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REVIEW

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Recent advances in acid-base physiology applied to critical care

Neuere Fortschritte bei der Säure-Basen-Physiologie als Teil der Intensivmedizin

Zusammenfassung Eine grundlegende Änderung in unserer Betrachtung der Säure-Basen-Homeostase zeichnet sich seit längerer Zeit ab. Neuere Fortschritte in der Zellbiologie und Physiologie lassen uns nun die Ungereimtheiten der traditionellen Säure-Base-Anschauung, welche durch physikalische Chemie seit Jahrzehnten identifiziert wurden, erklären. Weiter machte die breite Verfügbarkeit von Computern die Anwendung dieser Prinzipien in der klinischen Medizin möglich. Auf der Intensivstation zeigen die Patienten oft extreme Beispiele eines gestörten Säure-Basen-Haushaltes. Die Erkenntnisse der Ursachen vieler dieser Abnormalitäten sowie der Behandlungsmethoden werden durch dieses neue Paradigma stark beeinflusst. Häufigere Störungen wie Aspirationsalkalose, Verdünnungsazidose und laktische Azidose zählen diesbezüglich zu den besten Beispielen.

Schlüsselwörter Säure-Basen-Störung – metabolische Azidose

Summary A fundamental change in the way we think about acid-base homeostasis has been on the horizon for some time. Modern advances in cell biology and physiology now permit us to explain the inconsistencies in the traditional approaches to acid-base that have been identified by physical chemistry for decades. Furthermore, the widespread availability of personal computers has permitted the application of these principles to clinical medicine. In the ICU, patients frequently manifest extreme examples of acid-base imbalance. The understanding of the genesis of many these abnormalities as well as the approach to treatment are profoundly affected by this new paradigm. Common disorders such as suction alkalosis, dilutional acidosis, and lactic acidosis are among the best examples.

Key words Acid-base balance – metabolic acidosis – strong ion difference – lactate

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Introduction

Approximately 15 years ago Peter Stewart published a "new" approach to acid-base physiology that emphasized the physical chemical analysis (1, 2). This approach has generated a fair amount of controversy (3, 4) but little real interest until quite recently (5–18). It appears that the lack of interest has been due to the fact that the approach, while conceptually simple and elegant, is operationally complicated and unwieldy. Most clinicians retreat from the sight of complex polynomial equations and few can be easily convinced that "relearning" acid-base physiology is worth while when the traditional approach "works so well".

It is this last issue that deserves closer scrutiny, particularly in the critically ill. For patients in the intensive care unit (ICU), extreme derangements in physiology are common and traditional methods are often inadequate to explain the severe acid-base disorders present in some of these patients. Although the Stewart approach is based on the same physical chemical principles that more traditional approaches are based, this new approach is vastly different. The most important difference is that in this view, hydrogen ions (H^+) and

bicarbonate ions (HCO_3^-) are not independent variables but are instead determined by other factors. Changes in pH are not the result of the generation or removal of these ions per se, but rather are the result changes in other variables. This point cannot be overemphasized. Traditionally, we have looked to the removal or generation of H^+ and/or HCO_3^- as the control mechanisms of metabolic acid-base balance. Metabolic acid-base disorders are described in terms of H^+ production or HCO_3^- loss or regeneration. However, as we shall see, these mechanisms are inconsequential.

Though "newer", the Stewart approach has now been validated in a wide variety of patient types (5–8, 11) and experimental conditions (12–15). Recently, it has been shown that the SID is quantitatively very close to the standard base excess in that later describes the necessary change in the former to restore plasma pH to 7.40, given a PCO_2 of 40 mmHg (16, 17). The difference that this approach carries is not in the quantification of acid-base disorders but rather in the understanding of why these disorders occur and how to treat them. In this review, I will explain the fundamental aspects of the Stewart approach, review the implications for clinical medicine, particularly in the ICU, and consider some of the more practical aspects of acid-base management from this prospective. Several more detailed treatments of the Stewart approach are available in the literature (1, 2, 8, 18). The purpose of this discussion is to provide the reader with a general understanding of the approach and its implications. However, the interested reader is advised to seek out these other sources as well.

Fundamental principles of hydrogen ion regulation

Large living organisms seek to maintain plasma pH within strict limits. In fact, H^+ concentration is maintained within the nmol/L range (36–43 nmol/L). By contrast, most other ions are regulated in the mmol/L range. One reason H^+ concentration is so closely regulated is that these ions have very high charge densities and, consequently, very large electric fields. Furthermore, the strength of H^+ bonds (ubiquitous in biologic systems) are very sensitive to local H^+ concentration. Biochemical reactions as well as interactions of hormones and drugs with plasma proteins and cell surface receptors are also influenced by changes in H^+ concentration. In addition, fluctuations in intracellular H^+ concentration have major effects on cellular performance presumably by altering protein charge, thereby affecting structure and enzymatic function. Thus, in order to understand how the body regulates plasma H^+ concentration, we must first understand the physical-chemical determinants of H^+ concentration.

Biochemistry of aqueous solutions

Virtually all solutions in human biology contain water and aqueous solutions provide a virtually inexhaustible source of H^+. In these solutions, H^+ concentration is determined by the dissociation of water into H^+ and OH^- ions. Said another way, changes in H^+ concentration occur *not* as a result of how much H^+ is added or removed but as a consequence of water dissociation. The factors that determine the dissociation of water are the laws of physical chemistry. Two in particular apply here, *electroneutrality* (which dictates that, in aqueous solutions, the sum of all positively charged ions must equal the sum of all negatively charged ions) and *conservation of mass* (which means that the amount of a substance remains constant unless it is added or generated, or removed or destroyed). In pure water, according to the principle of electroneutrality, the concentration of H^+ must always equal the concentration of OH^-. In more complex solutions, we have to consider other determinants of water dissociation, but, still, the source of H^+ remains *water*. Fortunately, even in a solution as complex as blood plasma, the determinants of H^+ concentration can be reduced to three. If we know the value of these three determinants, the H^+ concentration can be predicted under any condition. These three determinants are the *strong ion difference* (SID), *pCO_2*, and *total weak acid concentration* (A_{TOT}).

SID, pCO_2, and A_{TOT}

The SID is the net charge balance of all strong ions present where a "strong" ion is one that is completely (or near-completely) dissociated. For practical purposes this means $(Na^+ + K^+ + Ca^{++} + Mg^{++}) - (Cl^- + lactate^-)$. This is often referred to as the "apparent" SID (SIDa) with the understanding that some "unmeasured" ions might also be present (12). In healthy humans, this value is 40–42 mEq/L, although it is often quite different in critically ill patients. Of note, neither H^+ nor HCO_3^- are strong ions. These ions can associate themselves with other ions (e.g., H^+ with OH^- to form water, HCO_3^- changed to CO_2, etc.). By contrast, the pCO_2 is an independent variable assuming that the system is open (i.e., ventilation is present). Finally, the weak acids (A^-), which are mostly proteins and phosphates, contribute the remaining charges to satisfy the principle of electroneutrality (Fig. 1). A^-, however, is not an independent variable because it changes with alterations in SID and pCO_2. A_{TOT}, $(AH + A^-)$ is the third independent variable because its value is not determined by any other. The essence of the Stewart approach (and indeed what is revolutionary) is the understanding that only these three variables are important. Neither H^+ nor HCO_3^- can change unless one or more of these three variables

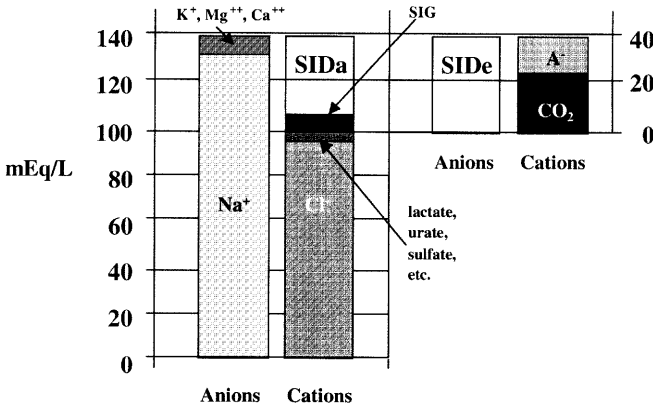

Fig. 1 Total charge balance in blood plasma. The strong ion difference (SID) is always positive (in plasma) and SID–SIDe (effective) must equal zero. The SID apparent (SIDa) and SIDe should be equal; any difference is referred to as the strong ion gap (SIG) and must represent unmeasured anions. A^- refers to the ionized weak acids (primarily albumin and phosphates). CO_2 includes: HCO_3^- and CO_3^{2-}

change. The principle of conservation of mass makes this point more than semantics. Strong ions cannot be created or destroyed to satisfy electroneutrality but H^+'s are generated or consumed by changes in water dissociation. Hence, in order to understand how the body regulates pH, we need only ask how it regulates these three independent variables (SID, pCO_2, and A_{TOT}). The traditional approach ignores these variables, and while it is possible to describe an acid-base disorder in terms of H^+ or HCO_3^- concentrations it is incorrect to analyze the pathology or to plan treatment on the basis of altering H^+ or HCO_3^-.

Clinical implications

This "new" approach changes nothing about the measurement or classification of acid-base disorders. All of the careful observations that have been made over the years are no less valid under this approach. What does change is the interpretation of these observations. In this review, I shall discuss some of the more common clinical implications of this approach but there are many others which will become obvious as one ponders the various aspects of this approach.

Metabolic alkalosis

One of the most common forms of metabolic alkalosis seen in the ICU is caused by the loss of gastric secretions. The loss of HCl from the stomach results in a hypochloremic metabolic alkalosis sometimes severe enough to require therapy. Of course this is the loss of H^+, but H^+ is also lost with every molecule of water removed from the body. Moreover, gastric secretions may reach a pH of 1.0, or a H^+ concentration of 10^8 nmol/L. If one liter of gastric fluid is lost, this would mean that 10^8 nmol (0.1 moles!) of H^+ would be removed. If one considers that plasma H^+ concentration is 40 nmol/L (or 4×10^8 mol/L, and if the majority of body fluids are at or near this concentration, one sees that the amount of total body-free H^+ is only about 1.6×10^{-7} moles. If physiology were just simple accounting, a patient with pyloric stenosis would rapidly run out of H^+. Of course this is not what happens and in reality the H^+ concentration decreases by a much smaller amount. The reason it decreases at all is because the plasma SID is increased and this is because Cl^- (a strong anion) is lost without loss of a strong cation. This *increased* SID forces a *decrease* in the amount of water dissociation and hence a *decrease* in the plasma H^+ concentration. When H^+ is "lost" as water rather than HCl, there is no change in the SID and hence no change in the plasma H^+ concentration. Next, consider the treatment of a hypochloremic metabolic alkalosis. Aside from preventing further Cl^- loss, the therapy is to give back Cl^-. Saline works in this regard because even though one is giving equal amounts of Na^+ and Cl^-, the plasma Cl^- concentration is always much lower than the plasma Na^+ concentration and thus Cl^- increases more than Na^+ when large amounts of saline are administered. KCl works better for this indication because, with a metabolic alkalosis, much of the K^+ goes intracellular leaving much of the Cl^- in the plasma to decrease the SID. From this vantage point, one sees no need to invoke complex renal tubular or hormonal mechanisms to account for the restoration of normal plasma pH. The principles of physical chemistry are quite sufficient. Moreover, one realizes that intact renal function is not necessary to produce these changes. Indeed, the use of renal replacement therapy to alter the Cl^- concentration will be just as effective. Failure to understand these principles will lead to the faulty assumption that H^+ or HCO_3^- ions must be directly added or removed from the body to affect the necessary changes in pH.

"Dilutional" acidosis

From the example above, one can easily understand not only how administration of 0.9% saline can correct a hypochloremic metabolic alkalosis but also how massive amounts would lead to a *decreased* plasma SID and thus a *hyper*chloremic metabolic *acidosis.* Although dilutional acidosis was first described over 40 years ago (19, 20), it has more recently been likened to Lewis Carroll's Cheshire cat in that it is more imaginary than real (21). In healthy animals, large doses of NaCl have been demonstrated to produce only a minor hyperchloremic acidosis (22). These studies have been inter-

preted to show that if dilutional acidosis occurs it is only in the extreme case and even then it is only mild. This line of reasoning cannot be applied to many critically ill patients for two reasons. First, large volume resuscitation is commonly required in patients with sepsis, trauma, and surgery. These patients may receive crystalloid infusions of 5–10 times their plasma volumes in a single day. The second problem with this line of reasoning is that it fails to consider the fact that critically ill patients are frequently not in normal acid-base balance to begin with. These patients may have lactic acidosis or renal insufficiency. Furthermore, critically ill patients might not be able to compensate normally by increasing ventilation and may have abnormal buffer capacity owing to hypoalbuminemia (23). In patients (5, 24) as well as in animals with experimental sepsis (25), dilutional acidosis does occur and can produce significant acid-base derangements.

From the preceding discussion, it is obvious how so-called "dilutional" acidosis occurs. However, it may be less obvious why critically ill patients are more susceptible. What appears to happen is that many critically ill patients have a significantly lower SID than to healthy individuals even when they have no evidence of a metabolic acid-base derangement (28). This is not surprising given that the positive charge of the SID is balanced by the negative charges of A^- and total CO_2 (Fig. 1). Since many critically ill patients are hypoalbuminemic, A^- tends to be reduced. Because the body defends pCO_2 for other reasons, a reduction in A^- leads to a reduction in SID by the body in order to maintain normal pH. Thus a typical ICU patient might have a SID of 30 mEq/L rather than 40–42 mEq/L. If this same patient then developed a metabolic acidosis (e.g., lactate) the SID would decrease further. If we then resuscitated this patient with a large volume of normal saline we would find that it produces a significant metabolic acidosis. The effects of hypoalbuminemia are demonstrated by example in Table 1. Note that as the SID decreases, so does the pH despite the "compensatory" hyperventilation. Also, note that the differential effects of severe hypoalbuminemia are not significant without a severe metabolic acidosis. Even moderate metabolic acidosis (equivalent to 15 mmol/L of lactic acid) is handled quite well. However the differences become striking once the acid load is increased to 25 mmol/L. Such an increase would be difficult to produce with saline alone but the cumulative effects of endogenous acidosis and saline may be significant.

The clinical implication for management of patients in the ICU is that when large volumes of fluid are used for resuscitation they should be more physiologic than saline. One alternative is lactated Ringers solution. This fluid contains a more physiologic difference between Na^+ and Cl^- and thus the SID is closer to normal (roughly 28 mEq/L compared to saline which has SID of 0 mEq/L). Of course this assumes that the lactate in lactated Ringers is metabolized, which as we will discuss below is almost always the case.

Table 1 Effects of metabolic acidosis given varying degrees of hypoalbuminemia

	SID (mEq/l)	pH	pCO_2 (mmHg)	SBE (mEq/L)
Albumin 45 g/L				
Baseline	40	7.40	40	0
Moderate metabolic acidosis	25	7.32	20	–15
Severe metabolic acidosis	15	7.00	10	–25
Albumin 20 g/L				
Baseline	33	7.40	40	0
Moderate metabolic acidosis	18	7.31	20	–15
Severe metabolic acidosis	8	6.84	10	–28
Albumin 5 g/L				
Baseline	29	7.40	40	0
Moderate metabolic acidosis	14	7.30	20	–15
Severe metabolic acidosis	4	6.69	10	–32

Results of moderate and severe acidosis (equivalent of 15 and 25 mmol/L of lactic acid respectively) in a hypothetical 70 kg man with no urine output and before any change in lactate concentration. Assumes a constant serum phosphorus of 1 mmol/L. SID = strong ion difference, SBE = standard base excess. Note that the calculated SBE is different among the three levels of albumin in the severe metabolic acidosis rows. This is an artifact of the SBE calculation, which looses accuracy outside of the "physiologic range"

Lactate and lactic acidosis

Lactate is a strong ion by virtue of the fact that, at pH within the physiologic range, it is almost completely dissociated (i.e., the pK of lactate is 3.9; at a pH of 7.4, 3162 ions are dissociated for every one that is not). Because the body can produce and dispose of lactate rapidly, it functions as one of the most dynamic components of the SID. Lactic acid therefore can produce significant acidemia. However, often critically ill patients have hyperlactatemia that is much greater than the amount of acidosis seen. Physical chemistry also allows us to understand how hyperlactatemia may exist without metabolic acidosis. First, acid is not being "generated" apart from lactate such as through "unreversed ATP hydrolysis" as some have suggested (27). Phosphate is a weak acid and does not contribute substantially to metabolic acidosis even under extreme circumstances. Furthermore, the H^+ concentration is not determined by how much H^+ is produced or removed from the plasma but rather by changes in one of the three independent variables (SID, pCO_2 or A_{TOT}). Virtually anywhere in the body, pH is above 6.0 and lactate behaves as a strong ion. Its generation will then decrease the SID and result in increased water dissociation and

thus increased H^+ concentration. How then might the plasma lactate concentration be increased and the H^+ concentration not? There are two possible answers. First, if lactate is added to the plasma, not as lactic acid but rather as the salt of a strong acid (i.e., sodium lactate), there will be little change in the SID. This is because a strong cation (Na^+) is being added along with a strong anion. In fact, as lactate is then removed by metabolism, the remaining Na^+ will increase the SID resulting in metabolic alkalosis. Hence it would be possible to give enough lactate to increase the plasma lactate concentration without any change in H^+ concentration. However, the amount of exogenous lactate required would be very large. This is because normal metabolism results in the turnover of approximately 1500–4500 mmol of lactic acid per day. Thus, only very large amounts of lactate infused rapidly will result in appreciable increases in the plasma lactate concentration. Levraut et al. (28) infused 1 mmol/kg of lactate over 15 min in 10 patients with acute renal failure on continuous renal replacement therapy. Their mean plasma lactate concentration increased from 1.4 to 4.8 mmol/L after the infusion but normalized rapidly. Under such conditions it is possible (if transiently) to produce hyperlactatemia without acidemia. Unfortunately, these authors do not report the acid-base status of their patients. However, in another recent study, Morgera et al. (29) showed that lactate-based hemofiltration resulted in *increased* plasma HCO_3^- concentration and pH as well as hyperlactatemia.

A more important mechanism whereby hyperlactatemia exists without acidemia (or with less acidemia than expected) is where the SID is corrected by the elimination of another strong anion from the plasma. This was demonstrated by Madius et al. (30). In the setting of sustained lactic acidosis induced by lactic acid infusion, these investigators found that Cl^- moves out of the plasma space to normalize pH. Under these conditions, hyperlactatemia may persist but base excess may be normalized by compensatory mechanisms to restore the SID.

Nonetheless, given that lactate is a strong ion and that lactic acidosis is a marker for mortality in many forms of critical illness, it is reasonable to search for the anatomic sources and pathophysiologic mechanisms that are responsible for increases in plasma lactate concentration. Conventional wisdom suggests that the gut and the muscle are the sources of this increased lactate. However, the results of a recent study suggest that, in sepsis, neither the muscle nor the gut release lactate (31). In fact, studies in animals as well as humans have shown that the lung may be a prominent source of lactate in the setting of acute lung injury (31–33). The source of this lactate is not entirely understood but correlates with the extent of lung injury (33) and is likely produced by inflammatory cells.

While studies such as these do not address the underlying pathophysiologic mechanisms of hyperlactatemia in sepsis, they do suggest that the conventional wisdom regarding lactate as evidence of tissue dysoxia is an oversimplification at best. Indeed, many authors have begun to offer alternative interpretations of hyperlactatemia in this setting (33–36). First, metabolic dysfunction from mitochondrial to enzymatic derangements can and do lead to lactic acidosis. In particular, pyruvate dehydrogenase (PDH), the enzyme responsible for moving pyruvate into the Krebs cycle, is inhibited by endotoxin (37). However, data from recent studies suggest that increased aerobic metabolism may be more important than metabolic defects or anaerobic metabolism. Gore et al. (38) observed increased glucose and pyruvate production and oxidation in patients with sepsis. Furthermore, when PDH was stimulated by dichloroacetate there was a further increase in oxygen consumption but a decrease in glucose and pyruvate production. Their results suggest that hyperlactatemia in sepsis occurs as a result of increased aerobic metabolism rather than tissue hypoxia or PDH inhibition. Finally, catecholamine use, especially epinephrine, also results in lactic acidosis presumably by stimulating hepatic glycolysis (39, 40).

Unexplained anions

Another important application of the Stewart approach is the investigation of unmeasured anions in the blood of patients with critical illness. As one can see from Fig. 1, the principle of electroneutrality can be used to detect the presence of unmeasured anions in the blood. By definition the SID must be equal and opposite to the negative charges contributed by A^- and total CO_2. This latter value is termed SID effective (SIDe) (12). Thus if SIDa > SIDe unmeasured anions must exist and if SIDa > SIDe, there must be unmeasured cations present. This difference has been termed the strong ion gap (SIG) to distinguish it from the anion gap (AG) (8). Unlike the AG, the SIG is normally zero and does not change with changes with pH or albumin concentration as does the AG. Thus, the accuracy of the AG is questionable in certain clinical situations (41), particularly in critically ill patients who are frequently hypoalbuminemic and acidotic. This has prompted some authors to adjust the "normal range" for the AG by the patient's albumin (42) or even phosphate (26) concentration. Each g/dL of albumin has a charge of 2.8 mEq/L at pH 7.4 (2.3 mEq/L at 7.0 and 3.0 mEq/L at 7.6) and each mg/dl of phosphate has a charge of 0.59 mEq/L at pH 7.4 (0.55 mEq/L at 7.0 and 0.61 mEq/L at 7.6). Except in cases of abnormal paraproteins, globulin does not contribute to the AG (12). Thus a convenient way to estimate the "normal" AG for a given patient is by use of the following formula:

"normal" AG = 2 (albumin g/dl) + 0.5 (phosphate mg/dl)

or for international units:

"normal" AG = 2 (albumin g/L) + 1.5 (phosphate mmol/L).

However, Salem and Mujais (41) found routine reliance on the traditional AG to be fraught with numerous other pitfalls in addition to those mentioned above. These problems are largely omitted by the SIG calculation (8) and this is the preferred method for quantifying unexplained anions when precision is required. In recent years, unmeasured anions have been reported in the blood of patients with sepsis (7, 43) and liver disease (8, 44). These anions may be the source of much of the unexplained acidosis seen in patients with critical illness (45). The presence of unexplained anions in the blood of both patients with sepsis and liver disease was investigated further in an animal model of sepsis using endotoxemia (14). In this study, it was found that, during control conditions, the liver cleared unmeasured anions from the circulation (mean flux –0.34 mEq/min). With early endotoxemia, however, the liver switched to release of anions (0.12 mEq/min, $p < 0.005$). These data suggest that the liver has a role in systemic acid-base balance by way of regulating anion fluxes apart from metabolism of lactate.

Treatment of metabolic acid-base disorders

This physical chemical approach also provides for a more logical basis for treatment of metabolic acid-base disorders. In metabolic acidosis the SID is narrowed and there is either an increased strong ion such as lactate, or the normal difference between Na^+ concentration and Cl^- concentration is reduced. The AG is reasonable screening test to distinguish these provided that the patients albumin concentration and phosphate concentration are near normal or one corrects the AG as described above. The distinction is very important since non-AG metabolic acidoses are the result of the bodys inability to maintain the normal Na^+ concentration and Cl^- concentration. Treatment therefore must include an assessment of the Na^+ concentration and Cl^- concentration and the reasons for their abnormality must be sought. If the disorder is characterized by a decreased (or at least normal) Na^+ concentration, administration of $NaHCO_3$ can prove effective. From the discussion above, it should be clear that it is the Na^+ concentration we are trying to influence not the HCO_3^- concentration. HCO_3^- is not an independent variable. Its concentration is determined by the three independent variables we have discussed. Therefore, only by increasing the Na^+ concentration relative to the Cl^- concentration can $NaHCO_3^-$ repair a metabolic acidosis. When the Na^+ concentration is already increased, there is no room for $NaHCO_3^-$ therapy. In such a condition it would be necessary to consider other options. These include removal of $Cl^- > Na^+$ perhaps by use of renal replacement therapy (e.g., hemofiltration) or administration of a weak base such as THAM (tris-hydroxymethyl-aminomethane). Theoretical, it would also be possible to remove Cl^- from the stomach via a nasogastric tube, but this is rarely done.

When the acidosis is produced by an anion that can be metabolized (e.g., lactate, ketones) the goal of therapy should be to augment metabolic removal and reduce production. In the case of lactate, hypoperfusion should be reversed when present although there are numerous other causes as detailed above and lactic acidosis should not be equated with hypoperfusion. Other metabolic triggers (e.g., epinephrine) should also be removed. In ketoacidosis, insulin repairs the metabolic defect and results in the metabolism of ketones. If therapies are given which increase the SID by increasing Na^+ concentration or decreasing Cl^- concentration, the result will be overshoot alkalosis when the causative anion is removed. Rarely, partial treatment is necessary in order to improve metabolic removal of the anions or to stabilize the patient until metabolic removal can occur. Severe acidemia impairs normal hepatic lactate metabolism for example (46) and therapy to increase the pH above perhaps 7.20 may be useful in some cases.

When correcting a metabolic acid-base derangement, the standard-based excess (SBE) can be used to quantify the amount of the abnormality. The SBE can be thought of as the amount of change in the SID that is required in order to restore the pH to 7.40, given a PCO_2 of 40 mmHg (a negative SBE refers to the amount the SID must *increase*). This is because the SID is essentially equal to the buffer base of Singer and Hastings (47) and base excess (BE) quantifies the change in buffer base. SBE is superior to BE because the former has been "standardized" to account for the difference between CO_2 equilibration *in vitro* compared to *in vivo*. Although SBE is not strictly comparable to the change in SID because it deals with whole blood as opposed to plasma (48), the two are generally close enough for most clinical circumstances (see Table 1). Thus, SBE provides an estimate of the amount of strong anion that needs to be removed or strong cation added in order to normalize the pH. For example, in order to change the SBE from –20 to –10 mEq/L by adding $NaHCO_3$, the serum Na^+ concentration would need to be increased by 10 mEq/L.

We have already examined the treatment of metabolic alkalosis and the principles are the same. The repair of the Cl^- concentration can be achieved by NaCl, KCl or HCl. In all cases, however, our goal is the same: to increase the Cl^- concentration relative to the Na^+ concentration. The HCO_3^- concentration will then be returned to the point set by the SID, pCO_2, and A_{TOT}.

Conclusion

If we wish to understand the causes of many of the acid-base derangements that are common in the ICU, we need only look at three independent variables (SID, pCO_2, and A_{TOT}). Metabolic acidemia results from a decrease in the plasma SID usually brought about by the addition of strong anions (lactate, Cl^-, other "unknown" anions). Conversely, metabolic alkalemia occurs when the plasma SID is increased either as a result of the addition of strong cations without strong anions (e.g., $NaHCO_3$) or by the removal of strong anions without strong cations (e.g., gastric suctioning).

This "new" understanding has considerable impact on how we think about gastric suction alkalosis, dilutional acidosis and lactic acidosis as well as how we approach the treatment of these disorders. Our understanding of many other medical conditions (e.g., renal tubular acidosis) relies on a paradigm of acid-base regulation that is inconsistent with established physical-chemical principles. We will need to rethink our approach to these areas in light of this fact.

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