Acid Base Homeostasis: Stewart Approach at the Bedside

7

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Contents

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IFA Commentary (MLNGM)

The Stewart approach to acid-base balance is a fascinating method that is increasingly being used by the medical community and especially intensive care physicians. First presented by the late Peter Stewart around 1980, the approach completely clarifies any acid base disturbance [1]. One of the key concepts of the new Stewart approach is that bicarbonate, or HCO_3^-, does not play any role in acid-base balance as opposed to the traditional and still generally used approach. This is usually very counterintuitive for most clinicians as the commonly used Henderson Hasselbalch approach advocates otherwise. Interestingly, Stewart does not deny the value of the Henderson Hasselbalch equation. In fact, this equation is actually one of the six equations that Stewart proposes to describe the acid-base equilibrium (Table 7.1).

This implies that both approaches are mathematically compatible and that the Stewart approach may provide the overall and bigger picture. According to the Stewart approach, there are only three independent variables that determine the concentration of H^+ and thus pH in any fluid, including plasma (Fig. 7.1). These variables are first, the partial pressure of carbon dioxide (PCO_2), second, the total amount of not completely dissociated weak acids (Atot, mainly albumin) and finally, the so-called Strong Ion Difference (SID). The strong ion difference is the sum of all positively charged fully dissociated ions (mainly Na^+) minus the sum of all negatively charged fully dissociated ions (mainly Cl^-). If PCO_2 or Atot decrease, the patient will become more alkalotic. However, if the SID decreases the patient will become more acidotic. Thus, while HCO_3^- may follow the change in one of these independent variables, it can never cause a change in the pH by itself.

One of the most fascinating aspects of the Stewart approach is that it becomes very easy to see how fluid therapy may alter acid base status. Normal concentrations of plasma sodium and chloride are about 140 and 110 mEq/L, respectively, which results in a normal SID of 40 mEq/L. If we now infuse normal saline with a sodium and chloride content of 154 mEq/L and thus a SID of 0 mEq/L, it can easily be understood that plasma SID will decrease resulting in metabolic (hyperchloremic) acidosis.

Acidbase.org has been serving the critical care community for over a decade. The backbone of this online resource consists of Peter Stewart's original text "How to understand Acid-Base" which is freely available to everyone. In addition, Stewart's Textbook of Acid Base, which puts the theory in today's clinical context, is available for purchase from the website. However, many intensivists use acidbase.org on a daily basis for its educational content and in particular for its analysis module. A recent review provides an overview of the history of this website, a tutorial and descriptive statistics of over 10,000 queries submitted to the analysis module [2].

At first glance, the Stewart approach may appear difficult, especially because it involves a number of equations. However, in this chapter we will show you that the Stewart approach is actually very easy to use and understand at the bedside. We will focus on a number of difficult cases that will be solved at the end. This chapter will

provide the reader the tools needed to apply the Stewart approach at the bedside. After completion you will be able to fully understand, quantify, and diagnose any acid base disturbance you may encounter in daily clinical practice.

Suggested Reading

1. Kellum JA, Elbers PWG. Stewart's textbook of acid-base. Amsterdam, 2009. AcidBase.org. Available online at www.acidbase.org.
2. Elbers PW, Van Regenmortel N, Gatz R. Over ten thousand cases and counting: acidbase.org is serving the critical care community. Anaesthesiol Intensive Ther. 2015;47(5):441–8. https://doi.org/10.5603/AIT.a2015.0060. Epub 2015 Oct 13. PMID: 26459229.

Table 7.1 The Stewart equations, all of which need to be satisfied simultaneously

1. Water dissociation equilibrium	$[H^+] \times [OH^-] = K'_W$
2. Weak acid dissociation equilibrium	$K_A \times [HA] = [H^+] \times [A^-]$
3. Conservation of mass for "A"	$A_{TOT} = [A^-] + [HA]$
4. Bicarbonate ion formation equilibrium	$[PCO_2] \times K_C = [H^+] \times [HCO_3^-]$
5. Carbonate ion formation equilibrium	$[K_3] \times [HCO_3^-] = [H^+] \times [CO_3^{2-}]$
6. Electrical neutrality equation	$SID + [H^+] - [HCO_3^-] - [A^-] - [CO_3^{2-}] - [OH^-] = 0$

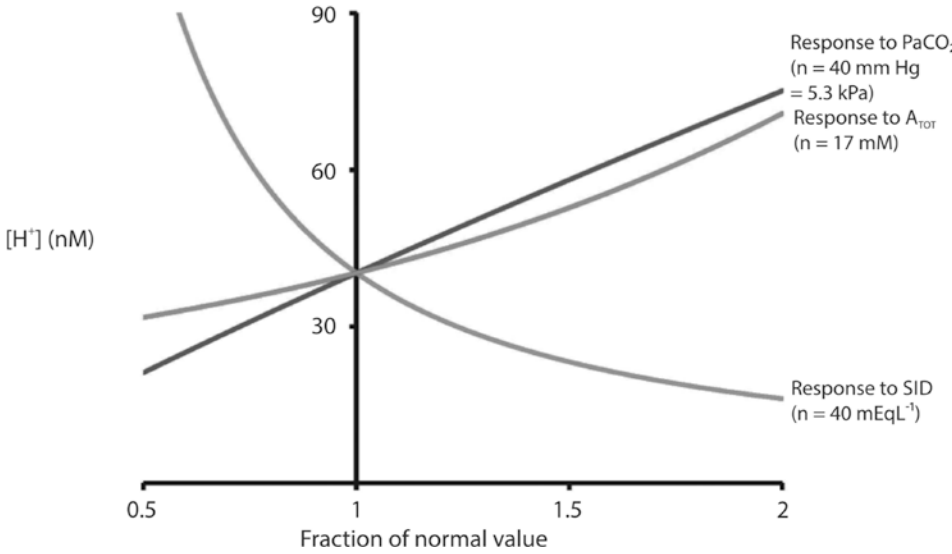

Fig. 7.1 The relative influence of the three independent parameters, SID, A_{TOT} and P_aCO_2 on H^+. pH 7.4 corresponds to $[H^+]$ = 40 nM, whereas pH = 7 and pH =8 correspond to $[H^+]$ of 100 and 10 nM respectively. *SID* strong ion difference. Reprinted and adapted with permission from Elbers et al. under the Open Access CC BY Licence 4.0 [2]

Learning Objectives

After reading this chapter, you will have learned:

1. To understand independent variables determining acid base homeostasis.
2. To understand concepts of total carbon di-oxide, strong ion difference (SID) and total non-volatile acid anion (Atot), their individual components, and the effects of these variables on acid base physiology.
3. To learn about Fencl's simplified methods (and calculations) to understand Stewart at bedside.
4. To understand the unified concept of base excess and Stewart.
5. To understand the impact of large volume resuscitation on plasma acid base homeostasis in light of Stewart approach.

Case Vignette

Mr. M, a 46 year-old male with a history of alcoholic liver disease was admitted to the Intensive Care Unit in a hypotensive state following variceal bleeding. On examination, he had evidence of peripheral circulatory shock. Blood gases done on admission showed: pH—7.40, $PaCO_2$—39 mmHg, HCO_3—24 mEq/L, BE—0. Laboratory reports revealed: Na −125 mEq/L, K −5.2 mEq/L, Cl −98 mEq/L, Albumin −13 g/L, Ca −3.2 mEq/L, and Pi −0.9 mEq/L.

Questions

Q1. Do we expect any acid base disturbance in Mr. M? If the answer is yes, how do we elucidate it from the given clinical and biochemical information?

Introduction

The traditional approach (described in the previous chapter), though useful for interpretation of acid base issues in most patients, has its limitations and fails to answer certain pertinent questions. It does not tell us about the mechanism of metabolic changes. How can $[H^+]$ with a tiny concentration in plasma (40 nmol/L at physiological pH of 7.4 and 38 °C temperature, compared to 55.3 mol/L for $[H_2O]$ or 140 mmol/L for $[Na^+]$) directly manipulate plasma pH? How $[HCO_3^-]$ independently determines the acid base balance when it is in equilibrium with CO_2? What about the role of buffer bases other than $PaCO_2$/HCO_3^-? What is the magnitude of changes in the metabolic component?

In the late 1970s, Peter Stewart, a Canadian biophysicist, described a quantitative approach to acid-base disorder. His approach was based on fundamental physicochemical properties of a solution that include principles of electroneutrality, law of conservation of mass, and dissociation equilibrium of all incompletely dissociated substances in a solution [1]. Although

quite comprehensive, Stewart's original approach failed to gain popularity because it demands the user to solve complicated equations limiting its utility at the bedside. In last three decades, various researchers have proposed modifications of the original Stewart approach. These modifications have now made it possible to utilize Stewart at the bedside, without losing much of its precision. In this chapter, we shall discuss simple bedside approach to Stewart's physicochemical approach to acid-base and its usefulness in critically ill patients. See also Chap. 6 to learn more about the traditional approach to acid-base.

Physicochemical Perspective

As mentioned earlier, Stewart approach looks at acid-base balance from physicochemical perspective. According to Stewart, [HCO_3^-] and pH in body fluids are dependent variables and are determined by three independent variables:

(a) Total CO_2 content (this incorporates $PaCO_2$, H_2CO_3, and HCO_3).
(b) Strong ion difference (SID).
(c) Concentration of weak nonvolatile acids (A_{tot}). Mostly determined by Albumin and Phosphate concentration.

Principle of electroneutrality states that concentration of all cations in plasma must be equal to the concentration of all anions to maintain the electrical equilibrium, as can be seen in the Gamblegram below (Fig. 7.2).

Strong ions are derived from substances that are almost completely dissociated in a solution. The strong ion difference (SID) is the sum of routinely measured strong plasma cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) minus the sum of routinely measured strong plasma anions (mostly Cl^-) ("**Apparent SID**").

$$\mathrm{SID} = \left(\left[\mathrm{Na}^+\right] + \left[\mathrm{K}^+\right] + \left[\mathrm{Ca}^{++}\right] + \left[\mathrm{Mg}^{++}\right]\right) - \left(\left[\mathrm{Cl}^-\right]\right)$$

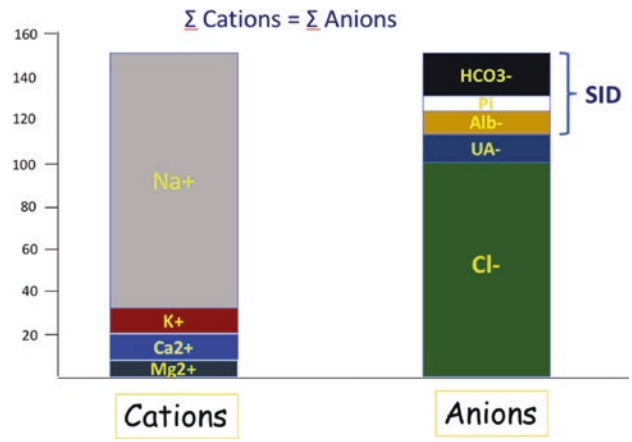

Fig. 7.2 Principle of electroneutrality: concentrations of all cations same as concentrations of all anions. *Alb*- albuminate, *UA*- unmeasured anion, *Pi*- phosphate

In physiological state, the gap between strong cations ([Na^+], [K^+], [Ca^{++}], [Mg^{++}]) and strong anions([Cl^-]) or SID, is filled up mostly by [HCO_3^-] and total amount of nonvolatile acids anions ([A_{tot}] comprising mostly of [Alb-] and to a lesser extent by [Pi-]) (as can be seen in Fig. 7.2). Thus, SID can also be calculated alternatively as the sum of [HCO_3^-] and [A_{tot}] ("**Effective SID**").

$$\text{SID} \sim \left[\text{HCO}_3^-\right] + \left[\text{A}_{\text{tot}}\right]$$

Any change in electrical charge between strong cations or strong anions (SID) or change in nonvolatile acid anion concentration (A_{tot}) distorts the dissociation equilibrium of weakly dissociating substances in plasma (including water itself) altering the balance between [H^+] and [OH^-]. Relative increase or decrease in [H^+] (compared to [OH^-]) produces acidosis and alkalosis, respectively—Arrhenius definition of acid/base.

SID and Acid Base Balance

SID can decrease with any gain in unmeasured strong anions (e.g., beta hydroxybutyrate or lactate) without an equivalent increase in strong cations. Otherwise, a decrease in SID can simply be because of [Cl^-] and [Na^+] moving closer together. [Na^+] and [Cl^-] can move closer together either because of water excess (lowering [Na^+]) or an increase in [Cl^-].

Decrease in SID in turn decreases the available space between strong cations and strong anions, resulting in a decrease in [HCO_3^-] (see the Gamblegram above). Decrease in [HCO_3^-] seen in metabolic acidosis is the effect (or marker) of metabolic acidosis rather than its cause.

On the other hand, an increase in SID results in metabolic alkalosis. SID can either increase as a result of an increase in [Na^+] (reflecting water deficit) or because of a decrease in [Cl^-]. With more available space, [HCO_3^-] increases with an increase in [SID].

Total Nonvolatile Acid Anion (A_{tot}) and Acid Base Balance

An increase in [A_{tot}] can result in metabolic acidosis and decrease in [HCO_3^-] (with unchanged SID). Similarly, decrease in [A_{tot}] (commonly due to hypoalbuminemia in critically ill) results in metabolic alkalosis and increase in [HCO_3^-].

Total CO_2

Stewart approach gives importance to [H_2CO_3]/[HCO_3^-] equilibrium. But maintains that ultimately what counts is the total CO_2, as long as there is sufficient carbonic anhydrase (an enzyme that modifies the reaction between H_2O and CO_2 generating HCO_3^- and H^+), intact circulation (that carries CO_2 from tissue to lung), and normal functioning lungs (that regulate $PaCO_2$).

Stewart at Bedside: Fencl-Stewart Approach

Fencl and Leith proposed a simplified approach to Stewart's physicochemical concept by determining the plasma values of independent variables and getting direct insight into the mechanism of acid base abnormality [2]. Acid–base status of the plasma can be considered normal only when all independent variables are within normal range. In contrast, abnormality of any one of these independent variables leads to acid–base disturbances. Values for all independent variables can either be obtained directly or may be easily calculated from the arterial blood gas analyzer and routine biochemistry.

1. **Water excess/deficit**: Any deviation in $[Na^+]$ **(Normal value 140 ± 2 mEq/L)**, low value signifying water deficit and high value water excess.
2. **$[Cl^-]$ excess or deficit:** Observed $[Cl^-]$ value needs correction for any dilution/ concentration of plasma. This can be done by following equation:
   (a) $[Cl^-]_{Corrected} = [Cl^-]_{Observed} \times ([Na^+]_{Normal}/[Na^+]_{Observed})$
   (b) Chloride excess/deficit = $[Cl^-]_{Normal} - [Cl^-]_{Corrected}$ **(Normal value—102 mEq/L)**
3. **Calculation of SID**: As can be seen from the Gamblegram above, the SID in plasma can be derived as the sum of $[HCO^+]$ plus the negative electric charges contributed by albumin [Alb-] and by inorganic phosphate [Pi-]. $[HCO_3^-]$ is available from arterial blood gas machine or routine biochemistry values. [Alb-] and [Pi-] (in mEq/L) can be calculated from the measured Albumin (in gm/L), [Pi] (mmol/L) and pH, as per equations proposed by Figge et al. [3] or more useful one by Fencl and colleagues [4].
   (a) [Alb-] in mEq/L = $(42 - [Alb\text{-}_{Measured}]) \times (0.148 \times pH - 0.818)$ **OR** [Alb-] = 0.25 × Alb (in g/L)
   (b) [Pi-] in mEq/L = $0.309 \times (pH - 0.46) \times (0.8 - [Phos_{Measured}])$ **OR** [Pi-] = 0.6 × Phosphate (in mg/dl)
   (c) SID = $[HCO_3^-]$ + [Alb-] + [Pi-] **(Normal Value—39 ± 1 mEq/L)**
4. **Unmeasured strong anions [UA-]:** [UA-] are strong anions other than Cl^- (included in the differential diagnosis of high Anion Gap metabolic acidosis e.g., lactate, ketoacids and other organic anions, sulfate). Value of [UA-] can be indirectly derived from the equation below:
   (a) Unmeasured Anion = $[Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [SID]$ (normal range—8 ± 2 mEq/L) (For routine purpose $[Mg^{2+}]$ may be replaced by 1.7.)

Fencl-Stewart: Putting It All Together

Following the discussion above, causes of acidosis (pH < 7.38) can be re-classified and are depicted in Fig. 7.3 [4].

Following schema can classify causes of alkalosis (pH > 7.42) following Fencl and Stewart approach (Fig. 7.4) [4].

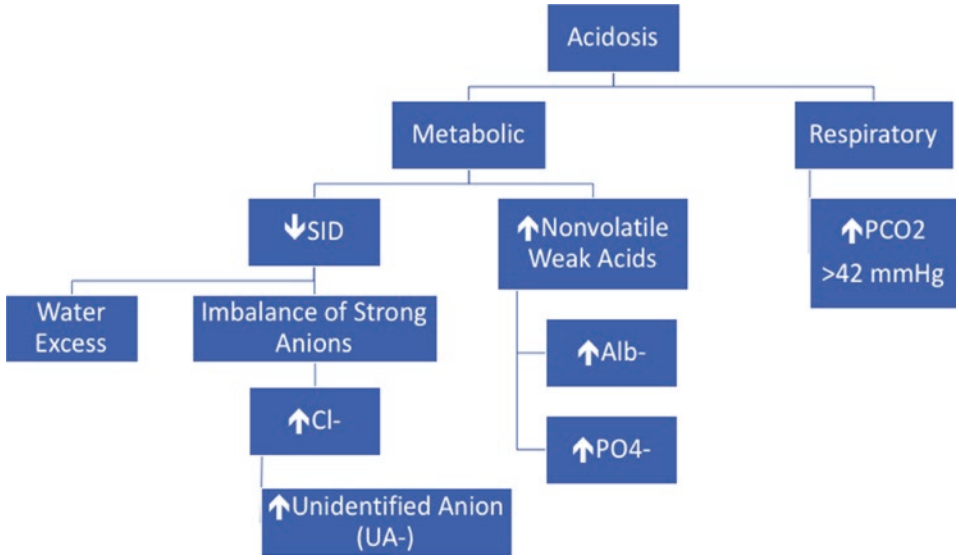

Fig. 7.3 Classification of acidosis

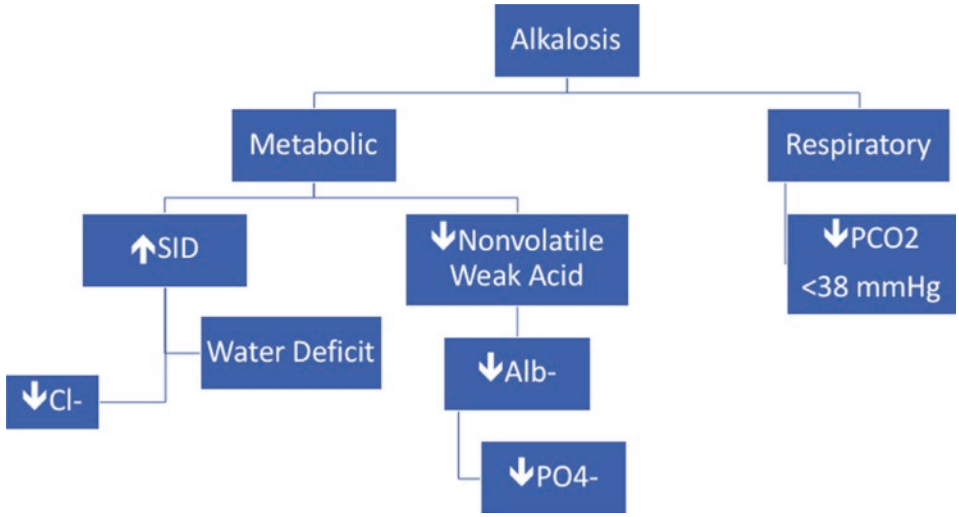

Fig. 7.4 Classification of alkalosis

Stewart at Bedside: Using Standard Base Excess

The concepts of base excess (BE) and standard base excess (SBE) were introduced by Siggaard-Anderson to provide a quantitative measure of the metabolic component of acid base disorders, independent of respiratory effect [5]. BE can be defined as the amount of

acid (in equivalent) required to bring the blood pH back to 7.40 with $PaCO_2$ kept constant at 40 mmHg. To nullify the effect of hemoglobin on acid base balance, Siggaard-Anderson also introduced the concept of standard base excess (SBE) that assumes hemoglobin concentration of the whole extracellular compartment of 5 g/L. Both BE and SBE are parameters, easily available from routine printouts of all blood gas machine.

Since BE is the single variable that may be used to quantify the overall metabolic component of acid base status, it can be assumed that changes in Stewart independent variables (SID and A_{tot}) will impact the BE. Several authors have proposed simplified approaches to Stewart's concept of acid base by utilizing the concept of BE [6–8]. In all these simplified approaches base excess effects of SID and A_{tot} were determined to quantify unmeasured anion.

Story et al. calculated the effects of changes in free water or sodium concentration ("**Sodium Effect**"), chloride concentration ("**Chloride Effect**"), and albumin ("**Albumin Effect**") on base excess, by using formulae that can be easily used at the bedside [7]. They further combined Sodium effect and Chloride effect to give a simplified effect of SID (called Sodium-Chloride effect). Finally, they subtracted Sodium-Chloride effect and Albumin effect from SBE to quantify effect of Unidentified anion on SBE (called unmeasured ion effect).

- **Sodium effect (in mEq/L)** = $0.3 \times [Na^+] - 140$)
- **Chloride effect (in mEq/L)** = $102 - ([Cl^-] \times 140/[Na^+])$
- **Sodium-Chloride effect (in mEq/L)** = Sodium Effect + Chloride Effect
  OR
- **Sodium-Chloride effect (in mEq/L)** = $([Na^+] + [Cl^-]) - 38$
- **Albumin effect (mEq/L)** = $0.25 \times [42 -$ Albumin (g/L)$]$
- **Unmeasured ion effect (mEq/L)** = SBE − (Sodium-Chloride effect + Albumin effect).

Effect of Different IV Fluids on Acid-Base Balance

Properties of intravenous fluids and consequences of large volume infusion of these fluids on plasma acid base balance can be explained by using Stewart's physicochemical approach. As crystalloid solutions do not contain Atot, rapid intravenous administration crystalloids will dilute plasma Atot, producing a trend towards metabolic alkalosis. The SID of all fluids including crystalloids also has its effect on plasma SID, potentially producing change in pH.

Infusion of large volumes of zero SID fluids (all saline solution with equivalent concentration of $[Na^+]$ and $[Cl^-]$ or Dextrose or Mannitol solutions without any strong ion) will reduce plasma SID by admixture and equilibration, forcing acid-base balance in the direction of a metabolic acidosis. Although this acidosis is commonly Hyperchloremic, it can also occur with low plasma $[Cl^-]$, depending on the fluid employed (as in cases of large volume Dextrose infusion resulting in water excess with low or normal $Cl^-_{Corrected}$).

Acidosis due to rapid infusion of large volume crystalloids can only be avoided by increasing crystalloid SID, which means replacing some [Cl^-] in the crystalloid with certain organic anions like lactate, acetate, gluconate, or maleate, that are rapidly metabolized in the body resulting in a large increase in SID. For example, Ringer's lactate contains L-Lactate at a concentration of 29 mEq/L. Unless there is severe impairment of hepatic function, L-Lactate is metabolized at 100 mEq/h, resulting in a calculated SID of 29 mEq/L. However, in normal body temperature, effective SID of RL is approximately 27 mEq/L because of incomplete dissociation.

In an in vitro experiment, Carlesso et al. had found that baseline [HCO_3^-] dictates the pH response to large volume rapid crystalloid infusion [8, 9]. If the [SID] of the crystalloid solution infused equals baseline [HCO_3^-], pH remains unchanged provided the $PaCO_2$ is constant. On the other hand, solutions with SID values higher or lower than plasma result in an increase or decrease in pH, respectively.

Case Vignette

Let us now look into the case vignette in the beginning of the chapter (**Case 1**) and try to understand acid base issues if any. With normal pH, $PaCO_2$, Base Excess and corrected Anion Gap (9.75) values, the patient apparently does not have any acid base disorder (following either Traditional or Siggaard-Anderson Approach). But that seems to be unusual considering the overall clinical status of the patient.

Following Fencl-Stewart approach as described above, following observations can be made.

- No respiratory abnormality ($PaCO_2$ 39 mmHg)
- Low [Na^+] (129 mEq/L) suggesting acidifying "Water Excess".
- High [$Cl_{corrected}$] (98 × (142/125) = 111 mEq/L) suggesting acidifying "Chloride Excess".
- Low [Albuminate-] (0.25 × 13 = 3.25 mEq/L) suggesting alkalinizing "Low [Alb-]".
- Normal Pi (0.9 mEq/L).
- High SID ([HCO_3^-] + [Alb-] + [Pi-]): 24 + 3.25 + 0.9 = 28.15 mEq/L) suggesting acidifying "Low SID".
- Normal unmeasured anion ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] − [Cl^-] − [SID] = 8.95 mEq/L).

Final Diagnosis: This patient has multiple acid base abnormalities including low SID "Metabolic Acidosis" (Water excess plus high corrected chloride) and hypoalbuminemic "Metabolic Alkalosis".

Some More Illustrative Case

Case 2: A 45 years old male, operated for Ileal perforation, developed multiple organ failure postoperatively. Arterial blood gas revealed, pH—7.33, $PaCO_2$—30 mmHg, HCO_3—15 mEq/L and BE—10. Serum biochemistry showed, Na −117mEq/L, K −3.9 mEq/L, Cl −92 mEq/L, Albumin −6 g/L, Ca −3 mEq/L, Pi −0.6 mEq/L.

Applying Fencl-Stewart approach:

- $PaCO_2$: 30 mmHg. Low value suggesting "Respiratory Alkalosis".
- $[Na^+]$: 117 mEq/L. Suggesting acidifying "Water Excess".
- $[Cl_{corrected}]$: $92 \times (142/117) = 112$ mEq/L. Suggesting acidifying "Chloride Excess"
- [Alb-]: $0.25 \times 6 = 1.5$ mEq/L. Alkalinizing "Low [Alb-]".
- [SID]: 15 + 1.5 + 0.6 = 17.1 mEq/L. Suggesting acidifying "Low SID".
- Normal Pi: 0.6 mEq/L
- Unmeasured Anion ($[Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [SID]$): 117 + 3.9 + 3 + 1.7 − 92 − 17.1 = 16.5 mEq/L. Acidifying "High [UA-]"

Final Diagnosis: This patient has "Metabolic Acidosis" due to a combination of "Low SID" (water excess and high corrected Chloride) and "High [UA-]" partially offset by "Metabolic Alkalosis" due to "Low [Alb-]" and "Respiratory Alkalosis".

Case 3: 72-years old female patient, a cardiac arrest survivor, was admitted to the ICU with hypoxic ischemic encephalopathy. Arterial blood gas revealed, pH—7.55, $PaCO_2$—29 mmHg, HCO_3—25.5 mEq/L, BE—+2. Biochemical analysis showed, Na −159 mEq/L, K −3.6 mEq/L, Cl −121 mEq/L, Albumin −9 g/L, Ca −4.2 mEq/L, Pi −0.5 mEq/L.

Applying Fencl-Stewart approach:

- $PaCO_2$: 29 mmHg. Suggesting presence of "Respiratory Alkalosis".
- $[Na^+]$: 159 mEq/L. Suggesting alkalinizing "Water deficit".
- $[Cl_{corrected]}$: $121 \times (142/159) = 108$ mEq/L. Suggesting acidifying "Chloride Excess"
- [Alb-]: $0.25 \times 9 = 2.25$ mEq/L. Presence of alkalinizing "Low [Alb-]".
- SID: 25.5 + 2.25 + 0.5 = 28.25 mEq/L. Suggesting acidifying "Low [SID]"
- Normal Pi: 0.6 mEq/L
- Unmeasured Anion ($[Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [SID]$): 159 + 3.6 + 4.2 + 1.7 – 121 − 28.25 = 19.25 mEq/L. High value suggesting presence of acidifying "High [UA-]".

Final Diagnosis: This patient has "Metabolic Alkalosis" due to "Water deficit" and "Low [Alb-]" along with "Metabolic Acidosis" due to "Chloride Excess" and "High [UA-]". She is also having evidence of "Respiratory Alkalosis".

Conclusion

Stewart's approach has the ability to identify and also quantify individual components of complex acid base abnormalities. Another unique ability of this approach is to identify hidden acid base disorder (not identified by traditional or base excess approach) as illustrated in the case vignette. By providing insight into the pathogenesis of complex metabolic acid base disorder, Stewart's approach can help the clinician in deciding probable ways to rectify the problem. Unmeasured anion, identified by modified Stewart's, is a powerful indicator of prognosis in critically ill patient. In a study on pediatric population, Balasubramanyan et al. found unmeasured anions to be more strongly associated with mortality compared to BE, anion gap, or lactate [5].

Take Home Messages

- Three variables independently determine acid base homeostasis in any fluid including plasma—total carbon di-oxide, strong ion difference (SID), and total nonvolatile acid anion (A_{tot}).
- These individual components can be easily quantified at the bedside by using modified Stewart approach provided by Fencl.
- Quantification of independent variables provides a direct insight into the mechanisms of acid base disturbances and any measure to be taken to correct them (if required).

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