolatile weak acids (A_{TOT}), and the arterial carbon dioxide tension ($Paco_2$). The strong ion approach distinguishes six primary acid-base disturbances (acidosis due to decreased SID, alkalosis due to increased SID, acidosis due to increased A_{TOT}, alkalosis due to decreased A_{TOT}, respiratory acidosis, or respiratory alkalosis) instead of the four primary acid-base disturbances (respiratory acidosis or alkalosis, or metabolic acidosis or alkalosis) differentiated by the traditional Henderson-Hasselbalch equation. Under normal conditions, the SID is approximately 40 mEq/L. Processes that increase the SID increase blood pH, whereas processes that reduce it decrease pH. For instance, in the case of massive volume resuscitation with normal saline, the major ions are Na^+ and Cl^-, which gives the fluid an SID of 0. Because infusions of saline would lower the normal SID of 40, this leads to a strong ion acidosis. With the Stewart approach, administering a solution with a high SID, such as sodium bicarbonate, should treat the resultant strong ion acidosis.

The major practical difference between the two theories (Stewart vs. Henderson-Hasselbalch) is the inclusion of the serum albumin concentration in the Stewart approach, which provides some increase in accuracy in certain clinical settings. If changes in serum albumin concentration are accounted for in measurement of the anion gap, the more complex Stewart approach does not appear to offer a clinically significant advantage over the traditional approach to acid-base disturbances.[16]

Compensatory Responses and Treatment

The compensatory responses for a metabolic acidosis include increased alveolar ventilation from carotid body stimulation and renal tubule secretion of hydrogen ions into urine. Chronic metabolic acidosis, as seen with chronic renal failure, is commonly associated with loss of bone mass because buffers present in bone are used to neutralize the nonvolatile acids.

Treatment of metabolic acidosis is based on whether an anion gap is present or not. Intravenous administration of sodium bicarbonate is often given for a nongap metabolic acidosis because the problem is bicarbonate loss. Management of an anion gap metabolic acidosis is guided by diagnosis and treatment of the underlying cause in order to remove the nonvolatile acids from the circulation. Tissue hypoxia leading to lactic acidosis should be corrected if possible with oxygen, fluid resuscitation, and circulatory support. Diabetic ketoacidosis requires intravenous fluid and insulin therapy. Minute ventilation can be increased in a patient who is mechanically ventilated to compensate until more definitive treatment takes effect.

Bicarbonate therapy is more controversial, but may be considered in the setting of extreme metabolic acidosis as a temporizing measure, particularly when a patient is hemodynamically unstable. Sodium bicarbonate administration generates carbon dioxide, which, unless eliminated by ventilation, can worsen any intracellular and extracellular acidosis. A common approach is to administer a small dose of sodium bicarbonate, and then repeat the pH measurement and monitor hemodynamics to determine the impact of treatment. Alkalinizing drugs, because of their osmotic properties, introduce the risk of causing hypervolemia and hypertonicity.

$$\begin{aligned} SID &= [\text{strong cations}] - [\text{strong anions}] \\ &= [Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - ([Cl^-] + [SO_4^{2-}] + [\text{organic acids}^-]) \\ &\approx [Na^+] + [K^+] - [Cl^-] \end{aligned}$$

Fig. 21.7 Calculation of the strong ion difference (SID): the difference between the completely dissociated cations and anions in plasma.

Metabolic Alkalosis

Metabolic alkalosis is present when the pH is higher than 7.45 due to gain of bicarbonate ions or loss of hydrogen ions. The loss of hydrogen ions is usually from the gastrointestinal tract or the kidney. The stimulus for bicarbonate reabsorption or gain is usually from hypovolemia, hypokalemia, or hyperaldosteronism (Box 21.4). In hypovolemia, because of insufficient chloride ions, bicarbonate is reabsorbed with sodium. With the adoption of low tidal volumes (4 to 6 mL/kg) and permissive hypercapnia for ventilatory management of ARDS patients, a compensatory metabolic alkalosis is often a common finding for the critically ill patient.

Compensatory Responses and Treatment

Compensatory responses for metabolic alkalosis include increased reabsorption of hydrogen ions by renal tubule cells, decreased secretion of hydrogen ions by renal tubule cells, and alveolar hypoventilation. The efficiency of the renal compensatory mechanism is dependent on the presence of cations (sodium, potassium) and chloride. Lack of these ions impairs the ability of the kidneys to excrete excess bicarbonate and results in incomplete renal compensation. Respiratory compensation for pure metabolic alkalosis, in contrast to metabolic acidosis, is never more than 75% complete. As a result, the pH remains increased in patients with primary metabolic alkalosis. Treatment of metabolic alkalosis should be aimed at reducing the acid loss (e.g., by stopping gastric drainage) or fluid repletion with saline and potassium chloride, which allows the kidneys to excrete excess bicarbonate ions. Occasionally, a trial of acetazolamide may be useful in causing a bicarbonaturia. Life-threatening metabolic alkalosis is rarely encountered.

Diagnosis

The diagnosis of an acid-base disorder should occur in a structured fashion. Fig. 21.8 shows a stepwise algorithm for blood gas interpretation. Step 1, which determines oxygenation, will be discussed later in this chapter. Step 2 involves determining whether the patient is acidemic (pH < 7.35) or alkalemic (pH > 7.45). Step 3 looks at whether the cause is from a primary metabolic or respiratory process. Metabolic processes involve a change in bicarbonate concentration from 24 mEq/L, and respiratory processes involve a change in P_{CO_2} from 40 mm Hg. If the primary process is respiratory in origin, then step 4 assesses whether the abnormality is chronic or acute (Box 21.5). If a metabolic alkalosis is present, then the next step is to skip to step 7 and determine whether appropriate respiratory compensation is present (Box 21.6). If the measured P_{CO_2} is more than expected, a concurrent respiratory acidosis is present. If the measured P_{CO_2} is less than expected, then a concurrent respiratory alkalosis is present. If a metabolic acidosis is present, then an anion gap should be calculated (step 5). If there is a gap, then a Δgap should be determined. The Δgap is the excess anion gap (anion gap minus 12) added back to the serum bicarbonate level. If the number is less than 22 mEq/L, then a concurrent nongap metabolic acidosis is present. If the number is more than 26 mEq/L, then a concurrent metabolic alkalosis is present. The last step, step 7, determines whether an appropriate respiratory compensation is present for the metabolic acidosis. If the measured P_{CO_2} is more than expected [as calculated by the formula $P_{CO_2} = (0.7 \times HCO_3^-) + 21$], then a concurrent respiratory acidosis is present. If the measured P_{CO_2} is less than calculated, then a concurrent respiratory alkalosis is present. See sample calculations in Fig. 21.9.

Box 21.4 Causes of Metabolic Alkalosis

Chloride Responsive
Renal loss—diuretic therapy
GI loss—vomiting, NG suction
Alkali administration—citrate in blood products, acetate in TPN, bicarbonate

Chloride Resistant
Hyperaldosteronism
Refeeding syndrome
Profound hypokalemia

GI, Gastrointestinal; *NG*, nasogastric; *TPN*, total parenteral nutrition.

OTHER INFORMATION PROVIDED BY ANALYSIS OF ARTERIAL BLOOD GASES AND pH

Aside from acid-base problems, additional measurements and information available from a blood gas analysis include the patient's ability to ventilate and oxygenate and cardiac output estimates.

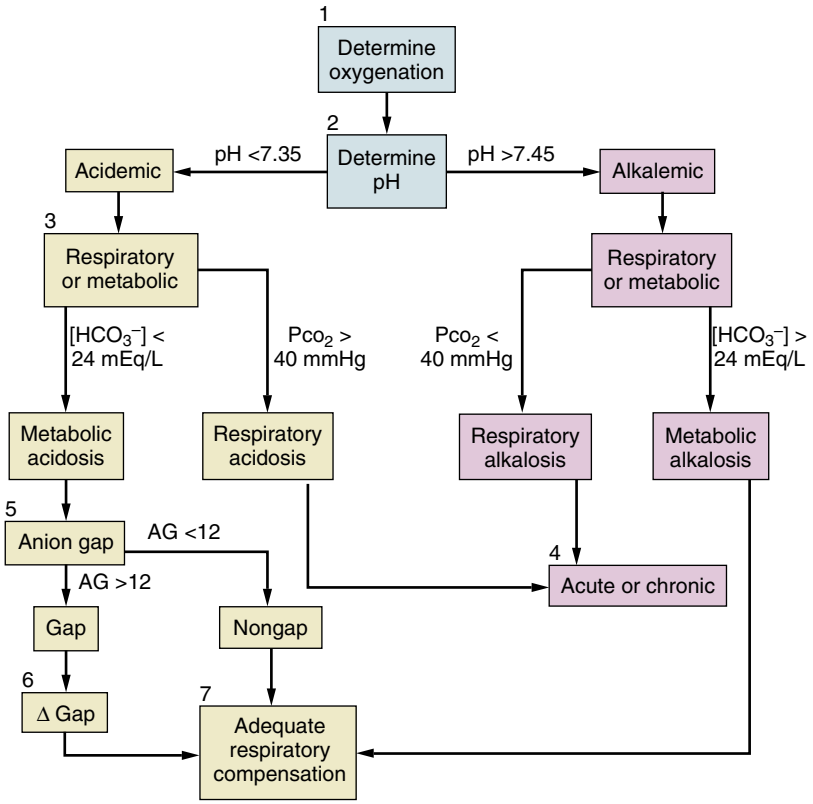

Fig. 21.8 Seven steps for acid-base diagnosis. Δgap = anion gap − 12 + [HCO_3^-]. If Δgap is less than 22 mEq/L, then concurrent nongap metabolic acidosis exists. If Δgap is greater than 26 mEq/L, then concurrent metabolic alkalosis exists. *AG*, Anion gap.

Box 21.5 Determining Whether Respiratory Process Is Acute or Chronic

Acute Process
pH Δ 0.08 for every 10 mm Hg Δ in P_{CO_2} from 40 mm Hg

Chronic Process
pH Δ 0.03 for every 10 mm Hg Δ in P_{CO_2} from 40 mm Hg

Ventilation

P_{aCO_2} reflects the adequacy of ventilation for removing carbon dioxide from blood. A measured P_{aCO_2} above 45 mm Hg suggests that a patient is hypoventilating relative to carbon dioxide production, whereas a P_{aCO_2} below 35 mm Hg suggests that a patient is hyperventilating. Increased dead space ventilation markedly decreases the efficiency of ventilation. The V_D/V_T ratio is the fraction of each tidal volume that is involved in dead space ventilation. This value is usually around 0.25 to 0.3 because of anatomic dead space. When minute ventilation is held constant during anesthesia, the gradient between P_{aCO_2} and end-tidal CO_2 ($ETCO_2$) will increase if dead space is increased (e.g., pulmonary embolus or reduced cardiac output).

Box 21.6 Determining Appropriate Compensation in Acid-Base Disorders

Metabolic Alkalosis
$P_{CO_2} = (0.7 \times HCO_3^-) + 21$
If measured P_{CO_2} > calculated P_{CO_2}, then concurrent respiratory acidosis is present.
If measured P_{CO_2} < calculated P_{CO_2}, then concurrent respiratory alkalosis is present.

Metabolic Acidosis
Winter's formula:
$P_{CO_2} = (1.5 \times HCO_3^-) + 8$
If measured P_{CO_2} > calculated P_{CO_2}, then concurrent respiratory acidosis is present.
If measured P_{CO_2} < calculated P_{CO_2}, then concurrent respiratory alkalosis is present.

Oxygenation

Oxygenation is assessed by measurement of P_{aO_2}. Arterial hypoxemia may be caused by (1) a low P_{O_2} in the inhaled gases (altitude, accidental occurrence during anesthesia), (2) hypoventilation, or (3) venous admixture with or

A 23-year-old man with insulin-dependent diabetes presents to the emergency room with somnolence, influenza-like symptoms, nausea, vomiting, and anorexia.

Laboratory values: Na 130 mEq/L, Cl 80 mEq/L, HCO_3^- 10 mEq/L
ABG: pH 7.20, P_{CO_2} 35 mm Hg, P_{O_2} 68 mm Hg on room air

Step 1: Determine oxygenation:
A-a gradient = $[(P_B - P_{H_2O})F_{IO_2} - Pa_{CO_2}/RQ] - Pa_{O_2}$
= $(150 - Pa_{CO_2}/0.8) - Pa_{O_2}$
= (150 – 35/0.8) – 68
= 38
There is an A-a gradient, possibly from pneumonia or aspiration.

Step 2: Determine pH: pH <7.4, so there is an acidosis.

Step 3: $[HCO_3^-]$ <24 mEq/L and P_{CO_2} <40 mm Hg
Primary abnormality is from metabolic acidosis.

Step 4: Not applicable here since we are going down metabolic acidosis pathway.

Step 5: Determine anion gap
Anion gap = [Na] – ([Cl] + $[HCO_3^-]$) should be <12
= 130 – (80 + 10)
= 40 mEq/L
There is an anion gap, probably from starvation or diabetic ketoacidosis.

Step 6: Determine Δ gap
Δ gap = anion gap – 12 + $[HCO_3^-]$
= 40 – 12 + 10
= 38 mEq/L
There is a concurrent metabolic alkalosis probably from vomiting.

Step 7: Is there appropriate respiratory compensation?
Winter's formula = 1.5 $[HCO_3^-]$ + 8 = expected P_{CO_2}
= 1.5 (10) + 8
= 23 mm Hg
There is also a respiratory acidosis probably from somnolence.

Fig. 21.9 Example for calculating acid-base abnormalities. *ABG*, Arterial blood gas.

without decreased mixed venous oxygen content. Acute hypoxemia causes activation of the sympathetic nervous system with endogenous catecholamine release, which augments blood pressure and cardiac output despite the vasodilating effects of hypoxemia. The increased cardiac output will increase oxygen delivery from the lungs to peripheral tissues.

Alveolar Gas Equation

The alveolar gas equation estimates the partial pressure of alveolar oxygen by accounting for barometric pressure, water vapor pressure, and the inspired oxygen concentration (Fig. 21.10). Atmospheric oxygen is a constant 21% of barometric pressure; however, barometric pressure diminishes with altitude such that the decrease in inspired oxygen can become significant. Hypoventilation leads to increased P_{CO_2}, which encroaches on the space available in the alveolus for oxygen and dilutes the oxygen concentration. The alveolar gas equation estimates this decrease in alveolar oxygen concentration by subtracting an amount equal to the carbon dioxide divided by the respiratory quotient.

Alveolar-Arterial Gradient

Calculation of the alveolar-arterial (A-a) gradient provides an estimate of venous admixture as the cause of hypoxemia (see Fig. 21.10). Venous admixture refers to deoxygenated venous blood mixing with oxygenated arterial blood through shunting. The A-a gradient formula calculates the difference in oxygen partial pressure between alveolar (P_{AO_2}) and arterial (Pa_{O_2}) blood. Normally, the A-a gradient is less than 15 mm Hg while breathing room air as a result of shunting via the thebesian and bronchial veins. Age increases the A-a gradient because of progressive increase in closing capacity relative to functional residual capacity (FRC). Increased fractional concentration of inspired oxygen (F_{IO_2}) can lead to a larger gradient (up to 60 mm Hg

Alveolar gas equation: $P_{AO_2} = (P_b - P_{H_2O})F_{IO_2} - P_{aCO_2}/RQ$

P_{AO_2} = alveolar partial pressure oxygen (mm Hg)
P_B = barometric pressure (760 mm Hg at sea level)
P_{H_2O} = partial pressure of water vapor (47 mm Hg at 37° C)
F_{IO_2} = fraction inspired oxygen concentration
RQ = respiratory quotient (0.8 for normal diet)

A-a gradient = $P_{AO_2} - P_{aO_2}$

For patient with P_{aO_2} of 363 mm Hg and P_{aCO_2} of 40 mm Hg breathing F_{IO_2} 1.0

P_{AO_2} = (760 – 47)(1.0) – 40/0.8
= (713) – 50
= 663 mm Hg

A-a gradient = 663 – 363
= 300 mm Hg

% shunt = 1% for every 20 mm Hg of A-a gradient
= 300/20
= 15%

Fig. 21.10 The alveolar gas equation, calculation of alveolar-arterial (A-a) gradient, and estimation of percentage of shunt.

while breathing F_{IO_2} 1.0). Vasodilating drugs (nitroglycerin, nitroprusside, inhaled anesthetics), which inhibit hypoxic pulmonary vasoconstriction and increase ventilation/perfusion ($\dot{V}/\dot{Q}$ mismatch), can also increase the A-a gradient.

Larger A-a gradients suggest the presence of pathologic shunting, such as right-to-left intrapulmonary shunts (atelectasis, pneumonia, endobronchial intubation) or intracardiac shunts (congenital heart disease). The A-a gradient provides an assessment of the patient's shunt fraction and is more sensitive than pulse oximetry. A patient may have an S_{aO_2} of 100% but have a P_{aO_2} of only 90 mm Hg while breathing 100% oxygen. Significant shunting secondary to a pulmonary or cardiac process has occurred despite the reassuring pulse oximeter reading. In patients with large shunts (>50%), administration of 100% oxygen will be unable to raise P_{aO_2}.

To estimate the amount of shunt present, when P_{aO_2} is higher than 150 mm Hg, the shunt fraction is approximately 1% of cardiac output for every 20 mm Hg difference in the A-a gradient. When P_{aO_2} is less than 150 mm Hg or when cardiac output is increased relative to metabolism, this guideline will underestimate the actual amount of venous admixture.

P_{aO_2}/F_{IO_2} Ratio

The P_{aO_2}/F_{IO_2} (P/F) ratio is a simple alternative to the A-a gradient to communicate the degree of hypoxemia. Standards have been created to define the P/F ratio for acute lung injury (ALI) versus ARDS in order to recruit more homogeneous research subjects. Patients with mild ARDS have a P/F ratio below 300, whereas patients with moderate ARDS have a P/F ratio below 200.[17] A ratio under 200 suggests a shunt fraction greater than 20%.

Cardiac Output Estimates

Normal mixed venous P_{O_2} ($P\bar{v}_{O_2}$) is 40 mm Hg and is a balance between oxygen delivery and tissue oxygen consumption. A true $P\bar{v}_{O_2}$ should reflect blood from the superior and inferior vena cava and the heart. It is usually obtained from the distal port of an unwedged pulmonary artery (PA) catheter. Owing to the complexity and risks of placing a PA catheter, many clinicians simply follow the trend from a central line placed in the superior vena cava.[18] If tissue oxygen consumption is unchanged, changes in $P\bar{v}_{O_2}$ reflect direct changes in cardiac output. The $P\bar{v}_{O_2}$ will decrease when there is inadequate cardiac output because the peripheral tissues have to increase oxygen extraction for aerobic metabolism. The $P\bar{v}_{O_2}$ will increase when there is high cardiac output (sepsis), peripheral shunting (arteriovenous [AV] fistulas), or impaired oxygen extraction (cyanide toxicity).

Fick Equation

If P_{aO_2}, $P\bar{v}_{O_2}$, and hemoglobin are measured, the cardiac output can then be calculated by using the Fick equation (Fig. 21.11), which states that the delivery of oxygen in the veins must equal the delivery of oxygen in the arteries minus what is consumed (V_{O_2}). The delivery of oxygen is cardiac output multiplied by the amount of

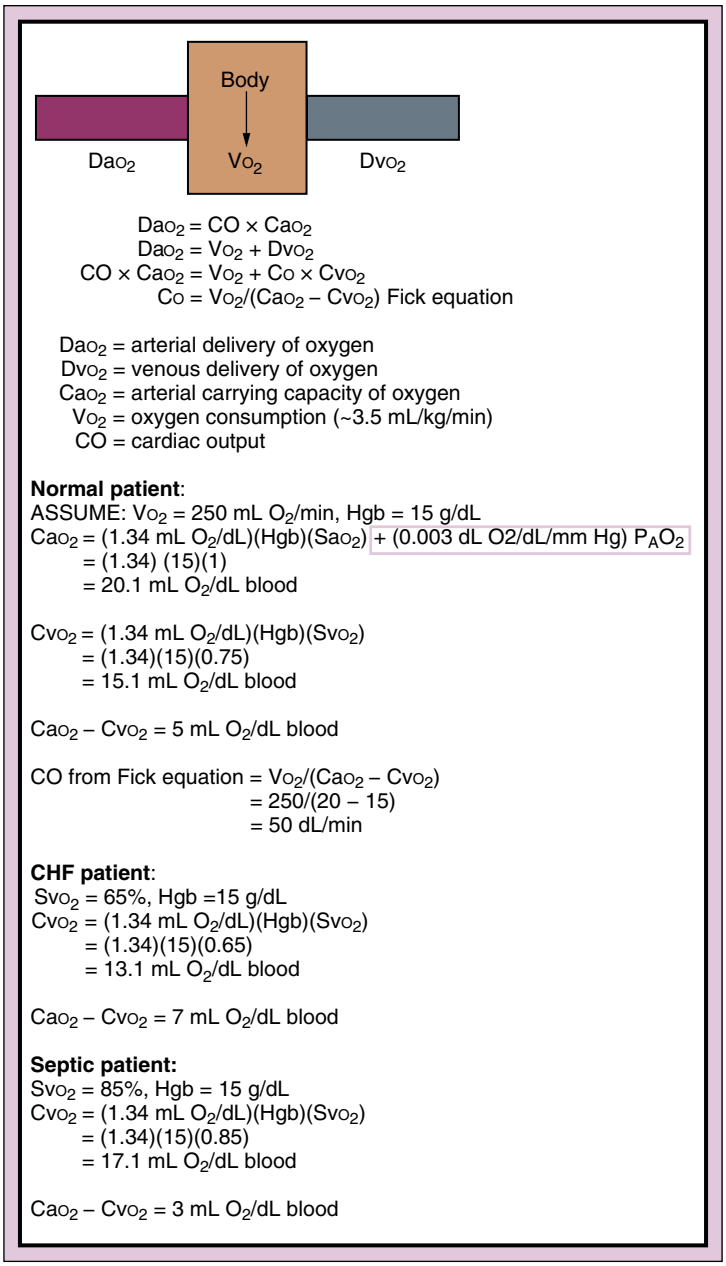

Fig. 21.11 Calculation of cardiac output via Fick equation, arterial and mixed venous oxygen content, and arteriovenous difference in normal, septic, and heart failure patients. *CHF*, Congestive heart failure.

oxygen carried in the blood. The total amount of oxygen in the blood is the amount bound to hemoglobin and the amount dissolved in solution. Because the vast majority of the oxygen content in blood is bound to hemoglobin, the amount dissolved can often be left out of the equation in order to simplify calculations. The amount dissolved becomes important in situations such as severe anemia, when the amount carried by hemoglobin is low.

Arteriovenous Difference

The difference between the arterial and mixed venous oxygen content (AV difference) is a good estimate of the adequacy of oxygen delivery (see Fig. 21.11). The normal AV difference is 4 to 6 mL/dL of blood. When tissue oxygen consumption is constant, a decreased cardiac output (congestive heart failure) leads to higher oxygen extraction, which increases the AV difference.

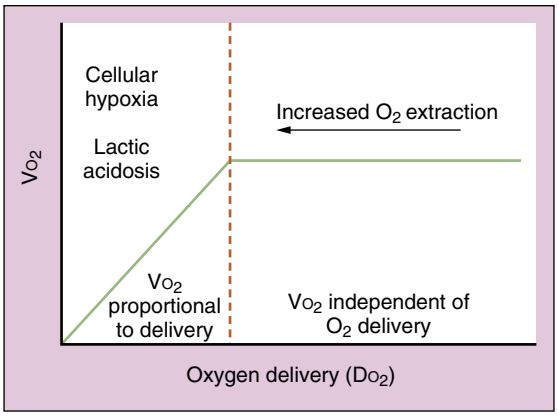

Fig. 21.12 Relationship of oxygen consumption (Vo_2) to oxygen delivery (Do_2): When oxygen consumption becomes supply dependent, cellular hypoxia occurs, which leads to progressive lactic acidosis and eventually death.

An increased cardiac output (sepsis) or lower extraction (cyanide poisoning) leads to a lower AV difference.

When the delivery of oxygen is first reduced, oxygen consumption remains normal because of the body's ability to increase extraction. With further reductions in oxygen delivery, a critical point is reached when oxygen consumption becomes proportional to delivery. When oxygen consumption becomes supply dependent, cellular hypoxia occurs, which leads to progressive lactic acidosis and eventual death if uncorrected (Fig. 21.12).

QUESTIONS OF THE DAY

1. What is the expected increase in minute ventilation for every 1 mm Hg increase in $PaCO_2$? What does the term *apneic threshold* mean in the context of a spontaneously breathing patient receiving general anesthesia?
2. A patient with lung disease develops chronic respiratory acidosis. What is the expected renal compensation and the time course of the compensatory response?
3. A hypothermic patient has an arterial blood gas drawn for analysis. Assuming unchanged ventilation and oxygenation, how do the serum bicarbonate, $PaCO_2$, and PaO_2 change with hypothermia?
4. What are the physiologic mechanisms for development of acute respiratory acidosis? If a patient receiving laparoscopic surgery developed increased end-tidal PCO_2, how would you determine the cause?
5. A patient presents to the emergency department with metabolic acidosis. How would you determine whether the process was acute or chronic? How would measurement of the anion gap help to determine the cause of the acidosis?
6. What is the alveolar gas equation? How is it used to calculate the alveolar-arterial (A-a) gradient in a patient? What are the causes of large A-a gradients?

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