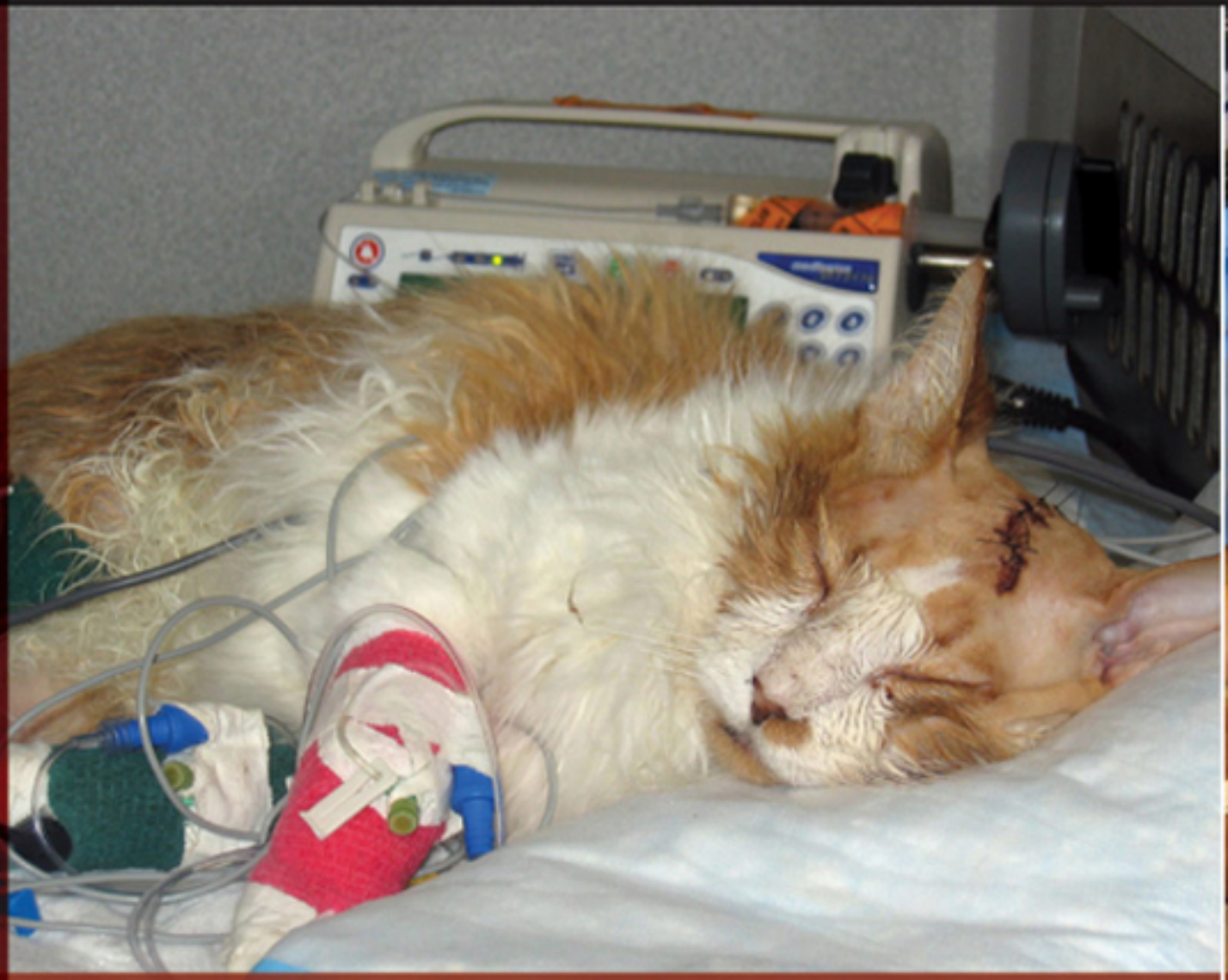
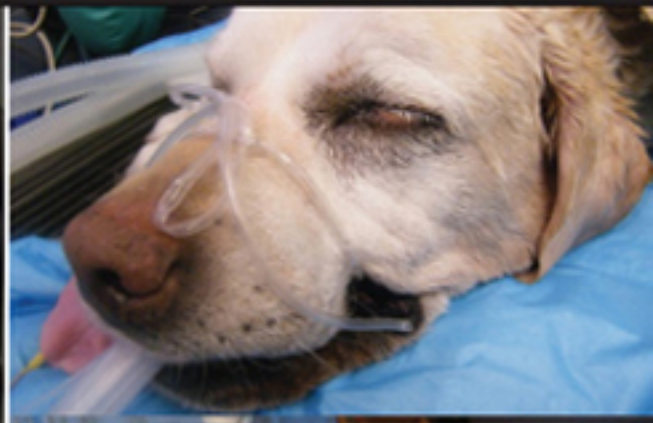
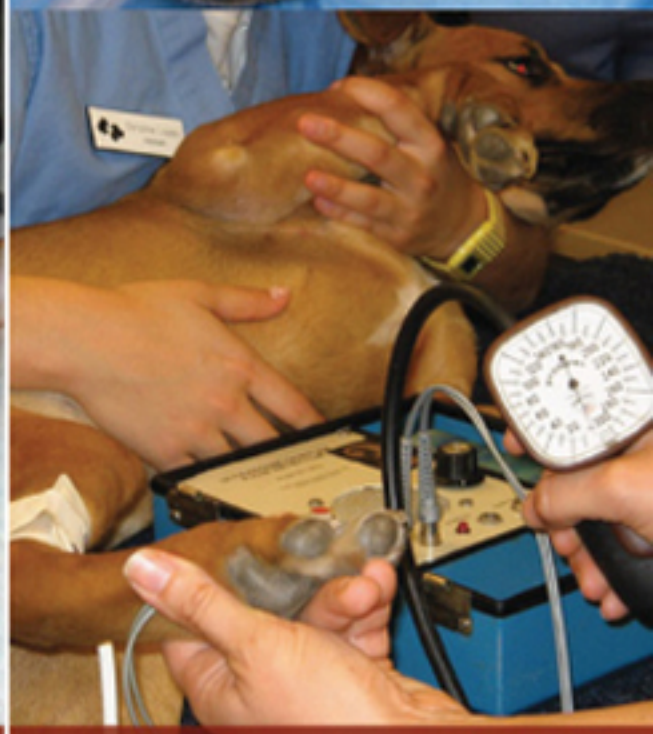
Advanced Monitoring and Procedures for **Small Animal Emergency and Critical Care**

Edited by: **Jamie M. Burkitt Creedon and Harold Davis**







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Acid-base evaluation

Steve C. Haskins

Overview of acid-base interpretation

Acid-base evaluation should be performed in any patient with a serious metabolic disturbance (Box 50.1). In these patients, the magnitude of acid-base derangement is difficult to ascertain by clinical signs alone, and the measurement of acid-base status is an important component of the initial assessment and ongoing patient monitoring.

The pH is a unitless expression of the hydrogen ion concentration. Normal plasma pH is about 7.40 ± 0.5 units. Values <7.35 represent an acidemia, whereas values >7.45 represent an alkalemia. Aberrations of pH are due to either respiratory or metabolic disturbances. The respiratory contribution to the acid-base disturbance is defined by arterial PCO_2. Normal $PaCO_2$ is about 40 ± 5 mm Hg (cats may be slightly lower) (Table 50.1). Values <35 mm Hg represent a respiratory alkalosis; values >45 mm Hg represent a respiratory acidosis. The metabolic component is best represented by the base deficit/excess calculation (SBE or BE_{ecf}) on analyzer printouts. Surrogate markers for BD/E include plasma standard bicarbonate concentration, bicarbonate concentration, and total carbon dioxide. The BD/E ranges between 0 and −4 mEq/L in dogs (cats may be slightly lower); normal plasma bicarbonate concentration ranges between 20 and 24 mEq/L, and total carbon dioxide concentration between 21 and 25 mEq/L (cats may be slightly lower). BD/E values more negative than the normal range or values below the normal range for any of the surrogate markers represent a metabolic acidosis; BD/E values more positive than the normal range or values above the normal range for any of the surrogate markers represent a metabolic alkalosis.

Sampling and storage of blood for acid-base measurement

Normal acid-base values are referenced to arterial blood, which should be used when evaluating the ability of the lung to oxygenate the blood (see Chapter 22, Blood Gas Analysis, for more information). For acid-base measurements, venous blood can generally be used. Venous pH tends to be 0.03–0.05 units lower, PCO_2 3–5 mm Hg higher, bicarbonate 1–2 mEq/L higher, and base deficit 1 mEq/L lower than arterial blood.[4,7] Unfortunately, certain common events in critically ill animals can increase the disparity between arterial and venous blood values: sluggish peripheral blood flow[8] and cardiac arrest,[9] and impaired carbon dioxide carriage (anemia,[10] administration of carbonic anhydrase inhibitor) increase PCO_2 and decrease pH in venous blood compared with arterial blood.

The technique for collecting a blood sample for pH and blood gas analysis is outlined in Protocol 50.1. Dilution of the blood sample by anticoagulant should be minimized. Heparin solution has a pH of about 6.66 and a PCO_2 of about 5 mm Hg.[11] The dead space of a 3-mL syringe and needle is about 0.094 mL,[11] which represents a 9.4% dilution of a 1 mL blood sample and a 3.1% dilution of a 3 mL blood sample. After drawing liquid heparin into the syringe, evacuate as much of it as possible; there will still be sufficient heparin remaining to anticoagulate the blood sample.

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Box 50.1 Interpretation of acid-base measurements

	Parameter (normal range for dogs)	Acidosis	Alkalosis
Overall hydrogen ion concentration	pH (7.35–7.45)	Below normal	Above normal
Respiratory contribution	$PaCO_2$ (35–45 mm Hg)	Above normal	Below normal
Metabolic contribution	Base deficit/excess (0 to −4 mEq/L)	More negative	More positive
	Standard bicarbonate (20–24 mEq/L)	Below normal	Above normal
	Bicarbonate (20–24 mEq/L)		
	Total carbon dioxide (21–25 mEq/L)		

Table 50.1 Arterial acid-base values for normal individuals

	Human[1]	Dog[2–4]	Cat[3,5,6]
pH	7.40 (7.35–7.45)	7.39 (7.35–7.43)	7.39 (7.33–7.45)
$PaCO_2$, mm Hg	40 (35–45)	37 (31–43)	32 (26–38)
Base deficit, mEq/L	0 (–2 to +2)	–2 (+1 to –5)	–6 (–3 to –9)
Bicarbonate concentration, mEq/L	24 (22–26)	22 (19–25)	18 (15–21)

Blood should be collected anaerobically. Exposure to small air bubbles allows equilibration of gases between the blood and the air, which has a PCO_2 of about 0.275 mm Hg and a PO_2 of about 160 mm Hg. Air mixing will lower the partial pressure of carbon dioxide, which will change the pH.

The sample should be analyzed as soon as possible after collection to minimize *in vitro* changes due to metabolism and diffusion of gases into and through the plastic wall of the syringe. Although this is particularly important for PO_2 measurements, it is also somewhat true for PCO_2 and pH. *In vitro* metabolism by nucleated cells increases the PCO_2. Diffusion of carbon dioxide into and through the walls of the plastic container decreases the PCO_2. If the time to analysis is greater than about 10 minutes, the blood sample should be stored in ice water.[12] Ice water storage for as long as 6 hours has been reported to result in very little change in PCO_2 and pH values.[13] Samples can be stored in screw-top or vacuum heparin collection tubes for at least 30 minutes with minimal changes in measured values.[14] Repeated measurements from the same syringe or container will result in changed values due to the repeated exposure of the blood sample to room air.[14]

If air is accidentally drawn into the analyzer during sample aspiration/insertion, pH and PCO_2 values may be erroneous. Measurements marked with error codes on the analyzer printout should be repeated. Measurements that seem unbelievable should not be believed and should be repeated.

Blood gases are measured at the temperature of the blood gas analyzer water bath, which is usually set at 37°C. When the animal's body temperature is lower than the water bath, the PO_2 and PCO_2 will increase and the pH will decrease when the blood sample is warmed to 37°C for analysis. The patient's temperature should always be input at the time of sample analysis so that the analyzer can calculate and report the values corrected to the patient's body temperature in addition to those measured at 37°C (the magnitude of temperature-induced changes can be readily observed). If one wants to know the values in the patient at the time of sampling, the temperature-corrected values should be used. This may be important if one is tracking blood gas and acid-base changes over time, which is also associated with changing body temperature. Published normal reference values were established for normothermic patients, however, and perhaps characterization of acid-base

Protocol 50.1 Protocol for collecting a blood sample for pH and blood gas analysis

Items Required

- Use either a commercial blood gas syringe with dry anticoagulant or prepare a sampling syringe by drawing an aliquot of liquid heparin solution into it and then blowing as much of the liquid heparin out of the dead space of the syringe as possible.
- If blood is to be taken from a catheter: (1) use a separate syringe with about 1 mL of heparinized saline to scavenge fluid and blood from the catheter prior to sample collection; (2) use a separate syringe with about 3 mL of heparinized saline to flush the catheter after the scavenged fluid and blood has been returned to the patient.

Procedure

Blood taken via direct vessels puncture:

1. Gather supplies.
2. Perform hand hygiene.
3. Clip the hair and aseptically prepare the skin over the intended puncture site.
4. Aseptically puncture the vessels and anaerobically obtain at least a 1 mL blood sample.

Blood taken from a catheter:

1. Scrub the injection port with antiseptic solution. The fluid infusion must be stopped.
2. Remove at least 3 mL of fluid and blood from the catheter so you can obtain a pure blood sample.
3. Take at least a 1 mL blood sample.
4. Return the scavenged fluid and blood to the patient.
5. Flush the catheter with heparinized saline.

Storage and analysis:

1. Analyze the samples immediately.
2. If the sample cannot be analyzed within 10 minutes, store it in ice water.
3. Mix the sample prior to analysis by vigorously rolling the syringe between your hands.
4. Insert the blood anaerobically into the analyzer as per the manufacturer's guidelines.
5. Input the patient's identification and temperature.

status and therapeutic decisions should be based on the values as measured at 37°C.

Hydrogen ion concentration

Hydrogen ions are highly reactive with anionic regions of macromolecules like proteins. This interaction changes charge distribution within the protein resulting in a change in conformation and function of the protein. Changing the catalytic activity of protein enzymes alters many physiologic cell functions such as mentation, hemoglobin affinity for oxygen, myocardial contractility and other skeletal muscle function, vasomotor tone and other smooth muscle function, coagulation, inflammation, digestion, hepatic metabolism, and renal excretion. Enzyme systems are most active within a narrow pH range and become inactive when the hydrogen ion concentration varies too far from normal. All aspects of cell function depend on a fairly normal hydrogen ion concentration.

The pH is a convenient negative logarithmic expression of the hydrogen ion concentration (or, more specifically, activity) that compresses a very wide range of hydrogen ion activities into a scale that is much easier to use (Appendix 50.1). The logarithmic pH scale is also useful clinically because the physiologic effects of changes in pH is more linearly related to pH than it is to hydrogen ion concentration (i.e., a pH decrease of 0.2 units would be similarly disruptive to cellular function as would an increase of 0.2 units even though the corresponding change in hydrogen ion concentration is dramatically different).

The pH is the net balance of all of the acids (hydrogen ion donors) and all of the bases (hydrogen ion acceptors) in the body at any point in time. Hydrogen ion concentration depends on the balance between intake and elimination of acids and bases. Buffers are acid-base pairs that cushion the effect on pH of a given acid or base load; they do not change the direction of change, just minimize the magnitude of change (Appendix 50.2). The pH is regulated by a respiratory component (carbonic acid) and a metabolic component (all of the other acids and bases).

The respiratory component of the acid-base balance

Carbonic acid (H_2CO_3) is in a two-way equilibrium with carbon dioxide and water, and with hydrogen and bicarbonate:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \qquad (50.1)$$

Each reaction obeys the law of mass action.* The left-hand reaction is between carbon dioxide and water, and carbonic acid. This reaction is greatly accelerated by

*All reactions have a proportional equilibrium (which depends on temperature and the environmental pH relative to the pK of the reaction). When reactant is added to one side of an equilibrium, some of it will move to other side so as to reestablish the proportional equilibrium.

carbonic anhydrase (located in red blood cells, renal tubular epithelial cells, and intestinal epithelial cells where rapid fluxes are important). When carbon dioxide increases, some of the CO_2 will combine with H_2O to form H_2CO_3. When H_2CO_3 increases, it will dissociate into hydrogen and bicarbonate in a 1:1 ratio. This is very acidifying because the normal H^+:HCO_3^- ratio (at 7.4) is about 0.00000167:1.

The respiratory contribution to the acid-base balance is defined by the $PaCO_2$. The medullary respiratory centers regulate $PaCO_2$ by adjusting alveolar minute ventilation. $PaCO_2$ is the marker of alveolar ventilation and of the respiratory contribution to the pH. Carbon dioxide production does not vary enough in comparison with how much ventilation can change (except in malignant hyperthermia) to be a material player in determining $PaCO_2$.

Surrogate markers of $PaCO_2$: venous PCO_2 ($PvCO_2$) and end-tidal PCO_2 ($PetCO_2$)

When arterial blood is not available, venous blood may be used for PCO_2 measurements. $PvCO_2$ values are normally 3–5 mm Hg higher than $PaCO_2$ (due to tissue metabolic CO_2 production). The arterial-venous gradient is not a fixed value, however, and it can increase in common disease states such as hypovolemia and anemia. $PvCO_2$ is actually a marker of tissue PCO_2, which in turn is the balance between $PaCO_2$, metabolic CO_2 production, and tissue perfusion. Changes in $PvCO_2$ will lag behind changes in $PaCO_2$ in transition states (e.g., acute hyperventilation following prolonged hypoventilation).

When a blood gas analyzer is not available, $PetCO_2$ may be used as a surrogate marker of $PaCO_2$. Normally $PetCO_2$ is only about 3–5 mm Hg below $PaCO_2$ (due to lung regions with high ventilation to perfusion ratios). $PetCO_2$ values are disproportionately lower than $PaCO_2$ when there is increased alveolar dead space ventilation (hypovolemia, pulmonary thromboembolism, or PPV with large tidal volumes) and tachypnea when there is mixing of anatomic dead space gases and functional alveolar space gases. See Chapter 26, Capnography, for more information about $PetCO_2$.

Respiratory acidosis

The causes of respiratory acidosis are cited in Box 50.2. $PaCO_2$ values >45 mm Hg define hypoventilation and respiratory acidosis; $PaCO_2$ >60 mm Hg may warrant treatment. Without supplemental oxygen therapy, this magnitude of hypoventilation is likely to be associated with hypoxemia. Without metabolic compensation, this magnitude of respiratory acidosis may be associated with a pH < 7.2. Hypercapnia causes cerebral vasodilation, which increases cerebral blood flow that may be harmful in patients with intracranial disease. With proper support and time for compensation, and in patients without intracranial disease, considerably higher PCO_2 values may be permissible without apparent harm to the patient.

Box 50.2 Cause of respiratory acidosis/alkalosis

Respiratory acidosis (hypercapnia)
- Hypoventilation
- Neuromuscular disease
- Airway obstruction
- Open pneumothorax or flail chest
- Anterior displacement of the diaphragm by abdominal space filling disorders
- Pleural space filling disorders
- Pulmonary parenchymal disease (late)
- Compensation for metabolic alkalosis
- Carbohydrate-rich IV feeding solutions in debilitated patients
- Bicarbonate therapy in patients with respiratory compromise
- Rebreathing of just exhaled alveolar gases due to mechanical dead space
- Malignant hyperthermia

Respiratory alkalosis
- Hypotension
- Fever and heat-induced illness
- Systemic inflammatory response and sepsis
- Excitement and exercise
- Pain
- Pulmonary thromboembolism
- Pulmonary parenchymal disease (early)
- Inappropriate ventilator settings
- Compensation for metabolic acidosis

The first treatment for hypercapnia is effective treatment for the underlying disease process that is causing the hypoventilation (relief or bypass of airway obstructions, removal of pleural filling disorders, etc.). The symptomatic therapy for hypoventilation is positive pressure ventilation until such time as effective treatment of the underlying disease can be implemented. The general guidelines for positive pressure ventilation of animals with relatively normal lungs are outlined in Box 50.3: (1) peak proximal airway pressure: 10–15 cm H_2O; (2) tidal volume: 10–15 mL/kg; (3) inspiratory time: about 1 second (just long enough to achieve a full tidal volume); (4) ventilatory rate: 10–15 times per minute; (5) minute ventilation: 150–250 mL/kg/minute. Diseased lungs are stiffer (less compliant) than normal lungs, and ventilator settings (except tidal volume) will

Box 50.3 Guidelines for positive pressure ventilation

Normal lungs
- Proximal airway pressure 10–15 cm H_2O
- Tidal volume 10–15 mL/kg
- Breathing rate 10–15 breaths/minute
- Inspiratory time 0.5–1 second
- Minute ventilation 150–250 mL/kg/minute

Diseased lungs
- Higher airway pressures (>15 cm H_2O) and breathing rates (>15/minute) as necessary but with smaller tidal volumes (<10 mL/kg)

probably need to be higher than those for normal lungs. The primary ways to improve ventilation are to increase respiratory rate or proximal airway pressure. Tidal volumes should not be increased above normal when there is diffuse lung disease because this predisposes to ventilator-induced lung damage.[15] Inspired oxygen, end-expiratory pressure, and inspiratory time are alterable parameters that primarily affect oxygenation and may have little on PCO_2. Make sure there is patient synchrony and that other untoward events (hyperthermia, pneumothorax) are not present. See Chapter 27, Mechanical Ventilation, for more information regarding positive pressure ventilation.

Respiratory alkalosis

The causes of respiratory alkalosis are listed in Box 50.2. $PaCO_2$ values <35 mm Hg define hyperventilation and respiratory alkalosis; $PaCO_2$ <20 mm Hg may warrant treatment. This magnitude of hypocapnia may be associated with cerebral vasoconstriction and cerebral hypoxia. Without metabolic compensation, a $PaCO_2$ <20 mm Hg may be associated with a pH > 7.6. The muscular effort necessary to maintain the hyperventilation may be associated with disproportionately high oxygen consumption. The first and only treatment for hypocapnia is effective treatment for the underlying disease process that is causing the hyperventilation.

The metabolic component of the acid-base balance

In contrast to the respiratory component, the metabolic component includes many acids and has many markers. This complexity has spawned a number of different ways by which its contribution to the acid-base balance can be characterized.

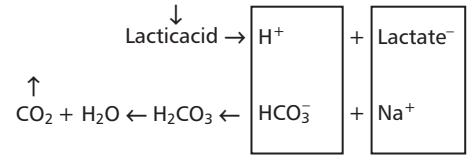


Figure 50.1 Lactic acid buffering by the carbonic acid-bicarbonate buffer system: the increased hydrogen combines with bicarbonate to form carbonic acid. The decrease in bicarbonate concentration approximately equals the increase in lactate concentration.

Overview of markers of the metabolic component

Bicarbonate

Plasma bicarbonate concentration is the time-honored overview marker of the metabolic contribution to acid-base balance. Bicarbonate is intimately associated with hydrogen in the carbonic acid equilibration equation and in the carbonic acid–bicarbonate buffer system (Eq. 50.1). The hydrogen ion of any added acid will bind with bicarbonate to form carbonic acid, which dissociates to carbon dioxide and water; the carbon dioxide is eliminated by alveolar ventilation (Fig. 50.1). Because it is ventilated to the atmosphere, carbon dioxide does not pile up on the left side of the carbonic acid equilibration; this allows bicarbonate buffering of additional lactic acid. Because the carbonic acid–bicarbonate buffer system is open ended, it is quantitatively the most powerful buffer system in the body. The binding of bicarbonate by the hydrogen of any acid will decrease the plasma bicarbonate concentration, which then can be used as a marker of the magnitude of the acidosis.

In a pH and blood gas analyzer, pH and PCO_2 are measured and bicarbonate concentration is calculated via the Henderson-Hesselbach equilibration:

$$pH = -\log(HCO_3 / H_2CO_3) \qquad (50.2)$$

There will be no error in the bicarbonate calculation; there can be only one bicarbonate concentration for the measured pH and PCO_2 values. If there were errors in sampling, storage, or measurement, there may, however, be unrepresentative pH or PCO_2 measurements that would, in turn, lead to incorrect bicarbonate concentration calculation.

Dogs normally have a bicarbonate concentration in the range of 20–24 mEq/L; cats are slightly lower (16–20 mEq/L) (Table 50.1). Values below these respective ranges represent hypobicarbonatemia and serve as a marker of metabolic acidosis; values above these ranges

represent hyperbicarbonatemia and mark a metabolic alkalosis.

Standard bicarbonate

Carbon dioxide and bicarbonate are both part of the carbonic acid–bicarbonate equilibration equation. A primary change in bicarbonate *does not* cause a change in arterial PCO_2 *in vivo* because $PaCO_2$ is monitored and controlled by medullary chemoreceptors. Changes in PCO_2 *do*, however, cause small changes in plasma bicarbonate concentration (approximately 0.15 mEq/L per mm Hg decrease in PCO_2 below 40 and 0.075 mEq/L per mm Hg increase in PCO_2 above 40).[16] Standard bicarbonate is a mathematically adjusted bicarbonate concentration (to a PCO_2 of 40 mm Hg) to eliminate the effect of changes in PCO_2 on bicarbonate concentration.

If both standard bicarbonate and an (undesignated) bicarbonate concentration are available on the printout from the analyzer, the standard bicarbonate would be the more accurate representation of the metabolic contribution to the acid-base balance.

Total carbon dioxide concentration

A blood gas analyzer is not always available to measure pH and PCO_2. Total CO_2 concentration can be easily measured and is a common component of commercial chemistry panels. Carbon dioxide exists in many forms in the plasma, almost all of which is as bicarbonate anion. Very small amounts exist in the form of carbonic acid, dissolved CO_2, and as carbamino groups on various proteins. Total CO_2 concentration is only about 1 mEq/L above bicarbonate concentration, and total CO_2 concentration can be interpreted as if it were bicarbonate concentration. Total CO_2 has nothing to do with the partial pressure of CO_2, and total CO_2 should not be considered to be a surrogate marker of PCO_2.

Base deficit/excess

The carbonic acid–bicarbonate buffer system is not the only buffer in blood; hemoglobin protein, plasma protein, and phosphate buffers also absorb hydrogen ion and also act to cushion the impact of a given load of acid on pH (there are also intracellular and bone buffers).

The quantitative impact of all of the buffer systems in whole blood has been determined by titrational experiments and is termed base deficit (a deficit of base indicates the presence of a metabolic acidosis) or base excess (an excess of base indicates a metabolic alkalosis). Base deficit/excess values are usually considered to be the most accurate index of the metabolic contribution to acid-base balance. Alignment nomograms were originally developed to hand-determine the base deficit/excess and bicarbonate and total CO_2 concentrations from the measured pH and PCO_2.[16] Nowadays these values are calculated by the blood gas analyzer and are displayed and printed out for the user. Acronyms for base deficit/excess include SBE and BE_{ECF}.*

The normal base deficit/excess ranges between 0 and –4 mEq/L for the dog and between –4 and –8 mEq/L for the cat (Table 50.1); more negative values mark a deficit of base and a metabolic acidosis; more positive values mark an excess of base and a metabolic alkalosis.

Anion gap

The anion gap is usually calculated by the following equation:

$$Na + K - Cl - HCO_3 \quad (50.3)$$

There can be no anion gap in reality (the number of cations always equals the number of anions), but not all of them are routinely measured. In this calculation, Na + K normally exceeds Cl + HCO_3 by 15 to 20 mEq/L.† Normally the negative charges on albumin comprise most of this apparent gap. Phosphorous and lactate make up a small portion of the gap in the normal animal, but this can increase in disease states.

An increase in anion gap is usually considered to mark the presence of an accumulation of unmeasured anions, most of which represent anions of organic acids such as lactic acid, ketoacids, phosphoric and sulfuric acids, or acid intoxicants such as glycolic acid from ethylene glycol, salicylic acid from salicylate, formic acid from methanol, or various acidic amino acids from rhabdomyolysis).

Hyperalbuminemia can also cause an increase in anion gap associated with a metabolic acidosis. Metabolic acidosis can also be caused by renal and gastrointestinal bicarbonate losses or hydrogen retention, without an increase in anion gap.

The anion gap calculation (with the standard formula) is difficult to interpret and rarely adds meaningful infor-

*SBE: standard base excess; the word *standard* implies the use of the *in vivo* buffer curve. BE_{ECF}: the "ECF" implies the use of the *in vivo* buffer curve. In both terminologies the term *negative base excess* is used instead of the term *base deficit*. The original experiments were done with blood in test tubes and constitute an *in vitro* buffer curve. The *in vivo* buffer curve, which incorporates the effects of dilution and buffering by the interstitial fluid compartment, is flatter than the *in vitro* buffer curve (less change in pH per change in bicarbonate or base deficit/excess).

†Sometimes potassium is eliminated from the calculation; normal values would then range between 10 and 15 mEq/L.

mation to the patient assessment. First, by the time one has the measurements needed to calculate the anion gap, there is usually enough information (historical, physical, or laboratory) with which to define the nature of the metabolic acidosis. If a patient has metabolic acidosis and signs of poor tissue perfusion, the odds-on bet would be a lactic acidosis; if a patient has metabolic acidosis and urine ketones, a ketoacidosis; a metabolic acidosis and uremia, a phosphoric acidosis, and so on.

Second, animals rarely have a pure acidosis from a singular source; most acid-base derangements represent a variable combination of acidotic and alkalotic processes that culminate in the measured acid-base abnormality. This may have the net effect of increasing or decreasing the calculated anion gap, or processes may cancel one another out so as to result in a normal anion gap calculation (e.g., hypoproteinemia and lactic acidosis). An increased anion gap surely marks the presence of unmeasured anions, the acids of which are possibly contributing to the metabolic acidosis. A normal value may be normal or may represent multiple off-setting acid-base derangements. A decreased value surely marks a hypoproteinemia.

The expanded anion gap

Albumin, phosphorous, and lactate are commonly measured, and their contributions to the anion gap can be easily calculated (Box 50.4):

$$\text{Na} + \text{K} + \text{Ca effect} + \text{Mg effect} - \text{Cl} - \text{HCO}_3 - \text{lactate} - \text{albumin effect} - \text{phosphate effect} \quad (50.4)$$

The expanded anion gap accounts for many of the usually unmeasured anions; normal values for the expanded anion gap range between 0 and 4 mEq/L. This residual anion gap is composed of the remaining unmeasured anions such as sulfates, ketones, and various amino acids. The expanded anion gap formula moves many of the relevant players in the anion gap calculation from an unknown to a known category, which allows for a more comprehensive evaluation of the acid-base status.

Strong ion difference

Strong ion difference (SID) is the difference between the strongly dissociated cations and the strongly dissociated anions; however the usual formula is much abbreviated:

$$\text{Na} + \text{K} - \text{Cl} \quad (50.5)$$

Box 50.4 Calculating the expanded anion gap

$$\mathbf{AG_{expanded} = Na + K + Ca\ effect + Mg\ effect - Cl - HCO_3 - lactate - albumin\ effect - phosphate\ effect}$$

For Na, K, Cl, HCO_3, and lactate, use the measured value (mEq or mM/L).

Calcium effect = ionized calcium mM/L × 2
= mEq/L (ionized calcium may be estimated as half of total calcium)
(mg/dL × 0.3 ≈ mM/L)

Magnesium effect
= ionized magnesium mM/L × 2
= mEq/L (ionized magnesium may be estimated as half of total magnesium)
(mg/dL × 0.45 ≈ mM/L)

Albumin effect = albumin g/dL × 3.7 (g/L × 0.37)

Phosphate effect =
phosphorous mg/dL × 0.58 (mM/L × 1.8)

The only difference between this SID formula and the traditional anion gap formula is the absence of HCO_3. In this context one might anticipate that the criticisms of anion gap would also apply to SID. It has been proposed that a decrease in SID can be used as a marker of metabolic acidosis and an increase in SID as a marker of metabolic alkalosis.[17–19] When the decrease in SID is due to a decrease in bicarbonate, it is indeed associated with a metabolic acidosis. However, hypoalbuminemia also decreases SID, and this would be associated with a metabolic alkalosis (see "Albumin" below). Increases in anions of salts (such as sodium lactate or sodium acetate) increase both anion gap and SID calculations, but they have no effect per se on acid-base balance. In the end, SID, like anion gap, provides a broad categorization of underlying events and is difficult to interpret without any further information. Broad categorical descriptions of acid-base balance are of limited use and one might be better served to evaluate the specific contributors insofar as possible (see "Markers of Specific Contributors to the Metabolic Component" below).

A_{TOT}

Strong ion difference describes an apparent gap between commonly measured strongly dissociated cations and

anions ($SID_{apparent}$). This gap is composed of the anions of weakly dissociated acids: albumin and phosphate (A_{TOT}). A_{TOT} (the albumin effect and the phosphate effect), as calculated for the expanded anion gap formula (Box 50.4). An increase in A_{TOT} caused by hyperphosphatemia (see "Phosphorous Effect" below) or hyperalbuminemia (see "Albumin Effect" below) would be associated with a metabolic acidosis, and *vice versa*. A_{TOT} is another grouping assessment, and one might be better served to evaluate the specific contributors insofar as possible (see "Markers of Specific Contributors to the Metabolic Component" below).

The remaining important weakly dissociated acid is carbonic acid; the conjugate anion is bicarbonate. A_{TOT} and HCO_3 comprise $SID_{effective}$. $SID_{apparent}$ and $SID_{effective}$ generally have a similar value because the former is an assessment of the stuff around the gap and the latter is an assessment of the stuff of the gap itself.*

The Stewart approach to acid-base balance

The Stewart approach to acid-base balance is a much discussed so-called new approach to acid-base interpretation. Stewart was a chemist who described acid-base balance from a chemical (not a clinical) point of view.[20] The Stewart approach is similar to the whole blood buffer base concept proposed by Singer and Hastings in 1948.[21] Because all cations and anions are always balanced, one can describe acid-base balance from several different perspectives. Stewart chose to solve his equations for bicarbonate as the dependent variable (i.e., bicarbonate concentration can be calculated from the concentration of all of the other cations and anions). Perhaps this is justified from the perspective that bicarbonate is a tricky anion to predict; it is involved with hydrogen in many other buffer systems and can disappear or reappear in the name of carbon dioxide. Stewart could just as well have solved his equations for any other cation or anion. There is nothing incorrect about Stewart's observations and calculations; however, one must take care not to misapply Stewart's proposals in the clinical management of patients.

According to the Stewart approach, the three causes of acid-base disturbances are changes in PCO_2, changes in $SID_{apparent}$, and changes in A_{TOT}. Bicarbonate has been relegated to "dependent" ion status, and as such it cannot primarily affect acid-base balance; it can only be affected by changes in the other parameters. This approach divides the very large metabolic component of the traditional approach (base deficit/excess or bicarbonate) into two (still fairly large) subgroups. The problems inherent in associating a specific directional change in $SID_{apparent}$ were discussed earlier and, again, one might be better served to evaluate the specific individual contributors to $SID_{apparent}$ and A_{TOT} (see "Markers of Specific Contributors to the Metabolic Component" below).

The value of the Stewart approach might be in its ability to suggest directional acid-base changes when pH and PCO_2 measurements are not available. The Fencl-Leith quantitative expansion of the Stewart approach might be useful to help define individual contributions to the overall base deficit/excess[22,23] (see Box 50.5). It seems that it should not so much be a debate of whether to use the traditional approach or the Stewart approach to acid-base interpretation as it is a discussion of how to use them both together to best define the patient's condition at the time of measurement.

Markers of specific contributors to the metabolic component

Lactate

Blood lactate concentration can now be measured by many commercial analyzers. In lactic acidosis, lactate accumulates in the plasma as the hydrogen ion is buffered by bicarbonate; the magnitude of the lactate increase is similar to the decrease in bicarbonate (if there were no other influences on the bicarbonate concentration). The lactate concentration can be used as a marker of the quantity of lactic acid that has been added to the extracellular fluid (ECF). Each 1 mEq or mM/L increase in lactate would have a 1 mEq/L base deficit effect. Normal animals generally have a lactate concentration below 1 mEq/L; the normal range is often considered to extend up to 2 mEq/L.

It is not the lactate anion that causes the acidosis; it is the hydrogen that came with it. Sodium lactate (such as in lactated Ringer or Hartmann solution) is a salt, not an acid, and will have no impact, per se, on acid-base balance (see "The Acid-Base Impact of Crystalloid Sodium Solutions" in Appendix 50.3). If a blood sample is contaminated with sodium lactate, the measured lactate may be very high but will not be associated with an acidifying effect.

Ketones

Acetoacetate can be measured in the urine by nitroprusside reaction on most urine reagent strips. This color-

*$SID_{apparent}$ and $SID_{effective}$ essentially calculate the same thing; $SID_{apparent}$ calculates the stuff around the gap (you can tell how big the hole is by what is missing; you measure it indirectly), whereas $SID_{effective}$ calculates the stuff in the gap (you can tell how big the hole is by measuring it directly).

Box 50.5 Quantitative assessment of the metabolic contributions to acid-base balance

Overall equation: Base deficit/excess
= –lactate – ketones ± phosphorous effect
± albumin effect ± water effect
± chloride-bicarbonate effect
± unmeasured effect

Lactate: enter measured lactate (mM/L)
Ketone: enter measured ketones (mM/L)
Phosphorous effect:

Change in phosphorous (in mg/dL) from normal
(4 mg/dL) × 0.58 = phosphorous effect (mEq/L)
(Equation 50.6)

Change in phosphorous (in mM/L) from normal
(1.3 mM/L) × 1.8 = phosphorous effect (mEq/L)
(Equation 50.7)

Albumin effect:

1 g/dL (10 g/L) change in albumin concentration
(from normal) × 3.7 mEq/L of BD/E effect
(Equation 50.8)

Water effect:

$(Na_{measured} - Na_{normal}) \times 0.25$ (Equation 50.9)

Na_{normal} = 145 mEq/L (mM/L) in the dog and 155 in the cat.
Chloride-bicarbonate effect:
Adjusted chloride concentration:
Normal [Cl^-] (145 for dog; 155 for cat)
± change in [Na^+] × 0.75
Chloride-bicarbonate effect:
Adjusted – measured chloride concentration
Unmeasureds effect: Base deficit/excess – all of above

indexed assessment is semiquantitative. Acetoacetate represents a much lower proportion of the ketoacids compared with β-hydroxybutyrate in ketoacidosis. Plasma β-hydroxybutyric acid can be measured in the laboratory or with handheld instrumentation by measuring the NAD^+:NADH ratio, a reduction/oxidation reaction. The units of measure are mM/L that have a 1:1 relationship with the mEq/L contribution to the acid base balance. Plasma ketones are normally zero.

Phosphate

Plasma inorganic phosphate is commonly measured and reported as elemental phosphorous in mg/dL or mM/L in serum chemistry testing profiles. Plasma phosphate anion is also associated with other plasma cations such as sodium, potassium, calcium, magnesium, and, of importance to the present discussion, with hydrogen as phosphoric acid. Phosphoric acid (H_3PO_4) could potentially exist as H_3PO_4, $H_2PO_4^{1-}$, HPO_4^{2-}, or PO_4^{3-}, depending on the pH of the fluid. At a pH of 7.4, approximately 90% of phosphoric acid exists as HPO_4^{2-} and 10% exists as $H_2PO_4^{1-}$.

The hyperphosphatemia of renal disease is associated with a phosphoric acidosis. A coexistent sulfuric acidosis (another end product of protein metabolism) would be expected but is not measured. The magnitude of the phosphoric acidosis contribution to the metabolic component can be calculated.*

Change in phosphorous (in milligrams per deciliter) from normal (4 mg/dL) × 0.58 = phosphorous effect (mEq/L) (50.6)

Change in phosphorous (in mM/L) from normal (1.3 mM/L) × 1.8 = phosphorous effect (mEq/L) (50.7)

Albumin

Albumin is a multivalent anion associated with many plasma cations: sodium, potassium, calcium, magnesium, and, of concern to this discussion, hydrogen. Hypoalbuminemia is associated with a decrease in the "H-Alb acid," resulting in a metabolic alkalosis, whereas hyperalbuminemia is associated with an acidosis. Changes in globulin have little effect on acid base balance.[24] The impact of changes in albumin concentration on acid-base balance can be calculated:

1 g/dL (10 g/L) change in albumin concentration × 3.7 mEq/L of BD/E effect (50.8)

An increase in albumin has an acidifying effect; a decrease has an alkalinizing effect.

*To convert from mg/dL to mM/L: mg/dL × 1 mM/31 mg × 10 dL/L (= phosphorous in mg/dL × 0.323). To convert mM/L to mEq/L: phosphorous in mM/L × 1.8 (90% HPO_4^{2-}; 10% $H_2PO_4^{1-}$).

Water

Water dissociates to a small extent, in a temperature-dependent manner, into H^+ and OH^-. Water has a pK of 7.00 at room temperature and a pK of 6.80 at body temperature. Compared with the body at a pH near 7.40, water is acidic. This acidic effect is magnified *in vivo* because once the water is equilibrated with existing levels of carbon dioxide it has considerable titratable acidity.[25]

The concentration of free water is not measured, but the consequence of changes in the concentration of free water (i.e., the sodium concentration) is commonly measured. Changes in sodium concentration are used to calculate the free water effect. Changes in sodium, per se, do not have an impact on acid-base balance; it is not the sodium, it is the water, even though it is sometimes referred to as the "sodium effect." The acid-base effect of changes in water concentration is calculated as follows:

$$(Na_{measured} - Na_{normal}) \times 0.25 \qquad (50.9)$$

Na_{normal} is often considered to be 145 mEq/L (mM/L) in the dog and 155 in the cat. An increase in free water (marked by a decrease in sodium concentration) has an acidifying effect; a decrease has an alkalinizing effect.

Chloride-bicarbonate effect

This category is sometimes referred to as the "chloride effect," suggesting it is the chloride that has the effect. Terminology like "hyperchloremic metabolic acidosis and hypochloremic metabolic alkalosis" further this concept. But changes in chloride concentration, per se, do not have an impact on acid-base balance. As noted earlier, bicarbonate is a rather complex anion that is influenced by several buffer systems and respiratory handling of carbon dioxide; bicarbonate concentration is difficult to predict. Many processes in the body, however, involve the reciprocal handling of chloride and bicarbonate (i.e., when one is lost, the other is retained, and vice versa). In this manner, changes in chloride concentration can be used as a marker for the change in bicarbonate concentration that would have occurred (equal and opposite) had there been no other influences operating on the bicarbonate concentration.

Like sodium, chloride is affected by changes in water concentration. Because the effect of changes in water concentration have already been considered, effect on chloride concentration must now be eliminated from consideration. This is done by calculating an "adjusted chloride concentration" reference value:

$$\text{Normal chloride concentration (110 mEq/L [mM/L] in dog; 120 in cat)} \pm (\text{change in sodium concentration} \times 0.75^*) \qquad (50.10)$$

A higher than anticipated measured chloride concentration marks a proportional base deficit effect (a metabolic acidosis); a lower than anticipated measured chloride concentration marks a base excess effect.

Metabolic acidosis

The causes of metabolic acidosis are listed in Box 50.6. The treatment of metabolic acidosis should be primarily aimed at correction of the underlying disease process and should be the only therapy necessary if the metabolic acidosis and the pH disturbance is mild to moderate and the underlying disease is readily treatable. If, however, the metabolic acidosis is severe (base deficit >10 mEq/L; bicarbonate concentration <14 mEq/L; pH <7.2) and the underlying disease is difficult to treat, symptomatic alkalinization therapy may be indicated. Sodium bicarbonate is the most common agent used to treat metabolic acidosis. Guidelines for the calculation of bicarbonate dosage are detailed in Protocol 50.2. Sodium bicarbonate may be associated with a number of problems when used in a cavalier manner; these problems and their avoidance are detailed in Box 50.7.

Metabolic alkalosis

The causes of metabolic alkalosis are listed in Box 50.6. Most cases of metabolic alkalosis encountered clinically are either mild (do not need symptomatic treatment) or iatrogenic. The treatment of metabolic alkalosis relies on effective treatment of the underlying disease process. On the rare occasion that acidifying therapy is warranted, a dilute solution of hydrochloric acid, lactic acid, or acetic acid could be administered. Saline, acetazolamide, potassium-sparing diuretics (spironolactone, amiloride, and triamterene) and ammonium chloride are also acidifying therapies. Coexistent electrolyte abnormalities such as hypochloremia and hypokalemia potentiate metabolic alkalosis and should be treated.

*The normal sodium-to-chloride ratio is about 4:3 (150:110). For each 4-unit change in sodium, there should be a 3-unit change in chloride in the same direction (example: a decrease in sodium from 150 to 122 (a decrease of 28) would be associated with a proportional decrease in chloride concentration to 89 ($-28 \times \frac{3}{4} = -21$; $110 - 21 = 89$).

Box 50.6 Causes of metabolic acidosis and alkalosis

Metabolic acidosis

Without anion gap:

- Gastrointestinal losses of bicarbonate (diarrhea, vomiting with reflux from the duodenum)
- Renal loss of bicarbonate (proximal tubular acidosis, carbonic anhydrase inhibitors)
- Renal hydrogen retention (distal tubular acidosis, hypomineralocorticism)
- Intravenous nutrition
- Large-volume saline administration
- Free water administration
- Compensation for respiratory alkalosis
- Ammonium chloride administration

With anion gap:

- Lactic and pyruvic acidosis
- Ketoacidosis (insulin deficiency, acute starvation)
- Phosphate and sulphate acidosis (oliguric renal disease)
- Ethylene glycol intoxication
- Methanol intoxication
- Salicylate poisoning
- Rhabdomyolysis

Metabolic alkalosis

- Gastric losses of hydrogen ion (vomiting due to a pyloric obstruction, gastric suctioning)
- Furosemide administration
- Hypermineralocorticism
- Organic anion (lactate, acetate, gluconate, citrate or ketone) metabolism
- Carbenicillin and other penicillin derivatives
- Free water deficit
- Alkalinization therapy
- Compensation for respiratory acidosis
- Hypochloremia
- Hypokalemia

Protocol 50.2 How to calculate and administer a dose of bicarbonate

Procedure

1. Pick a conservative base deficit or bicarbonate concentration treatment goal (such as a base deficit of -5 mEq/L [mM/L] for the dog [-8 for the cat] or a bicarbonate concentration of 18 mEq/L [mM/L] for the dog [15 for the cat]).
2. Determine the difference between the measured and the goal value.
3. Multiply this difference times the estimated extracellular fluid space (0.3 × kg body weight).
4. Administer slowly over a minimum of about 30 minutes.
   - A single undiluted dose of sodium bicarbonate can be administered intravenously.
   - Undiluted solutions (1 mEq or mM/L) have an osmolality of 2000 mOsm/kg, which will cause phlebitis with extended infusions and a sodium concentration of 1000 mEq or mM/L, which can cause hypernatremia with large infusions.
   - Sodium bicarbonate can be administered with other fluids.
   - However, it will bind divalent cations (calcium and magnesium) as carbonates.

Box 50.7 Dangers of sodium bicarbonate administration and their avoidance

Excessive alkalinization of the patient: calculate dosages carefully; monitor acid-base balance.

Excessive alkalinization of the vascular fluid compartment: administer calculated dose over at least 30 minutes.

Hypotension, restlessness, nausea and vomiting, collapse, and death: administer calculated dose over at least 30 minutes.

Hypokalemia: administer carefully and with concurrent potassium in hypokalemic patients; monitor potassium concentration.

Hypo(ionized)calcemia: administer carefully and with concurrent calcium in hypocalcemic patients; monitor ionized calcium.

Hypercapnia: administer carefully and with carbon dioxide monitoring in patients with ventilator compromise and with ventilator support in patients that develop hypercapnia.

"Paradoxical" intracellular acidosis: avoid hypercapnia.

Phlebitis with continuous infusions: dilute with other fluids (a 1:3 dilution with a sodium-free solution such as 5% dextrose in water will decrease the osmolality to 500 mOsm/kg).

Hypernatremia with large infusions: monitor sodium with repeated dosages of sodium bicarbonate, dilute with distilled water (usually as 5% dextrose in water) as necessary (a 1:3 dilution with a sodium-free solution such as 5% dextrose in water will decrease the sodium concentration to 250 mEq or mM/L).

Expected compensation for a primary abnormality

When a primary change occurs in either the respiratory or the metabolic component, the other component should change in a direction so as to return pH toward normal (i.e., a primary metabolic acidosis should be compensated by a respiratory alkalosis). The general concept is that compensatory mechanisms do not overcompensate. Therefore, the component that varies in the same direction as the pH is probably the primary abnormality, whereas the component that varies in a direction opposite to that of pH is probably the secondary, compensatory abnormality. This is not always a safe assumption because many acid-base disturbances in critically ill

Table 50.2 Expected magnitude of compensation for a primary abnormality[6]

Primary Event	Expected Compensation
Metabolic acidosis	↓ $PaCO_2$ of 0.7 mm Hg per 1 mEq/L ↓ HCO_3
Metabolic alkalosis	↑ $PaCO_2$ of 0.7 mm Hg per 1 mEq/L ↑ HCO_3
Respiratory acidosis	↑ 0.15 to 0.35* mEq/L HCO_3 per 1 mm Hg ↑ $PaCO_2$
Respiratory alkalosis	↓ 0.25 to 0.55* mEq/L HCO_3 per 1 mm Hg ↓ $PaCO_2$

patients are multifactorial and what might otherwise appear to be a "secondary, compensatory" component may well be driven by one or several primary abnormalities. Calculating expected magnitudes of compensation is an attempt to determine whether or not there may be a coexistent problem within the compensatory component. In humans and dogs, but not cats, normal ranges of expected compensation have been established (Table 50.2).

The clinical relevance of calculating expected magnitudes of compensation is limited because the assumptions inherent in the calculation may not be true for the patient. Compensation assumes a stable primary component for a sufficient period of time to allow full compensation. Although this may be true in some chronic medical conditions, it is unlikely a valid assumption in acute critical illnesses. So levels of compensation that do not fall within the predicted range do not prove a problem with the compensatory component nor the presence of co-driving disease. Similarly levels of compensation within the predicted range do not prove the competence of compensation or the absence of coexistent disease. Critically ill patients often have multiple problems causing their acid-base derangement; a full list of differentials should be considered for each identified abnormality.

Appendix 50.1

The correlation between hydrogen ion concentration (activity) and pH

$[H^+]$ (nM/L)[a]	$[H^+]$ mEq or mM/L[b]	pH (units)[c]	
0.0001	0.000,000,000,1	14.0	
10	0.000,010	8.0	Upper pH limit of survivability
26	0.000,026	7.6	Upper treatable pH level
40	0.000,040	7.4	Normal
63	0.000,063	7.2	Lower treatable pH level
100	0.000,100	7.0	
160	0.000,160	6.8	Lower pH limit of survivability
1,000,000,000 (1 M)	1,000	1.0	

[a]Nanomoles are the traditional unit used to express the small concentrations of hydrogen ion in the mammalian body at normal pH; 1 nanomole = 0.000,000,001 moles (1×10^{-9}).
[b]$[H^+]$ expressed in units similar to other common electrolytes (mEq/L or mM/L) to illustrate that hydrogen concentrations are very low in comparison.
[c]Corresponding pH values to illustrate that the pH scale logarithmically compresses a very wide range of hydrogen ion concentrations into numbers that are much easier to use.

Appendix 50.2 Buffers

Buffers are acid-base pairs with pK values near 7.4. The pK is the pH at which an acid or base is 50% undissociated and 50% dissociated. A buffer functions to absorb added acids or bases so as to diminish their impact on pH. Buffers combine with acids and bases so as to eliminate much of their influence on pH. The primary buffer systems are carbonic acid–bicarbonate (pK 6.1), phosphoric acid–phosphate ($H_2PO_4^- - HPO_4^{2-}$)(pK 6.8), and various proteins (hemoglobin, albumin, intracellular) ($HPr - Pr^-$) (pK 5.5–8.5). Compounds with pK values more than about 2 pH units away from 7.4 are too highly dissociated at normal-range body pH to function as effective buffers. HCl (pK 1.0), lactic acid (pK 3.5), hydroxybutyric acid (pK 4.7), acetoacetic acid (pK

3.6), phosphoric acid ($H_3PO_4 - H_2PO_4^-$) (pK 2.0) are totally dissociated acids at body pH; the anionic dissociated component will not bind hydrogen and cannot act as a buffer. These substances should be considered strong acids.

Appendix 50.3 The acid-base impact of crystalloid sodium solutions

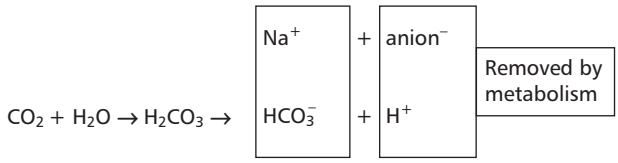
Granular sodium chloride, sodium lactate, sodium acetate, sodium gluconate, and sodium citrate have no acid-base impact when added to whole blood *in vitro*. Sodium and the respective anion increase in proportion to the amount added and SID changes (decreases with sodium chloride; increases with sodium lactate, acetate, gluconate, and citrate), but pH does not change. The same would be true *in vivo* if the organic anions (lactate, acetate, gluconate, and citrate) were not metabolized.

The addition of distilled water to whole blood has an acidifying effect by two mechanisms. First, distilled water at body temperature has a pH of about 6.8 and is therefore acid when compared with plasma at a pH of 7.4. Water itself has very little titratable acidity (0.2 mM/L)[25], which means that its addition would have little quantitative effect on acid-base balance. But when water is equilibrated to a PCO_2 of 40 mm Hg, the carbonic acid–bicarbonate buffer system is "activated," the pH decreases to between 4.9 and 5.6, and the titratable acidity increases to 24 mM/L.[25]

Second, the water dilutes the bicarbonate concentration (to a proportionately greater extent than it does the hydrogen concentration) causing carbonic acid to dissociate, which adds more hydrogen ions to the milieu.

When sodium chloride, sodium lactate, sodium acetate, sodium gluconate, and sodium citrate *solutions* are added to whole blood *in vitro*, they will have a mild acidifying effect similar to that of adding the same amount of distilled water. It is the water, not the electrolytes, that causes the initial acidifying effect. The same thing occurs when these solutions are initially administered to patients (before the anions are not metabolized). With saline, the chloride is not metabolized, but the bicarbonate is diluted and a mild metabolic acidosis would occur until the animal compensated.

The organic anions of the remaining sodium solutions are metabolized. As they are metabolized, an equal number of hydrogen ions are also removed. As the hydrogen ions are removed from the plasma, additional carbonic acid dissociates and bicarbonate is generated. These organic anions are not *metabolized to bicarbonate*; they are *replaced by* bicarbonate (via new carbonic acid dissociation). So the metabolism of these organic anions has an alkalinizing effect and the magnitude of the alkalinization depends on their relative concentration in the crystalloid compared with that of bicarbonate in plasma. In lactated Ringer and Hartmann solutions, where the lactate concentration is about the same as plasma, there will be minimal net effect on acid-base. In Normosol R and Plasmalyte 148, where the acetate plus gluconate concentrations far exceed plasma bicarbonate, there will be a net alkalinizing effect.



Metabolism of the organic anion and an accompanying hydrogen causes dissociation of additional carbonic acid and the generation of "new" bicarbonate.

Whether a patient actually develops the predicted acidosis or alkalosis associated with the administration of these fluids depends on variables such as volume and rate of administration, time of sampling compared with the time of administration, and the animal's ability to maintain acid-base homeostasis.

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