CHAPTER 61

ASSESSMENT OF ACID–BASE BALANCE: A PHYSICAL-CHEMICAL APPROACH

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The management of acid–base disorders is one of the most fundamental aspects of the management of critically ill patients and especially those with respiratory disorders. At the bedside, clinicians commonly use sets of rules for interpreting acid–base disorders and determining management plans. However, to properly manage unusual situations and to properly evaluate treatment options, one must have a clear understanding of the principles of acid–base regulation.

Traditional teaching of acid–base regulation is based on the Henderson-Hasselbalch equation, which is a statement of the mass-action equation of the equilibrium relationship of partial pressure of carbon dioxide (P\(CO_2\)), carbonic acid (H\(_2\)CO\(_3\)), hydrogen ion (H\(^+\)), and bicarbonate (HCO\(_3^-\)). The equation is

\[
pH = 6.1 + \log([\text{HCO}_3^-]/[0.0301 \times P\text{CO}_2]) \tag{61-1}
\]

where 0.031 is a constant to account for the solubility of CO\(_2\) in water and the equilibrium constant between P\(CO_2\) and carbonic acid and 6.1 is the pK\(_a\) of the dissociation of carbonic acid and the dissociation of carbonate ion. In the classic approach, one first determines if there is an acid–base disturbance by observing whether there is a deviation of the pH from the physiologically neutral value of 7.4. Increases or decreases in the P\(CO_2\) are used to determine if there is a respiratory component, and variations in HCO\(_3^-\) are used to determine if there is a metabolic component. A complex set of equations can then be used to determine if the changes are acute or chronic and compensated or uncompensated. This approach has by and large served clinicians adequately. However, although the respiratory part of the classic analysis gives a mechanistic understanding of the processes that are disturbing the normal acid–base balance, the metabolic component provides no insight into physiologic mechanisms and potentially produces some very faulty reasoning.

The limitations of the metabolic component of the conventional approach were pointed out by Peter Stewart who presented a physical-chemical approach to acid–base balance.\(^1\) The most important point of Stewart's analysis is that in water solutions, H\(^+\) and HCO\(_3^-\) are dependent variables and not independent variables as they are traditionally treated in biochemical analysis. This means that the addition of H\(^+\) or HCO\(_3^-\) to a solution does not necessarily result in a change in the concentration of [H\(^+\)] or [HCO\(_3^-\)] that is equal to the amount added. In fact, as is shown below, all solutions in the body, with the exception of gastric juices, are actually alkaline, that is [H\(^+\)] < [hydroxide ion (OH\(^-\))] (the notation [ ] is used to refer to concentration), and in alkaline solutions, the addition of H\(^+\) never produces a change in its concentrations that is equal to what was given. Stewart pointed out that the three independent variables that determine [H\(^+\)] (and [HCO\(_3^-\)]) are the P\(CO_2\), strong ion difference [SID], and the concentration of weak proteins A\(_{\text{Total}}\) (Figure 61-1). The significance of each of these is discussed in the next sections.

NEUTRAL PH

We begin with some definitions. An acid solution is defined as one in which [H\(^+\)] > [OH\(^-\)], a neutral solution is one in which [H\(^+\)] = [OH\(^-\)], and an alkaline solution is one in which [H\(^+\)] < [OH\(^-\)].\(^1\) Pure water at body temperature of 37°C has a pH of 6.68 but is pH neutral because [H\(^+\)] = [OH\(^-\)]. The pH of pure water decreases with decreases in temperature because the dissociation constant of water increases with temperature (Figure 61-2A) and results in increasing amounts of both [H\(^+\)] and [OH\(^-\)], but the solution is neutral from the acid–base point of view (Figure 61-2B). The addition of other components to pure water can change the pH, but if [H\(^+\)] is equal to [OH\(^-\)], the solution is still neutral.

Blood pH is tightly regulated over a narrow range in all organisms because the conformation and thus function of enzymes and structural proteins are highly pH dependent. For physiologic studies and clinical purposes, pH 7.4 is called “normal,” for this is the normal value in the blood, although intracellular pH is usually somewhat lower.\(^1-3\)
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However, it is important to appreciate that blood at a pH of 7.4 is not a “neutral” solution and that when the pH is below 7.4, blood is not actually an acidic solution. This is because in all of the solutions in the body, with the exception of the gastric contents after fasting, $[H^+]/[OH^-]$ and the solutions are thus alkaline. The definition of 7.4 as normal is thus just a useful reference point in the same way that one calls the freezing point of water 0°C even though true “zero” is a much lower value. Thus, as in the traditional approach, in the physical-chemical analysis of acid–base balance, a blood pH below 7.4 is still called an acidemia and pH greater than 7.4 an alkalemia even though what is called acidemia is really just a less alkaline solution and what is called alkalemia a more alkaline solution.

PARTIAL PRESSURE OF CARBON DIOXIDE

$P_{CO_2}$ is an independent variable because $CO_2$ production is determined by metabolic activity, and $P_{CO_2}$ in the blood is determined by ventilation, which is normally tightly controlled by the brain. As in the conventional approach, $P_{CO_2}$ is an important determinant of $[H^+]$, and it defines the respiratory component of acid–base disorders. The Henderson-Hasselbach equation presented in Equation 61-1 was derived from the mass-action relationship of the $P_{CO_2}$ to carbonic acid in the blood and the dissociation of $H_2CO_3$ into $[H^+]$ and $HCO_3^-$:

$$P_{CO_2} \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \quad (61-2)$$

where $K_1$ is a constant that relates the solubility of $CO_2$ in plasma and the equilibrium relationship with $H_2CO_3$ and $K_2$ is the equilibrium constant for the relationship of $H_2CO_3$, $H^+$, and $HCO_3^-$.

However, it needs to be appreciated that once the value of $P_{CO_2}$ is fixed by a well-functioning ventilatory center, the dissociation of $H_2CO_3$ is determined by the rate constants of the reaction and by other factors in the solution, including the [SID] and $[A_{total}]$, which are discussed below. Since one side of Equation 61-2, the $P_{CO_2}$, is fixed by ventilation, the products of this equilibrium reaction, $H^+$ and $HCO_3^-$, are dependent variables. An interesting historical point made by Stewart is that the emphasis on the importance of $HCO_3^-$ in acid–base physiology occurred because it became possible to measure total $CO_2$ in a solution before it was possible to measure $P_{CO_2}$. This was done by making the SID of a $CO_2$-containing solution negative, which drives all the $HCO_3^-$ into $H_2CO_3$ and dissolved $CO_2$. The dissolved $CO_2$ is then converted to the gas phase by placing the sample in an evacuated container. A close approximation of the

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**FIGURE 61-1** Principles of the physical-chemical approach to acid-base analysis. The three independent variables are the SID, $P_{CO_2}$, and concentration of weak acids (HA). $H^+$ and $HCO_3^-$ are dependent variables.

**FIGURE 61-2** The effect of temperature on the $K'w$, the product of the dissociation constant of water and the water concentration, is shown in A. Increasing temperature increases the dissociation of water. The effect of the temperature dependent change in $K'w$ on $pH$, $H^+$, and $OH^-$ is shown in B. Increasing temperature increases $H^+$ and decreases the pH. However, the solution is still acid base neutral, because $H^+$ equals $OH^-$. 
PCO₂ can then be made by using the Henderson-Hasselbach equation to calculate PCO₂ with the measured pH and the total CO₂ as an estimate of the HCO₃⁻. Ironically, today, the actual HCO₃⁻ is calculated from the measured PCO₂ and the pH.

In the physical-chemical approach, as in the traditional approach, a PCO₂ > 40 mm Hg is called a respiratory acidosis and a PCO₂ < 40 mm Hg a respiratory alkalosis. The suffix “-osis” refers to an acidifying or alkalinizing process. These definitions are true even if the pH is not acidemic or alkalemic relative to the normal value of 7.4. In the physical-chemical analysis, it is not necessary to refer to compensated or uncompensated conditions but rather to the metabolic or respiratory processes that are actually occurring. As will be seen, the physical-chemical approach allows quantification and mechanistic understanding of the processes involved in metabolic acid–base disturbances and the compensatory mechanisms, without having to resort to empiric rules.

**STRONG ION DIFFERENCE**

A very important regulator of the metabolic component of acid–base balance that is not considered in the traditional approach is the [SID]. SID is the difference in concentrations (measured in equivalents) of the strong cations and strong ions in the solution. A strong ion is an ion that exists in essentially a dissociated form in solution. Examples of strong cations are Na⁺, K⁺, Mg²⁺, and Ca²⁺. Examples of strong anions are Cl⁻, SO₄²⁻, and lactate. On the other hand, as will be seen later, phosphate behaves as a weak acid. The key principle that makes the [SID] of the solution so important is the principle of electrical neutrality, which says that in a macrosolution all positive charges must equal all negative charges. To consider the significance of electrical neutrality, consider a sphere of 1 mm in diameter with a charge difference between the positive and negative ions of 1 × 10⁻⁷ Eq/L. Using Coulomb’s law it can be calculated that the net charge would be 400,000 volts. Thus, even a small charge difference in a solution produces a very strong force that affects other molecules in the solution that are not totally dissociated for the charge must be balanced. In a solution with only strong electrolytes in water, the only other source of ions is water. The electrical charge from the [SID] thus alters the dissociation of water and the final [H⁺] and [OH⁻].

The predominant strong ions in plasma are Na⁺ and Cl⁻, and because the concentration of the strong cations (mainly Na⁺ in the extracellular space) is much greater than the concentration of the strong anions (mainly Cl⁻ in the extracellular space), the [SID] is positive in almost all biologic solutions. The normal [SID] of plasma is about +42 mEq/L. The relative magnitude of the ions in plasma can be seen by examining a “Gamblegram” of the plasma electrolytes (Figure 61-3). The other strong ions in plasma, such as K⁺, Mg²⁺, Ca²⁺, and SO₄²⁻, are found in much smaller quantities, that is, 1 to 4 mEq/L. Since small deviations of their concentrations from the normal values have major physiologic effects, they do not play a significant role in changes in the plasma [SID], and changes in [Na⁺] and [Cl⁻] dominate the regulation of the [SID]. Furthermore, [Na⁺] is very important for the regulation of plasma osmolality and volume status of the extracellular space. Therefore, changing plasma and extracellular [Na⁺] is not a very viable option for the maintenance of the normal [SID]. Thus, the only electrolyte that can be readily altered to regulate plasma [SID] is Cl⁻, and it becomes clear that regulation of [Cl⁻] is critical for maintenance of the normal [SID] and normal acid–base balance.

**DISORDERS OF THE STRONG ION DIFFERENCE**

**Principles**

It often seems that H⁺ is directly added to a solution and that H⁺ is thus an independent determinant of acid–base balance. This misconception likely occurs because the distinction between the dependent and independent behavior of [H⁺] is not evident in solutions with a negative [SID]. Take, for example, a solution in which the only two ions are Na⁺ and Cl⁻ and [Cl⁻] is greater than [Na⁺]. The [SID] of this solution is thus negative. When an acid, such as HCl, is added to this solution, the Cl⁻ must remain in the solution as an ion for it is a strong ion. The change in [H⁺] in this solution will equal the change in [Cl⁻] for there are no other cations in the solution to balance the change in Cl⁻. It thus appears as if [H⁺] was directly added to the solution and is an independent variable for [H⁺] increased by the same amount as that added. However, the dependent behavior of [H⁺] becomes evident when HCl is added to a solution with a positive [SID]. Take, for example, a solution in which [Na⁺] is greater than [Cl⁻] as occurs in extracellular fluid. When HCl is added to a solution with a positive [SID], the Cl⁻ again must remain dissociated for it is a strong ion. However, this time the change in [H⁺] will be smaller than the change in [Cl⁻]. This is because the addition of
chloride decreases the electrical force that had altered the dissociation of water. If this electrical force had not been present, [H+] would have been equal to [OH−] instead of being much lower (and the pH very high). However, in contrast to Cl−, H+ is a very weak ion and does not have to remain dissociated. Therefore, some of the added H+ associates with OH− and forms water. To determine the final concentration of H+ in the new solution, one must take into account two laws of nature, the mass-action equation for the dissociation of water and the principle of electrical neutrality, which accounts for all the changes in the solution. The solution of these two equations determines the final [H+]. Since nearly all major biologic fluids have a positive SID, the addition of an acid to these fluids never produces an increase in H+ that is equal to the increase in the anion and the true dependent nature of H+ becomes evident.

Consider what happens to the same solution with [Na+] greater than [Cl−] and [Na+] is increased by the addition of NaOH. The principle of electrical neutrality requires that there must be a negative ion to balance the increase in [Na+]. Since OH− is the only available anion to balance the increase in Na+ from the dissociation of water and the OH− added with the Na+, the change in the charge difference of strong ions will alter the dissociation equilibrium of water and increase the [OH−] in the solution. A very small amount of the OH− will react with H+ and decrease the H+ and increase the pH and thus produce an alkalinizing effect. However, the magnitude of the OH− concentration is orders of magnitude higher than that of the H+ so that it will seem that OH− increased by an equal amount to the increase in Na+. It will appear that the addition of OH− had the alkalinizing effect when, in fact, it was the addition of Na+ that was responsible for the change in [H+]. In summary, the narrowing of the SID of plasma has an alkalinizing effect and looks like the addition of HCl. The widening of the SID has an alkalinizing effect and looks like the addition of NaOH.

The SID can be altered by changes in the amount of water or by the gain or loss of a strong ion. Let us first consider changes in water.

**Changes in Water**

Figure 61-4 shows a beaker with 1 liter of water, [Na+] = 140 × 10−6 Eq/L and [Cl−] = 100 × 10−6 Eq/L. The [SID] is thus 40 × 10−6 Eq/L, and the pH of the solution is 10.6. If 1 liter of water is added, [Na+] decreases to 0.70 × 10−6 Eq/L, [Cl−] to 0.50 × 10−6 Eq/L, and the [SID] to 0.20 × 10−6 Eq/L. This gives a pH of 10.1. Thus, just adding water changed the pH, and this demonstrates a dilutional acidosis. In contrast, a loss of water will increase the [SID], which has an alkalinizing effect.

**Changes in Chloride**

As already noted, the primary strong anion in blood is Cl−, and Cl− is thus the most important strong anion available for the regulation of acid–base balance. A good example of the role that Cl− plays in acid–base balance is the metabolic acidemia commonly seen after resuscitation with normal saline. This is easily explained by the physical-chemical approach by considering the effect of saline resuscitation on the [SID] and blood pH. Since normal saline has equal [Na+] and [Cl−], the [SID] is 0. Thus, the administration of normal saline narrows the [SID] of blood, which is an acidifying effect. The kidney counters increases in [Na+] faster than it counters increases in [Cl−], so the excretion of Cl− lags behind the excretion of Na+, which further contributes to the smaller [SID] and the acidifying effect. This is seen as a hyperchloremic acidemia.

The role of Cl− is central in the pathophysiology of renal tubular acidosis. In the traditional approach, the explanation for renal tubular acidosis is that there is a failure to reabsorb HCO3−, but HCO3− is a dependent variable and is determined by the PCO2 and [SID]. From a physical-chemical approach, there is a failure to excrete Cl−, which is a common problem in renal disease. For the kidney to excrete Cl−, to satisfy the principle of electrical neutrality a cation is needed to balance the negative charge of Cl− in the urine. The cation cannot be Na+ for, besides the consequent decrease in plasma osmolality, the equal loss of Na+ and Cl− would produce a steady decrease in the [SID] of blood, which would have an acidifying effect. Normally, the kidney balances the negative charge of Cl− in the urine by producing ammonia (NH3), which freely moves across the tubular membranes into the urine, where it forms NH4+, a weak base. NH3 must be produced from metabolism of amino acids. The diseased kidney is unable to do so and is thus only left with Na+ to balance Cl− and fails to correct the academia.

Another situation where the [SID] is narrowed because of hyperchloremia is diarrhea. In the upper bowel, the fluid is normally alkaline with a low [Cl−] compared with plasma and a large [SID]. When diarrhea is present, the more rapid transit in the bowel results in a failure to reabsorb Na+ and loss of water (possibly also owing to a failure to excrete Cl−) in the distal bowel. The loss of volume and decrease in
[Na+] has an acidifying effect by narrowing the [SID].Retention of Cl− by the kidneys as part of the compensation for the salt loss would narrow the [SID] further and increase the acidosis. The situation also is made worse when normal saline is used as the resuscitation fluid because, in contrast to the normal extracellular fluid, the [Na+] and [Cl−] of this solution are equal and will further narrow the [SID], as discussed above for the metabolic acidosis associated with saline resuscitation.

The opposite occurs when there is gastric suction. In this situation there is a loss of Cl− without a loss of Na+, and thus [SID] widens and there is an alkalosis. It needs to be appreciated that this will only occur when the stomach contents are acidic for otherwise the loss of Na+ could be greater than the loss of Cl−, in which case acidosis could even occur. Note again that it is the loss of Cl− that is important and not the loss of H+. The H+ is derived from the dissociation of water, and concentration of water is 10^9 times greater than that of H+ (the concentration of H2O at 37°C is 55.3 M and the concentration of H+ is 40 × 10^-9 M.)

**Addition of Other “Strong” Ions**

Another way the [SID] can be changed is by the addition of ions that are not strong ions, but at the pH of plasma they are fully dissociated and thus act in the solution like strong ions. These are usually anions, and examples of effectively strong anions that can accumulate in pathologic conditions include lactate, formate, oxalate, β-hydroxybutyrate, acetocacetate, and salicylate. These will be recognized as the ion in classic “wide anion gap” acidosis. It is important to appreciate that for acid-base balance, the effect of the addition of a strong ion, such as lactate, has the same effect as the addition of Cl−. The only difference is that lactate can be metabolized, whereas Cl− has to be excreted.

The understanding that these substances produce an acidosis by narrowing the [SID] helps explain why the administration of NaHCO3 cannot successfully treat an acidosis that results from the production or absorption of a strong anion (Figures 61-5 and 61-6). The addition of NaHCO3 corrects the acidemia by the addition of Na+, which widens the [SID], and not by the addition of HCO3−. HCO3− is a dependent variable and, in an open system, is controlled by the excretion of carbon dioxide by ventilation. Thus, to correct a lactic acidemia of 10 mmol/L, [Na+] would have to increase by 10 mEq/L, which would produce severe hypernatremia with consequent effects on cellular volumes. Furthermore, it is likely that the kidney or bowel will excrete the excess Na+ or water will be retained so that normal osmolality is maintained, and therefore the body will not even allow the Na+ to increase.

The use of NaHCO3 solutions can, however, be of help in patients with renal failure and acidosis that is related to a failure to clear Cl−. The infusion of NaHCO3 provides a cation, Na+, that can be excreted with Cl−, whereas based on Equation 61-2, HCO3− is in equilibrium with H2CO3, which is in equilibrium with PCO2, and the PCO2 is regulated by ventilation.

The administration of NaHCO3 to patients with severe lung injury who are being managed with permissive hypercapnia and thus have a respiratory acidosis seems to be of clinical benefit. A possible explanation is that in these patients ventilation is relatively constant and does not change with changes in PCO2. Thus, CO2 no longer behaves as an independent variable and with the addition of HCO3− can act as a dependent variable and be increased by the addition of NaHCO3. In this situation, the HCO3− could combine with H+ in plasma and decrease [H+].

An interesting observation and application of Stewart’s principles was recently made by Prange and coworkers, who showed that the decrease in partial pressure of oxygen (PO2) in venous blood results in increased binding of Cl− to hemoglobin. This reduces the oxygen affinity of oxyhemoglobin and partly explains the Haldane effect. It also accounts for the increase in red blood count (RBC)-ICF [Cl−] that occurs in venous blood by what is known as the chloride shift. The binding of Cl− to hemoglobin means that there is less free Cl− in the intracellular fluid than expected and therefore less of a decrease in intracellular [SID] of the red cells on the venous side of the circulation than would otherwise have
occurred from the influx of Cl\textsuperscript{-}. Because the influx of Cl\textsuperscript{-} does not narrow the SID as much as would otherwise have occurred, there is less of an acidifying effect from the influx of Cl\textsuperscript{-}. The authors propose that this binding of Cl\textsuperscript{-} to hemoglobin explains why [H\textsuperscript{+}] is lower (and pH higher) and [HCO\textsubscript{3}\textsuperscript{-}] higher than predicted in venous blood.

**WEAK ACIDS**

**PRINCIPLES**

Weak acids are substances that only partially dissociate in a solution. The two important variables for determining their effect on [H\textsuperscript{+}] are the total amount added (referred to as \(A\textsubscript{Total}\)) and the pK\textsubscript{a} of the reaction for this defines how much of the substance is dissociated at a given pH. Weak acids that are particularly important for acid-base balance have pK\textsubscript{a}s within an order of magnitude of the pH of normal plasma. If the pK\textsubscript{a} is much below the pH of plasma, the substance will be mainly dissociated and function more like a strong ion in the solution. If the K\textsubscript{a} is much higher than the pH of plasma, it will be largely associated at normal pH and have no effect on acid-base balance.

Weak acids with pK\textsubscript{a} close to the pH of blood are often considered “buffers,” but the concept of a buffer first needs to be reviewed. A buffer is defined as a substance that reduces the change in pH or [H\textsuperscript{+}] when a base or acid is added to a solution.2 This is defined mathematically as:

\[
\beta = \frac{d\beta}{d\phi} \tag{61-3}
\]

where \(\beta\) is the buffer strength, \(d\beta\) is the amount of base added, and \(d\phi\) is the change in pH. A potentially confusing point that can lead to erroneous predictions is the standard definition of a base as a proton acceptor. Thus, Cl\textsuperscript{-} is defined as a base because it “accepts” a proton, H\textsuperscript{+}. However, nothing of the sort happens. Cl\textsuperscript{-} is a strong anion, which means that it binds minimally with cations in the solution, and its charge is balanced by H\textsuperscript{+}, but it is not bound to it. As already discussed, the dependent behavior of [H\textsuperscript{+}] becomes obvious when HCl is added to a solution with a positive [SID] for in a solution with a positive [SID], the addition of HCl results in a smaller change in [H\textsuperscript{+}] than the change in [Cl\textsuperscript{-}]. This occurs even without a weak acid, or so-called buffer, being present. It is the change in [SID] that determines the change in [H\textsuperscript{+}], and what really happens when buffer strength is tested is that the addition of a strong cation or anion changes the [SID] and the change in [SID] changes pH.

Weak acids are either volatile, which is the case for H\textsubscript{2}CO\textsubscript{3} in biologic solutions, or nonvolatile. In a solution with strong electrolytes, a positive [SID], and essentially no nonvolatile weak acids (ie, no protein), for example, interstitial fluid, the addition of a strong acid or base only produces a small change in pH, and the solution seems to be “buffered.” The addition of a nonvolatile weak acid to create a solution similar to plasma or the intracellular environment has some important consequences. There are now two important variables that determine [H\textsuperscript{+}], the [SID] and [A\textsubscript{Total}], where [A\textsubscript{Total}] is the total concentration of weak acids, which are classically viewed as “buffers.” Over the range of [SID] from 0 to [A\textsubscript{Total}], [H\textsuperscript{+}] actually increases more rapidly than is the case in a solution where there is no weak acid—the opposite of what a buffer should do.1 What the weak acid does, though, is markedly lower the pH and thus lower the pH of the solution observed for a given change in [SID] over the range of [SID] = 0 to [SID] = [A\textsubscript{Total}]. If the dissociation constant of the weak acid is within an order of magnitude of normal plasma, which is the case for what are usually considered to be physiologically important buffers, and [SID] is increased, negative ions are needed to balance the positive charge difference, and this drives the dissociation of the weak acid. When the [SID] equals [A\textsubscript{Total}], the weak acid is almost completely dissociated and no longer affects the solution.

**ALBUMIN**

The most important normal weak acid in plasma is albumin. The pK\textsubscript{a} of the histidine side chains is close to the value of normal plasma pH, and therefore changes in plasma [SID] have a major effect on their dissociation. These ions account for most of the normal “anion gap,” so a decrease in albumin
is associated with a decrease in the anion gap.\textsuperscript{7-9} This effect of albumin on the pH of the solution is traditionally referred to as buffering, but as already noted, what this weak acid really does is set a range over which there are small changes in pH for given changes in SID. A major difficulty for the application of the physical-chemical approach to clinical acid–base analysis is assigning an “equivalents” value to the anion of albumin. This problem was dealt with empirically by Figge and coworkers,\textsuperscript{9,10} who performed titration curves on blood with different albumin concentrations and different SID. They thus were able to provide a formula for the anion equivalence of albumin at different values of pH that can be used to obtain the “charge effect” of weak acids that are dominated by albumin as follows:

\[
\text{Albumin equivalence} = (0.123 \times \text{pH} - 0.631) \\
\times (\text{[albumin]})
\]  

(61-4)

where albumin is in g/L.

A decrease in albumin concentration is very common in critically ill patients.\textsuperscript{7,8,11} The reduction in this weak acid has an alkalinizing effect, and an increase in the albumin concentration has an acidifying effect. For example, with a constant PCO\textsubscript{2}, a decrease in albumin from 42 to 20 g/L has the same alkalinizing effect as a decrease in a strong anion of 6 mEq/L. This means that this decrease in albumin would have the same effect on [H\textsuperscript{+}] as a decrease in lactate from 8 mEq/L to 2 mEq/L.

A decrease in water with dehydration increases the albumin concentration, which has an acidifying effect. On the other hand, as discussed above, dehydration can widen the [SID], which has an alkalinizing effect. The final effect will depend upon how normal regulatory mechanisms respond to the increase in [Na\textsuperscript{+}] and [Cl\textsuperscript{-}]. Since [Na\textsuperscript{+}] is normally well regulated, it is likely that the increase in [Na\textsuperscript{+}] will be regulated first, and that would narrow the [SID] and lead to acidemia. Indeed, this has been observed during a cholera outbreak.\textsuperscript{12}

The second weak acid of potential clinical importance is phosphate (PO\textsubscript{4}\textsuperscript{3+}). The dissociation of phosphoric acid to PO\textsubscript{4}\textsuperscript{3+} has three steps with three pK\textsubscript{a}. At 37°C the first pK\textsubscript{a} is only 1.91, and therefore this component acts as a strong anion and is essentially totally dissociated. The second pK\textsubscript{a} is 6.66, which is close to normal pH and is very much affected by the other components of plasma. The third pK\textsubscript{a} is very high, 11.8, and is therefore only minimally dissociated in the plasma.\textsuperscript{10} Normal [PO\textsubscript{4}\textsuperscript{3+}] in plasma is only around 1 mmol/L, and therefore changes in its dissociation actually have little effect on [H\textsuperscript{+}], but [PO\textsubscript{4}\textsuperscript{3+}] can play a role when the concentration increases with disease. The relationship, again from Figge and colleagues,\textsuperscript{10} is

\[
\text{Pi}^- = \text{Pi} \times (0.309 \times \text{pH} - 0.469)
\]  

(61-5)

where Pi\textsuperscript{-} is the ionized portion and Pi is the total phosphate.

**CLINICAL APPROACHES AT THE BEDSIDE**

**STEWART’S ORIGINAL PRESENTATION**

The first physical-chemical approach to the analysis of acid–base balance was presented by Stewart, who gave a comprehensive analysis of the regulation of [H\textsuperscript{+}] in the body. His approach was further developed by Figge and colleagues\textsuperscript{9,10} and Fencil and Rossing.\textsuperscript{13} Stewart provided six equations that could be solved simultaneously by combining them into a quadratic equation to calculate [H\textsuperscript{+}].\textsuperscript{1} He then calculated the effect of changes in PCO\textsubscript{2} and [SID] at a fixed A\textsubscript{Total} and plotted these together. This is shown in Figure 61-7. The analysis is begun by plotting the pH (or H\textsuperscript{+}) and PCO\textsubscript{2} and determining the expected [SID]. For example, if a patient’s PCO\textsubscript{2} is increased and pH is normal and the [SID] is the normal value of 42 mEq/L, then the problem is purely respiratory, and the clinical solution is to treat the respiratory problem. In contrast, if there is a decrease in pH with a decrease in PCO\textsubscript{2} and a decrease in the SID, there is a metabolic problem.

The next step is to determine why the [SID] is abnormal. This is done by determining the sum of [Na\textsuperscript{+}] + [K\textsuperscript{+}] − [Cl\textsuperscript{-}], the common major strong ions in the plasma, for this gives the inorganic [SID]. If this value is not the same as that given by the nomogram, then the next step is to determine whether this is because of an increase in [Cl\textsuperscript{-}] or a decrease in [Na\textsuperscript{+}]. If [Na\textsuperscript{+}] and [K\textsuperscript{+}] are normal, and [SID] differs from the value predicted by the nomogram, unidentified anions must be present. These anions are the same as those that explain the traditional wide anion gap acidosis.

Stewart also pointed out that if the nomogram is not available, then the expected [SID] can be estimated by [SID] = HCO\textsubscript{3}\textsuperscript{-} + [A\textsubscript{-}], and [A\textsubscript{-}] can be estimated from the [SID] − [HCO\textsubscript{3}\textsuperscript{-}], that is, [Na\textsuperscript{+}] + [K\textsuperscript{+}] − [Cl\textsuperscript{-}] − [HCO\textsubscript{3}\textsuperscript{-}], which is the anion gap. This estimate, however, leaves out the variability of [A\textsubscript{-}] with changes in pH as demonstrated in Figge and colleagues’ equation.\textsuperscript{10}

A weakness in the simple approach first presented by Stewart is that it did not factor in changes in A\textsubscript{Total} or give a process for quantitatively analyzing them for the assumption in the nomogram in Figure 61-7 that [A\textsubscript{Total}] is constant, which usually is not the case in critically ill patients.

**PRESENTATION BY JONES**

An early advocate of the Stewart approach was Norman Jones.\textsuperscript{14,15} He used essentially the same approach as Stewart but elaborated on the relationship of the measured and predicted [SID] and introduced the concept of a [SID] gap. Building on Stewart’s work, he used the nomogram in Figure 61-7 to predict the [SID] and compared it with [SID] obtained from the measurement of plasma electrolytes. He also pointed out that since [SID] − [HCO\textsubscript{3}\textsuperscript{-}] − [A\textsubscript{-}] = 0 one can assess the role of each of these three factors in the acid–base disorder.

**CONCEPT OF STRONG ION GAP**

The concept of strong ion gap (SIG) was further elaborated by Kellum and colleagues, who built on concepts presented by Fencil and Leith.\textsuperscript{16} Based on the work of Stewart\textsuperscript{1} and Figge and colleagues,\textsuperscript{10} SIG is defined as the difference
between the apparent strong ion difference \([\text{SID}]_a\) and the effective strong ion difference \([\text{SID}]_e\) where

\[
[\text{SID}]_a = [\text{Na}^+] + [\text{K}^+] + [\text{Mg}^{2+}] + [\text{Ca}^{2+}] - [\text{Cl}^-] - [\text{lactate}] - [\text{urate}]
\]

(all ionized concentrations are in mEq/L) and

\[
[\text{SID}]_e = 1,000 \times (2.46 \times 10^{-11}) \times (\text{PCO}_2/(10^{-\text{pH}}))
\]

\[
+ ([\text{albumin}] \times (0.123 \text{ pH} - 0.631))
\]

\[
+ ([\text{PO}_4] \times (0.309 \text{ pH} - 0.469))
\]

([PO\text{$_4$}] is in mmol/L and albumin is in g/L). The formula for calculating all the components of the analysis are given at a Web site created by Kellum called The Acid Base pHorum:


The SIG should normally be zero. If it is not, there are unexplained anions. By using the formula provided by Figge and colleagues, this approach accounts for changes in albumin concentration. Thus, Kellum and colleagues proposed that the SIG should be used instead of the anion gap for evaluating patients. An unexpected observation in their studies was that there are often large amounts of unknown anions in patients with sepsis and liver disease.

A number of investigators have now used this approach to evaluate the abnormalities of various conditions, as
well as the effect of interventions.\textsuperscript{23-25} The basic approach is to first examine whether the [SID] deviates from the normal value of 42 mEq/L. If it is abnormal, the next question is what measured ions are abnormal to account for the abnormality. For example, is the lactate increased? If there is a SIG with a [SID]e less than the [SID]a, unmeasured anions are present that are greater in number than the unmeasured cations and if SIG is positive, there must be unexplained cations.

**BASE EXCESS AND BASE EXCESS GAP**

Magder and colleagues introduced another approach, which classifies metabolic abnormalities into those owing to water, Cl\textsuperscript{−}, albumin, and “other” factors.\textsuperscript{26} The “other” factors are calculated by using the base excess (BE) rather than the SIG. This approach is based on one used by Fencil and Leith but never published (personal communication).

In this approach, and in all of the physical-chemical approaches, the first step in evaluating acid–base balance is to determine if there is an acidemia or alkalalemia, and this is done by simply determining if there is a deviation in pH from the physiologic normal value of 7.40. If the pH is greater than 7.40 there is an alkalalemia, and if the pH is less than 7.40 there is an acidemia. However, it must be remembered that a pH in plasma <7.40 does not actually mean that the blood is an acid solution in the chemical sense for [H\textsuperscript{+}] is still much less than [OH\textsuperscript{−}]. It is really just less alkaline. However, this terminology is common usage and convenient for interpreting deviations from normal.

The next step is to evaluate the respiratory component. This is done by examining the deviation of PCO\textsubscript{2} from the standard value of 40 mm Hg. If the PCO\textsubscript{2} is >40 mm Hg, by definition there is a respiratory acidosis regardless of the pH for the PCO\textsubscript{2} defines a process. If the PCO\textsubscript{2} is <40 mm Hg, there is a respiratory acidosis regardless of the pH.

The metabolic components are examined next. First one examines the role of changes in the concentrations of electrolytes that are a result of changes in “water.” Since the amount of extracellular water is determined primarily by the [Na\textsuperscript{+}], [Na\textsuperscript{+}] is used to assess water effects. This is done by comparing the measured [Na\textsuperscript{+}] with the [Na\textsuperscript{+}] reference value, which is 140 mEq/L, and by assuming normal [SID] of 42 mEq/L as follows:

\[
\text{Water effect (mEq/L)} = \frac{(\text{Na} - 140)/140}{0.3} \times (\text{Na}^+ - 140)
\]

As discussed above, the major mechanism available to the body to regulate the [SID] is the regulation of [Cl\textsuperscript{−}]. Therefore, an important step is the evaluation of the change in [Cl\textsuperscript{−}]. To do this, one must first account for the effect of changes in water on [Cl\textsuperscript{−}] for this was already accounted for in the previous step. This is done by correcting the measured [Cl\textsuperscript{−}] by the ratio of the standard value of [Na\textsuperscript{+}] of 140 mEq/L, and the measured [Na\textsuperscript{+}]:

\[
[\text{Cl}^{-}] - \text{corrected (mEq/L)} = [\text{Cl}^{-}] \times 140/[\text{Na}^{+}]
\]

The effect of the change in [Cl\textsuperscript{−}] can then be calculated from

\[
\text{Chloride effect (mEq/L)} = 102 - ([\text{Cl}^{-}] - \text{corrected (mEq/L)})
\]

where 102 mEq/L is the standard [Cl\textsuperscript{−}] value.

The third metabolic factor is the effect of changes in albumin for albumin is the major determinant of the effect of weak acids and the one to have a change in concentration in pathologic conditions. The ionic equivalents of a change in albumin can be determined by an adaptation of the empiric formula developed by Figge and colleagues\textsuperscript{10}:

\[
\text{Albumin effect (mEq/L)} = 42 - \frac{[\text{albumin}] 	imes (0.123 \times \text{pH} - 0.631)}{10}
\]

where albumin is in g/L and 42 represents the standard value of albumin.

Once the effect of these three factors—water, [Cl\textsuperscript{−}], and albumin—is accounted for, the presence of any “other” factors can be determined by the use of the SIG as described above. Alternatively, we found that it is very convenient to use the base excess (BE), which is given with the outputs from most blood gas machines. To do so, one adds the value in mEq/L of the water effect, chloride effect, and albumin effect and subtracts this sum from the calculated BE, which is also in the units of mEq/L:

\[
\text{“Other” (mEq/L)} = \text{BE} - (\text{water effect} + \text{chloride effect} + \text{albumin effect})
\]

To understand the rationale for this last step it is necessary to understand the concept of BE. BE is a concept that was developed in the early part of the century to account for the nonrespiratory component of an acid–base disturbance and was best elaborated by Sigggaard-Andersen.\textsuperscript{27} He first restored the PCO\textsubscript{2} back to 40 mm Hg to eliminate the respiratory contribution to any alteration in the pH. Next he performed titrations with a strong base or strong acid to restore the pH to 7.40. This was essentially a titration of the [SID] and is thus an empiric assessment of the SIG. Indeed, there is a tight relationship between measurements of “other” by this method (or as it could also be called the BE gap) and the SIG.\textsuperscript{26}

The BE reported on blood gases today comes from a nomogram created empirically by Sigggaard-Andersen to determine the BE. Because the electrolytes in plasma are in equilibrium with the interstitial space, a titration in a test tube of blood is not the same as a titration on whole blood or, for that matter, on serum. This has often been viewed as being due to a greater “buffering effect” of hemoglobin in the test tube, and because of this, BE is often given as “standard base excess,” which is based on a hemoglobin value of 50 g/L, which takes into account the distribution of electrolytes throughout the extracellular space.\textsuperscript{28,29} However, the differences are really quite small, and we have used the BE based on a hemoglobin of 150 g/L. The reason why the effect is small is that hemoglobin does not actually “buffer” the plasma because it is not in contact with it. The only way red cells in the plasma can affect [H\textsuperscript{+}] is by electrolyte shifts between the intracellular space and the plasma, which then
can alter plasma [SID]. However, the RBC intracellular volume is small compared with that of plasma. In the body, the intracellular compartment of RBC interacts with the whole extracellular volume and therefore has only a minimal effect on electrolyte concentrations.

The analysis based on the effects of water, chloride, albumin, and BE has the advantage of indicating which major regulator is causing the acid–base abnormality. It is also easier to calculate than the full equation for determining the apparent [H\(^+\)]. The disadvantage to this approach, however, is that it introduces another empiric measurement, that is, the BE, and therefore has the potential for other confounding factors that may not have been accounted for in the original titration experiments that were used to obtain the BE nomogram. The effects of other factors, such as phosphate, also become more of a problem at the extremes of the range of phosphate values, but this can also be accounted for by the formula introduced by Figge and colleagues as given above.

**SUMMARY**

Appreciation of the physical-chemical factors that determine [H\(^+\)] is essential for understanding the mechanisms behind acid–base disorders. Once one understands the basic processes, an examination of the electrolytes can give a quick, but not quantitative, insight into the basic mechanism. For example, a low [Na\(^+\)] indicates a major water effect, a high [Cl\(^-\)] indicates a “non-anion gap” metabolic acidosis, and a low albumin indicates a metabolic alkalosis. An abnormal BE in the absence of major [Cl\(^-\)] abnormalities means that there are very likely abnormal anions present. When more quantitative analysis is desired, one can calculate the SIG or use the calculations given above to quantify the water effect, chloride effect, albumin effect, and “other.”

**REFERENCES**