

# Hyperchloremic Metabolic Acidosis: More than Just a Simple Dilutional Effect

S.S. ABDEL-RAZEQ and L.J. KAPLAN

## Introduction

Fluid resuscitation lies at the heart of acute care medicine. Despite the central role occupied by plasma volume expansion therapeutics, there remains little consensus regarding the ideal fluid for plasma volume expansion. However, the unintended consequences of excessive plasma volume expansion as well as those untoward events directly ascribed to the prescribed fluids have come to the fore. Anasarca, pulmonary edema, myocardial stress, acute lung injury (ALI), acute kidney injury, as well as the secondary abdominal compartment syndrome have all been described as unintended consequences of plasma volume expansion following critical illness or injury [1–3]. It is important to note that these events occur with both crystalloid and colloid therapy, although at different rates.

Equally importantly, both crystalloids and colloid may create hyperchloremic metabolic acidosis. It is clear that colloids will do so at a slower rate than crystalloids principally related to their improved efficiency with regard to plasma volume expansion. Since colloid resuscitation generally requires less total volume, less total chloride is delivered and hyperchloremic metabolic acidosis occurs less rapidly. The genesis of hyperchloremic metabolic acidosis, as well as its significance, has been hotly debated over the last several decades [4–6]. Previously, the forces creating hyperchloremic metabolic acidosis were ascribed to simple dilution, and the significance of the acidosis minimized to a laboratory curiosity. Current investigations into hyperchloremic metabolic acidosis and its consequences embrace a diametrically opposed perspective. The focus of this chapter is to explore the mechanisms underpinning hyperchloremic metabolic acidosis as well as the impact of hyperchloremic metabolic acidosis on immunobiology, resuscitation, clotting, and oxygen delivery.

## Mechanisms Underpinning pH Regulation: A Physico-chemical Approach

Plasma volume expansion impacts acid-base balance in predictable manners depending on the type and volume of infused fluid. The physical chemical approach articulated by Stewart provides a mechanistic means of understanding how plasma volume expansion alters pH by assessing changes in plasma charge [7–10]. The physico-chemical approach describes three independent variables that determine the pH in an aqueous milieu, such as human plasma: The strong ion difference (SID), the sum of associated and dissociated weak acid ( $A_{\text{tot}}$ ), and  $\text{CO}_2$ .

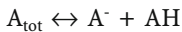
Strong ions are cations and anions that are dissociated from their partner ions at physiologic pH. Examples of strong ions include  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$  and  $\text{Cl}^-$ . At physiologic pH, anions with  $\text{pK}_a$  values  $\leq 4.0$  including lactate, sulfate, and  $\beta$ -hydroxybutyrate also exist as strong ions. Strong cations predominate in the body leading to a net positive plasma charge that is described as the SID by the following formula:

$$\text{SID} (\sim +40) = [\text{Na}^+ + \text{K}^+ + \text{Ca}^{2+} + \text{Mg}^{2+}] - [\text{Cl}^- + \text{lactate}^-]$$

This net positive charge must be counterbalanced with an equal negative charge to satisfy the Law of Electrical Neutrality.

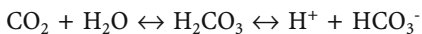
The balancing negative charge derives from nonvolatile weak acids accounted for as  $A_{\text{tot}}$ . In plasma, these weak acids include albumin and inorganic phosphates. While the same is true of interstitial fluid, total concentrations in this compartment are very small. On the other hand, the predominant source of such acids in red cells is hemoglobin.

Non-volatile weak acids dissociate in body fluids as follows:



$A_{\text{tot}}$  reflects this dynamic equilibrium and provides the second independent control mechanism for pH as well, as approximately -40 mEq/l of anionic charge to maintain electrical neutrality. The vast majority of this charge stems from albumin and phosphate in patients without organ failure. Sulfates,  $\beta$ -hydroxybutyrate, and other anionic entities may contribute in those with organ failure.

Finally, the partial pressure of  $\text{CO}_2$  ( $\text{PCO}_2$ ) is a direct measure of blood-dissolved  $\text{CO}_2$  versus pulmonary  $\text{CO}_2$  clearance efficiency. The arterial  $\text{PCO}_2$  ( $\text{PaCO}_2$ ) is, therefore, an equilibrium value determined by the balance between  $\text{CO}_2$  production ( $\sim 15,000$  mmol/day) and pulmonary  $\text{CO}_2$  elimination (ventilation). In areas where  $\text{PCO}_2$  is less directly controlled by alveolar ventilation (e.g., venous blood and interstitial fluid during low flow states), the total  $\text{CO}_2$  concentration ( $\text{TCO}_2$ ) becomes a significant independent variable [11]. The relative charge balance between SID and  $A_{\text{tot}}$  determines the direction of the following equation, which describes water dissociation in human plasma:

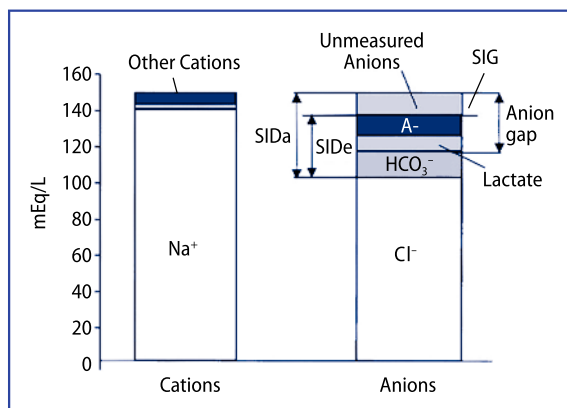


Other nomenclatures that need to be recognized and understood are as follows:

- The *apparent* strong ion difference (SIDa) is the difference between the sums of all measured cations and strong anions.
- The *effective* strong ion difference (SIDE), on the other hand, represents the effect of the corrected  $\text{PCO}_2$  and the non-volatile weak acids on the balance of electrical charges in plasma.
- The difference between the calculated SIDa and SIDE defines the strong ion gap (SIG). The calculated SIG is, therefore, an estimation of the *actual* SIG as only the most abundant ions are measured and used for its calculation.

In healthy humans, the SIG should equal zero, although ranges of  $\pm 2$  have been reported in healthy volunteers as well as hospitalized patients without critical illness [12, 13]. Increases or decreases in SIG occur with critical illness as well as with plasma volume expansion [12, 14]. For instance, an increased SIG, defined as  $> 2$  mEq/l, indicates the accumulation of unmeasured anions in blood as a cause of acidosis [15]. A strong correlation between the SIG and the albumin- and lactate-corrected anion gap

**Fig. 1.** Charge balance in blood plasma. “Other cations” include  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$ . The strong ion difference (SID) is always positive (in plasma) and  $\text{SID} - \text{SIDe}$  (effective) should equal zero. Any difference between  $\text{SIDe}$  and apparent SID ( $\text{SIDa}$ ) is the strong ion gap (SIG) and presents unmeasured anions.  $\text{A}^-$  is the dissociated weak acids (mostly albumin and phosphates). From [55] with permission



has been demonstrated [16]. It is unclear what species contribute to SIG elevation or depression and these species are therefore termed ‘unmeasured ions’ (Fig. 1).

Understanding the principles that govern the three independent pH control mechanisms allows one to explore how different fluids generate hyperchloremic metabolic acidosis.

## Effects of Plasma Volume Expansion on pH

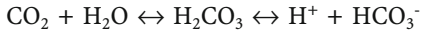
Commonly utilized fluids for plasma volume expansion are either absolutely or relatively hyperchloremic with regard to human plasma (Table 1). For instance, 0.9 % saline solution has 154 mEq/l of both sodium ( $\text{Na}^+$ ) and chloride ( $\text{Cl}^-$ ). This generates a  $\text{SIDa}$  of zero for saline. While the  $\text{Na}^+$  is higher than plasma, the  $\text{Cl}^-$  is markedly higher, making saline absolutely hyperchloremic with regard to plasma. Lactated Ringer’s solution has 130 mEq/l of  $\text{Na}^+$  and 110 mEq/l of  $\text{Cl}^-$ . The  $\text{Na}^+$  is below that of plasma while  $\text{Cl}^-$  is at the upper limit of many laboratory reference ranges. Thus, lactated Ringer’s solution is relatively hyperchloremic since the  $\text{Na}^+$  is much lower than normal. Delivering both of these fluids should predictably increase plasma  $\text{Cl}^-$  concentrations.

The net effect of hyperchloremia may be most easily understood by evaluating its impact on  $\text{SIDa}$ . As  $\text{Cl}^-$  concentration increases, the net positive charge of the  $\text{SIDa}$  diminishes. As a result, compensatory mechanisms designed to preserve plasma

**Table 1.** Composition of common crystalloids

	$\text{Na}^+$ (mEq/l)	$\text{K}^+$ (mEq/l)	$\text{HCO}_3^-$ (mEq/l)	$\text{Cl}^-$ (mEq/l)	$\text{Ca}^{2+}$ (mEq/l)
0.9 % sodium chloride (normal saline)	154	–	–	154	–
0.45 % sodium chloride (half-strength normal saline)	77	–	–	77	–
Hartmann’s solution	131	5	29	111	2
Lactated Ringer’s solution	130	4	28	109	2.7

electrical neutrality act to increase the plasma positive charge. Humans are 55 molar with respect to water, providing a readily available and exchangeable pool of protons. By driving the following equation to the right, plasma positive charge increases as a result of increased proton concentration that one clinically detects as a diminished pH.



Other compensation mechanisms similarly act to decrease the plasma negative charge, minimizing the absolute increase in proton concentration (and decreased pH) required to restore electrical neutrality. According to the Law of Conservation of Mass, the most readily available pool of negative charge that may be consumed to change the attributable charge is albumin; approximately 78 % of the negative charge stems from exposed histidine residues [17]. Thus, the decrease in albumin observed with plasma volume expansion, which is often attributed to simple dilution, truly reflects albumin consumption to decrease plasma negative charge. Moreover, since phosphate exists in small concentration in plasma, renal excretion as well as bone uptake will serve to decrease the negative charge of SIDe as well

Thus, the genesis of hyperchloremic metabolic acidosis is readily understood based on changes in plasma charge as a result of electrolyte derangements, not just simple dilution. An in-depth analysis of the various permutations of pH derangements has been published previously [18]. The previously unanswered question is whether the decreased pH derived from hyperchloremia is clinically relevant or just an unimportant laboratory curiosity. Several lines of evidence highlight hyperchloremic metabolic acidosis as a clinically relevant entity that deserves therapeutic abrogation and, perhaps more importantly, conscious avoidance.

## Clinical Consequences of Hyperchloremic Metabolic Acidosis

The clinical consequences of hyperchloremic metabolic acidosis may be conveniently grouped into several discrete domains, including fluid resuscitation and electrolyte manipulation, pulmonary compensation, ALI, coagulation cascade, microvascular flow, and immune activation or suppression. Exploring the data underpinning each of these areas will highlight the clinical relevance of hyperchloremic metabolic acidosis and the attendant therapeutic interventions available to the intensivist.

### Fluid Resuscitation and Electrolyte Manipulation

It is clear that well-intentioned plasma volume expansion with sufficient volume of hyperchloremic solutions will lead to hyperchloremic metabolic acidosis. However, recognition of acidosis in the early phase of critical illness or injury often incorporates arterial blood gas analysis, or increasingly, venous blood gas analysis with some manipulation to correct for the expected increase in venous  $\text{PCO}_2$  compared to the arterial side. These analyses are often accompanied by a lactate level, further enabling acid-base analysis. Later, especially for patients in the intensive care unit (ICU), arterial access is limited, and acid-base analysis hinges on the relationship between bicarbonate and standard base excess (SBE).

Metabolic acid-base disturbances arise from abnormalities in SID,  $A_{\text{tot}}$ , or both. Of note, neither SID nor  $A_{\text{tot}}$  need to be measured independently to quantify the

metabolic acid-base status at the bedside: The SBE was developed to specifically address this situation [13, 14, 19, 20]. The SBE is calculated from buffer base offsets by assuming a mean extracellular hemoglobin concentration of 50 g/l and relies on the measured plasma bicarbonate level to arrive at its value according to the following formula:

$$\text{SBE} = 0.93 \times \{[\text{HCO}_3^-] + 14.84 \times (\text{pH} - 7.4) - 24.4\}$$

A standard reference range for SBE is  $\pm 3.0$  mEq/l. The range around zero reflects the change in extracellular SID needed to normalize metabolic acid-base status without changing  $A_{\text{tot}}$ . A negative deviation exceeding  $-3.0$  mEq/l reflects the increase in extracellular SID needed to correct an existing metabolic acidosis. Likewise, if the SBE is greater than  $+3.0$  mEq/l, a metabolic alkalosis exists and the positive deviation from zero represents the extracellular SID needed to correct this.

Given the reliance of the SBE on the measured plasma bicarbonate level, and understanding that bicarbonate is a dependent variable, hyperchloremic metabolic acidosis will necessarily decrease the plasma bicarbonate and, therefore, the SBE. If this relationship is not appreciated, a decreased bicarbonate and SBE may be misinterpreted for acidosis related to hypoperfusion [21]. Paradoxically, the prescription (plasma volume expansion) may worsen the underlying problem (acidosis) by further worsening hyperchloremia.

The clinician has several options open to correct a pre-existing hyperchloremic metabolic acidosis, usually related to plasma volume expansion. Since the underlying mechanism is providing a chloride excess (relative to sodium), providing fluids that are hypochloremic with regard to plasma creates a simply applied repair strategy. The authors employ the following fluids to achieve this goal:

- Maintenance: 5 % dextrose in water + 75 mEq/l  $\text{NaHCO}_3$  at a body weight calculated rate
- Plasma volume expansion: half strength normal saline solution + 75 mEq/l  $\text{NaHCO}_3$  provided at bolus fluid volumes.

Colloids are also used as another mechanism to decrease total chloride loading. Since the authors are constrained to use US Food and Drug Administration (FDA) approved plasma volume expanders, Hextend (6 % hydroxyethyl starch [HES] in a balanced salt solution; Hospira; Abbott Park, IL) is the fluid of choice as albumin is suspended in saline. Hextend is suspended in a less hyperchloremic solution ( $\text{Cl}^- = 120$  mEq/l) than is 5 % albumin ( $\text{Cl}^- = 154$  mEq/l).

### Pulmonary Compensation/Acute Lung Injury

The most critically ill patients often require massive plasma volume expansion, especially in the current era heralded in by the sentinel early goal-directed therapy study in 2001 [22]. An emergency department study interrogating the interplay of plasma volume expansion and the onset of ALI for patients with non-pulmonary injury delineated a strong correlation between the post-resuscitation base deficit (more strongly than fluid volume or injury severity score [ISS]) and the likelihood of developing ALI [23]. Patients who developed ALI received approximately four additional liters of plasma volume expansion compared to those who did not. Those additional four liters of plasma volume expansion translated into a lower pH and a greater base deficit (SBE) that was judged to be due to hyperchloremic metabolic acidosis as lactate levels and organ failures were similar on arrival in the emergency room.

The juxtaposition of ALI and massive plasma volume expansion (with or without blood component transfusion) creates a vast potential for ventilator-induced lung injury (VILI). Since critical illness and injury commonly create a capillary leak syndrome, extravascular lung water accumulation is predictable, and contributes markedly to decreased compliance. As the pulmonary compensation for acute acidosis is an increased minute ventilation to deliberately decrease  $PCO_2$  and increase pH, this strategy carries a significant risk of accelerated intra-tidal shear and bio-trauma due to an increased frequency of gas exchange through swollen, narrowed airways and partly collapsed alveolar units [24, 25].

Furthermore, acidosis interacts with the inducible nitric oxide (NO) synthase (iNOS) enzyme pathway according to a rat model of pulmonary epithelium. Overactivity of iNOS can lead to peroxynitrite-induced protein destruction and provide an apoptotic trigger for endothelial cells. Rat lung function was assessed at two different pHs (7.36 and 7.14) [26]; acidotic rats demonstrated increased iNOS activity as well as lower  $PO_2$  levels in the absence of another cause for ALI. Of note, interleukin (IL)-6 levels were also markedly increased in acidotic rats compared to their normal pH counterparts. Thus, acidosis of any cause impairs pulmonary function on multiple levels, providing a strong impetus for pH correction and avoidance of iatrogenically induced acidosis.

## VI

### Coagulation Cascade

The 'lethal triad' of hypothermia, acidosis and coagulopathy is well described following injury [27]. The interplay of acidosis and coagulopathy is less well described, and often these entities are thought of as accompanying each other rather than having a causal relationship. Recall that the clotting cascade relies on both platelet conformational changes as well as the activity of serine proteases. As clotting factors have pH optima and enzyme kinetics that are impaired by both acidosis and hypothermia [28, 29]. Since the dominant fluid utilized in conjunction with blood component therapy infusion is saline, careful attention should be paid to avoiding hyperchloremic metabolic acidosis in that setting. Clearly, relatively small volumes (< 2000 ml) will have little impact on pH. However, patients with exsanguinating hemorrhage often receive plasma volume expansion with large volumes of crystalloid fluids in addition to massive transfusion of blood component elements.

While enhanced survival is reported with massive transfusion protocol activation following near-exsanguination after injury, recent attention has focused on the ratio of packed red blood cells (RBCs) to units of fresh frozen plasma (FFP) citing improved survival with a 1:1 ratio [30]. While blood components generally have normal electrolytes, these components are transfused into patients who have already undergone plasma volume expansion with dilution of clotting cascade elements in the setting of lactic acidosis that is compounded by an iatrogenic hyperchloremic metabolic acidosis. Thus, avoiding hyperchloremic metabolic acidosis is an intelligent means of supporting the activity of the clotting cascade, which is already impaired from hypoperfusion-associated acidosis and further crippled by hypothermia [31].

A provocative operating room study assessed patients undergoing open abdominal aortic aneurysm repair as a model for large volume blood loss and resuscitation [32]. Patients were resuscitated intra-operatively with either saline or lactated Ringer's solution according to a pre-established protocol. The saline resuscitated patients demonstrated the predicted acidosis, received sodium bicarbonate infusion

to correct the acidosis, and evidenced greater cell saver volumes of shed blood and required greater amounts of packed RBC, FFP, and platelet transfusion. The increased resource utilization and allogeneic exposure was linked to the induced acidosis in this study.

### Microvascular Flow

While tremendous effort has been devoted to measuring and supporting cardiac performance as a means of providing oxygen delivery to support oxygen utilization, less effort is devoted to measuring microvascular flow at the organ level. Several studies have investigated microvascular flow in the buccal mucosa, and skeletal muscle domains [33–35].

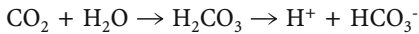
Two important studies bear directly on this topic with regard to acidosis. The first study evaluated deltoid tissue oxygen by means of an implanted probe pre-, intra-, and post-operatively for the 1<sup>st</sup> 24 hours after elective major surgery [36]. Two groups were created based on the fluid choice for plasma volume expansion – one group received lactated Ringer's solution and one received a low molecular weight (130 kDa) and degree of molar substitution (0.4) HES. Resuscitation was performed according to a protocol including blood transfusion for hemoglobin concentration < 8 g/dl. While no demographic or care differences were noted between the groups, the deltoid tissue PO<sub>2</sub> was markedly decreased in the crystalloid group and enhanced in the colloid group by the end of surgery and was more pronounced by the following morning. The explanation for this observation stems from the second study.

Normal human RBC were assessed in media of different pH and queried for RBC volume and viscosity at low and high flow rates [37]. Importantly, acidosis predictably increased RBC volume by ~7 % (as assessed by hematocrit) – an effect that was reversed by acidosis abrogation with NaOH, akin to correction of pH with NaHCO<sub>3</sub> in the clinical circumstance. It is currently unclear whether the RBC volume increase is sufficient to impair spectrin function in supporting RBC rheology, but merits further investigation [38, 39]. Moreover, acidosis also resulted in an increase in viscosity at both low and high flow rates. These data support the need to correct hyperchloremic metabolic acidosis, and indeed any acidosis, as a means of supporting microvascular flow. Moreover, these data may provide an explanation for the 'no-reflow' phenomenon identified after tissue ischemia and oxygenated reperfusion.

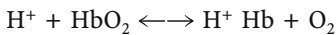
The no-reflow phenomenon was comfortably attributed to lipid peroxidation and endothelial dysfunction as a result of toxic oxygen metabolites during oxygenated reperfusion of previously dysoxic tissue beds [40, 41]. However, it is important to recall that these beds are also vasodilated and acidic from anaerobic metabolism with high regional lactate concentrations [42]. Flow resumption directs RBCs into a zone of significant acidosis, which in turn leads to RBC swelling. If swollen RBCs are delivered to capillary beds that are in tissue beds swollen from edema accrued during plasma volume expansion, the capillary cross-sectional diameter may be narrowed leading to RBC sludging, capillary obstruction and rouleaux formation [43]. This hypothetical scheme is plausible based upon the above physiology, and would also help understand how restoration of systemic oxygen delivery may not meet oxygen utilization during the reperfusion phase after significant hypoperfusion [44, 45]. Hyperchloremic metabolic acidosis may also impair hemoglobin's ability to transport and unload oxygen at the tissue level as a result of the Haldane effect.

Initially articulated in 1914, the Haldane effect relates the interplay of hemoglobin with oxygen, chloride, and protons [46]. The Haldane effect hinges on the premise

that the reduced (deoxygenated) form of hemoglobin is a better proton acceptor than the oxidized (oxygenated) form. Le Chatelier's principle is described by the following equation:



Accordingly, it is apparent that deoxygenated hemoglobin will drive the reaction to the right as a result of the Law of Mass Action. Therefore, the enhanced affinity of deoxyhemoglobin for protons enhances the synthesis of bicarbonate, which is the major transport form that  $\text{CO}_2$  assumes in blood. In essence, more  $\text{HCO}_3^-$  is carried in the RBC interior than would otherwise be possible, and consequently more  $\text{H}^+$  binds to hemoglobin. Conversely, the Haldane effect promotes the dissociation of  $\text{CO}_2$  from hemoglobin in the presence of oxygen. Thus, the summative equation for the Haldane effect may be best summarized as:



It has been demonstrated that the reversible binding of chloride to hemoglobin in deoxygenated blood occurs at those sites that have been newly protonated by the Haldane effect [47]. Accordingly, the converse may also be true:  $\text{Cl}^-$  binding enhances the Haldane effect, as  $\text{Cl}^-$  binding electrostatically stabilizes the deoxygenated state (with the effect that  $\text{Cl}^-$  decreases hemoglobin's oxygen affinity). Thus, hyperchloremic metabolic acidosis may impair tissue level oxygen delivery by stabilizing hemoglobin in the deoxygenated state while enhancing hemoglobin's  $\text{CO}_2$  transport ability [48].

## VI

### Immune Activation or Suppression

Fluid resuscitation strategies have employed several different regimens spanning crystalloids and colloids including albumin, starches of different molecular weights and degrees of molar substitution as well as dextrans. When incubating human polymorphonuclear leukocytes (PMNs) with each of these different solutions, the most potent trigger of oxidative burst activity is crystalloids [49]. Thus, it would appear that standard US resuscitation strategies prime human neutrophils for immune activation and inflammation.

A rat cecal ligation and puncture model of intra-abdominal sepsis explored the immune activating effects of deliberate acidosis induction using a 0.1N HCl solution [50]. The more negative the SBE, the lower the achieved mean arterial pressure (MAP). Nitrite levels peaked in the group with SBE of -5 to -10 mEq/l and then decreased with progressive acid load. A separate study tied NO activity to lipopolysaccharide (LPS) stimulation as a necessary component to increase nitrite production in a RAW cell model [51]. In this model, NO production was maximal at a pH of 7.0 and then declined at a pH of 6.5, perhaps reflecting enzymatic derangements with progressive acidosis. Similar pH-linked effects were noted for IL-6 and IL-10 release in this model as well. However, when assessing the IL-6:IL-10 ratio as a measure of the intensity of inflammatory to anti-inflammatory influences, maximal pro-inflammatory activity was noted at the lowest pH range (6.5). These data support the notion that acidosis progressively and independently increases inflammation. The clinically relevant corollary is that acidosis merits correction as a means of potentially reducing inflammatory stimuli in an integrated approach to managing patients with severe sepsis and septic shock.

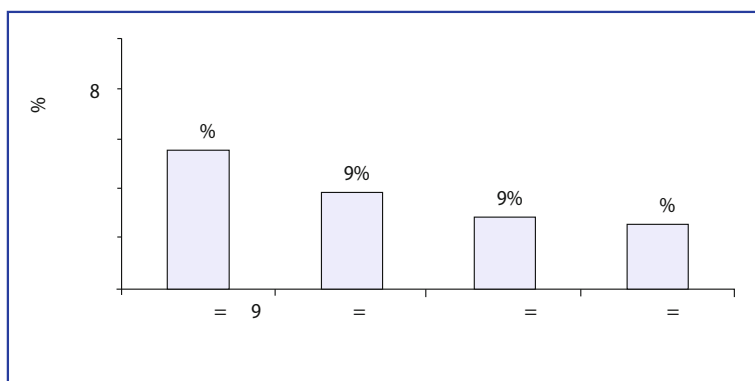
Nuclear factor-kappa B (NF- $\kappa$ B) activity has been hailed as a means of assessing subcellular triggering along inflammatory pathways. Similar to the IL-6:IL-10 ratio,

LPS-stimulated cells demonstrate enhanced NF- $\kappa$ B activity compared to unstimulated cells. Curiously, all acidoses do not appear similar with regard to immunomodulation (in this model). While a general pattern of decreased activity or production in a wide variety of inflammatory markers was demonstrated for decreased pH ranges from the addition of lactic acid to the media, a different pattern was observed when pH was decreased using HCl. In particular, increased NO activity and iNOS mRNA were noted with HCl (similar to hyperchloremic metabolic acidosis) while these were decreased at identically decreased pH ranges due to lactic acid.

### Survival

Whether hyperchloremic metabolic acidosis impacts survival in an independent fashion has been assessed in a variety of pre-clinical and clinical studies. Using an *Escherichia coli* LPS (endotoxin) infusion sepsis model, rats were resuscitated with either saline, lactated Ringer's solution or Hextend to identical pre-determined goals. Predictable and anticipated changes in SID as a result of chloride loading were noted in the saline animals with concomitant decreased SBE and pH (i.e., hyperchloremic metabolic acidosis) [52]. Mean survival time inversely correlated with the absolute increase in  $\text{Cl}^-$  concentration and was, therefore, significantly reduced for the saline resuscitated animals compared to those resuscitated with Hextend (lowest total chloride delivery group).

Lactic acid represents a readily measurable metabolic acid the absolute value of which as well as its trend over time has been utilized to predict outcome after injury [6, 53]. In a recent retrospective study of overall hospital mortality, lactic acidosis portended the worst prognosis (mortality rate = 56 %) compared to other forms of acidosis [54]. In this study, acidosis derived from unmeasured ions (i.e., SIG-associated) accrued a 39 % mortality rate, while that attributable to hyperchloremic metabolic acidosis was 29 % (Fig. 2). It is important to note that patients without acidosis who required critical care had a 26 % mortality rate.



**Fig. 2.** Mortality associated with the major ion contributing to the metabolic acidosis [54]. Hospital mortality associated with the various etiologies of metabolic acidosis (standard base excess (SBE) < -2). Mortality percentage is mortality within each subgroup, not a percentage of overall mortality. 'Lactate' indicates that lactate contributes to at least 50 % of the SBE; 'SIG', SIG contributes to at least 50 % of SBE (and not lactate); 'hyperchloremic', absence of lactate or SIG acidosis and SBE < -2; 'none', no metabolic acidosis (SBE  $\geq$  -2 mEq/l). SIG, strong ion gap.  $p < 0.001$  for the four-group comparison.

## Conclusion

It is increasingly clear that plasma volume expansion in sufficient quantity to alter plasma electrolyte concentrations may significantly impact plasma acid-base balance. As evidence mounts that iatrogenically driven electrolyte abnormalities create deleterious effects on diverse systems, it becomes increasingly incumbent upon the practitioner to regard plasma volume expanders as medications instead of as expected commensals of care. This chapter has explored how hyperchloremic metabolic acidosis influences the pulmonary system, coagulation, immune activation, and survival. Insufficiently explored aspects of electrolytically driven acidosis and immune activation includes how fluid selection drives unmeasured ion genesis and how those species influence survival [12, 14]. Early data suggest a negative impact upon survival, but longitudinal study is required. At present, the clinician can understand how hyperchloremic metabolic acidosis is generated, repair strategies once hyperchloremic metabolic acidosis is established, and the deleterious consequences of leaving hyperchloremic metabolic acidosis unrepaired.

## VI

## References

1. Maerz L, Kaplan LJ (2008) Abdominal compartment syndrome. *Crit Care Med* 36 (Suppl 4): S212–215
2. Cope DK, Grimbert F, Downey JM, Taylor AE (1992) Pulmonary capillary pressure: a review. *Crit Care Med* 20: 1043–1056
3. Kalra PR, Anagnostopoulos C, Bolger AP, Coats AJ, Anker SD (2002) The regulation and measurement of plasma volume in heart failure. *J Am Coll Cardiol* 39: 1901–1908
4. Scheingraber S, Rehm M, Sehmisch C, Finsterer U (1999) Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology* 90: 1265–1270
5. Healey MA, Davis RE, Liu FC, Loomis WH, Hoyt DB (1998) Lactated ringer's is superior to normal saline in a model of massive hemorrhage and resuscitation. *J Trauma* 45: 894–899
6. Kaplan LJ, Bailey H, Kellum JA (1999) The etiology and significance of metabolic acidosis in trauma patients. *Curr Opin Crit Care* 5: 458–463
7. Stewart PA (1981) How to Understand Acid-base. *A Quantitative Acid-base Primer for Biology and Medicine*. Elsevier, New York
8. Stewart PA (1983) Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol* 61: 1444–1461
9. Kellum JA (2000) Determinants of blood pH in health and disease. *Crit Care* 4: 6–14
10. Wooten EW (2004) Science review: Quantitative acid-base physiology using the Stewart model. *Crit Care* 8: 448–452
11. Morgan TJ (2005) Clinical review: The meaning of acid-base abnormalities in the intensive care unit- effects of fluid administration. *Crit Care* 9: 204–211
12. Kaplan LJ, Kellum JA (2008) Comparison of acid-base models for prediction of hospital mortality after trauma. *Shock* 29: 662–666
13. Kellum JA, Pinsky MR (2002) Use of vasopressor agents in critically ill patients. *Curr Opin Crit Care* 8: 236–241
14. Kaplan LJ, Philbin N, Arnaud F, Rice J, Dong F, Freilich D (2006) Resuscitation from hemorrhagic shock: fluid selection and infusion strategy drives unmeasured ion genesis. *J Trauma* 61: 90–97
15. Kellum JA (2003) Closing the gap on unmeasured anions. *Crit Care* 7: 219–220
16. Moviat M, van Haren F, van der Hoeven H (2003) Conventional or physicochemical approach in intensive care unit patients with metabolic acidosis. *Crit Care* 7: R41–R45
17. Kellum JA, Kramer DJ, Pinsky MR (1995) Strong ion gap: a methodology for exploring unexplained anions. *J Crit Care* 10: 51–55
18. Kaplan LK, Kellum JA (2007) Acid-base disorders. In: Wilson W, Grande CM, Hoyt DB. *Anesthesia, Trauma, and Intensive Care*, 1<sup>st</sup> Edition. Informa Healthcare, New York, pp 793–810

19. Siggaard-Andersen O (1977) The Van Slyke equation. *Scand J Clin Lab Invest Suppl* 146: 15–20
20. Siggaard-Andersen O, Fogh-Andersen N (1995) Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid-base disturbance. *Acta Anesth Scand Suppl* 107: 123–128
21. Brill SA, Stewart TR, Brundage SI, Schreiber MA (2002) Base deficit does not predict mortality when secondary to hyperchloremic acidosis. *Shock* 17: 459–462
22. Rivers E, Nguyen B, Havstad S, et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345: 1368–1377
23. Eberhard LW, Morabito DJ, Matthay MA, et al (2000) Initial severity of metabolic acidosis predicts the development of acute lung injury in severely traumatized patients. *Crit Care Med* 28: 125–131
24. dos Santos CC, Slutsky AS (2006) The contribution of biophysical lung injury to the development of biotrauma. *Annu Rev Physiol* 68: 585–618
25. Habashi NM (2005) Other approaches to open-lung ventilation: airway pressure release ventilation. *Crit Care Med* 33 (Suppl 3):S228–240
26. Haque IU, Huang CJ, Scumpia PO, Nasiroglu O, Skimming JW (2003) Intravascular infusion of acid promotes intrapulmonary inducible nitric oxide synthase activity and impairs blood oxygenation in rats. *Crit Care Med* 31: 1454–1460
27. Eddy VA, Morris JA Jr, Cullinane DC (2000) Hypothermia, coagulopathy, and acidosis. *Surg Clin North Am* 80: 845–854
28. Schreiber MA (2005) Coagulopathy in the trauma patient. *Curr Opin Crit Care* 11: 590–597
29. Martini WZ, Pusateri AE, Uscilowicz JM, Delgado AV, Holcomb JB (2005) Independent contributions of hypothermia and acidosis to coagulopathy in swine. *J Trauma* 58: 1002–1009
30. Holcomb JB, Jenkins D, Rhee P, et al (2007) Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma* 62: 307–310
31. Johnston TD, Chen Y, Reed RL 2<sup>nd</sup> (1994) Functional equivalence of hypothermia to specific clotting factor deficiencies. *J Trauma* 37: 413–417
32. Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR (2001) Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. *Anesth Analg* 93: 817–822
33. Cammarata GA, Weil MH, Castillo CJ, et al (2009) Buccal capnometry for quantitating the severity of hemorrhagic shock. *Shock* (in press)
34. Povoas HP, Weil MH, Tang W, Moran B, Kamohara T, Bisera J (2000) Comparisons between sublingual and gastric tonometry during hemorrhagic shock. *Chest* 118: 1127–1132
35. Weil MH, Nakagawa Y, Tang W, et al (1999) Sublingual capnometry: a new noninvasive measurement for diagnosis and quantitation of severity of circulatory shock. *Crit Care Med* 27: 1225–1229
36. Lang K, Boldt J, Suttner S, Haisch G (2001) Colloids versus crystalloids and tissue oxygen tension in patients undergoing major abdominal surgery. *Anesth Analg* 93: 405–409
37. Reinhart WH, Gaudenz R, Walter R (2002) Acidosis induced by lactate, pyruvate, or HCl increases blood viscosity. *J Crit Care* 17: 68–73
38. Hansen J, Skalak R, Chien S, Hoger A (1997) Spectrin properties and the elasticity of the red blood cell membrane skeleton. *Biorheology* 34: 327–348
39. Li J, Lykotrafitis G, Dao M, Suresh S (2007) Cytoskeletal dynamics of human erythrocyte. *Proc Natl Acad Sci USA* 104: 4937–4942
40. Kaplan LJ, Bellows CF, Blum H, Mitchell M, Whitman GJ (1994) Ischemic preconditioning preserves end-ischemic ATP, enhancing functional recovery and coronary flow during reperfusion. *J Surg Res* 57: 179–184
41. Kaplan LJ, Blum H, Bellows CF, Banerjee A, Whitman GJ (1996) Reversible injury: creatinine kinase recovery restores bioenergetics and function. *J Surg Res* 62: 103–108
42. Seal JB, Gewertz BL (2005) Vascular dysfunction in ischemia-reperfusion injury. *Ann Vasc Surg* 19: 572–584
43. Cicha I, Suzuki Y, Tateishi N, Maeda N (2003) Changes of RBC aggregation in oxygenation-deoxygenation: pH dependency and cell morphology. *Am J Physiol Heart Circ Physiol* 284: H2335–2342
44. Chiara O, Pelosi P, Segala M, et al (2001) Mesenteric and renal oxygen transport during hemorrhage and reperfusion: evaluation of optimal goals for resuscitation. *J Trauma* 51: 356–362

45. Kaplan LJ, Bellows CF, Carter S, Blum H, Whitman GJ (1995) The phosphocreatine overshoot occurs independent of myocardial work. *Biochimie* 77: 245–248
46. Benesch RE, Rubin H (1975) Interaction of hemoglobin with three ligands: organic phosphates and the Bohr effect. *Proc Natl Acad Sci USA* 72: 2465–2467
47. Giovannini I, Chiarla C, Boldrini G, Terzi R (1999) Quantitative assessment of changes in blood CO<sub>2</sub> tension mediated by the haldane effect. *J Appl Physiol* 87: 862–866
48. Prange HD, Schumaker Jr JL, Westen EA, Horstkotte DG, Pinshow B (2001) Physiological consequences of oxygen-dependent chloride binding to hemoglobin. *J Appl Physiol* 91: 33–38
49. Rhee P, Wang D, Ruff P, et al (2000) Human neutrophil activation and increased adhesion by various resuscitation fluids. *Crit Care Med* 28: 74–78
50. Kellum JA, Song M, Venkataraman R (2004) Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest* 125: 243–248
51. Kellum JA, Song M, Li J (2004) Lactic and hydrochloric acids induce different patterns of inflammatory response in LPS-stimulated RAW 264.7 cells. *Am J Physiol Regul Integr Comp Physiol* 286:R686–692
52. Kellum JA (2002) Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acid-base balance with Hextend compared with saline. *Crit Care Med* 30: 300–305
53. Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, Greenspan J (1993) Lactate clearance and survival following injury. *J Trauma* 35: 584–589
54. Gunnerson KJ, Saul M, He S, Kellum JA (2006) Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. *Crit Care* 10:R22
55. Gunnerson KJ, Kaplan JA (2003) Acid-base and electrolyte analysis in critically ill patients: are we ready for the new millennium? *Curr Opin Crit Care* 9: 468–473