Critical care nephrology: management of acid–base disorders with CRRT

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Normal acid–base homeostasis is severely challenged in the intensive care setting. In this review, we address acid–base disturbances, with a special focus on the use of continuous (rather than intermittent) extracorporeal technologies in critical ill patients with acute kidney injury. We consider hypercapnic acidosis and lactic acidosis as examples in which continuous modalities may have different roles and indications than the traditional intermittent approaches to renal replacement therapy. Hypercapnic acidosis develops as a consequence of alveolar hypoventilation. In this condition, correction of pH above 7.2 is not currently recommended, and may even abrogate the beneficial effects of hypercapnic acidosis on overall outcomes. Extracorporeal technologies support lung protection while maintaining overall patient homeostasis. Similarly, in lactic acidosis, current evidence does not support bicarbonate infusions to correct acidosis. The management of lactic acidosis should correct the underlying causative disturbances. Most often, lactic acidosis is a biomarker denoting unfavorable outcomes, rather than an intrinsic pathogenetic mechanism. Extracorporeal procedures may assist in the removal of pathogenic drugs or toxins, as well as partially correcting acidemia. Whether or not these approaches will permit normalization of systemic pH, and the impact of these approaches on patient outcomes, needs to be addressed with prospective controlled trials.

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> 'The constancy of the milieu supposes a perfection of the organism such that the external variations are at each instant compensated for and equilibrated…. All of the vital mechanisms, however varied they may be, have always one goal, to maintain the uniformity of the conditions of life in the internal environment…. The stability of the internal environment is the condition for the free and independent life.' Claude Bernard[1]

Critically ill patients are faced with severe homeostatic challenges to the '*milieu interiéur*'.[1] Advances in the understanding of physiological processes[2] and emerging extracorporeal technologies provide opportunities to restore homeostasis and to hasten the recovery of a 'free and independent life'. To achieve this goal, a variety of inputs must be amalgamated, including biochemistry, physical chemistry, physiology, pharmacology, nephrology, and critical care. When such patients develop acute kidney injury (AKI) and acid–base disorders requiring intermittent hemodialysis or continuous renal replacement therapy (CRRT), the process by which buffers are delivered changes: instead of infusion into the central circulation, buffers are infused into the extracorporeal circuit, either directly (hemoperfusion) or across the membrane (dialysis).[3] These differences in delivery, as well as the continuous adjustment of buffer stores permitted by continuous modalities, has changed the approach to acid–base disturbances during CRRT. This review focuses on the contemporary management of hypercapnic respiratory acidosis (HCA) and lactic acidosis in the critically ill patient with AKI. We also highlight the acid–base implications of the use of citrate anticoagulation during CRRT.

We use the 'physiological' approach[2,4] as a simple and serviceable method applicable to patients with compromised renal function in the critical care setting. Recent reviews[5–7] address alternative approaches for interpreting acid–base disorders. We assume, in the absence of prospective comparisons, that the application of the physiological approach or alternative interpretations of acid–base equilibrium is ultimately focused on providing optimal patient outcomes.

ACUTE AND CHRONIC RESPIRATORY ACIDOSIS

Figure 1 emphasizes the central role of the partial pressure of dissolved carbon dioxide (the $PaCO_2$) in the normal

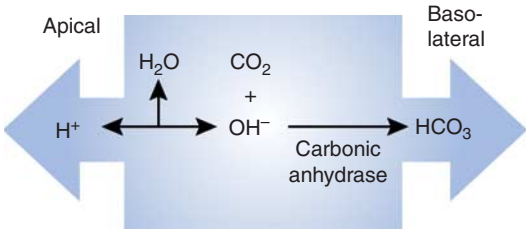

Figure 1 | Central role of carbon dioxide (CO_2) in the regulation of epithelial proton secretory processes. A number of proton secretory mechanisms move H^+ across the apical membrane into the luminal membrane (urinary compartment). If the luminal buffer is bicarbonate, then the result is bicarbonate reabsorption without any net acid excretion. If the luminal bicarbonate has been reduced (for example, in the distal nephron), then there are non-bicarbonate luminal buffers that will accept the secreted protons, with generation of an intracellular base equivalent. In the presence of carbonic anhydrase, 'new' bicarbonate is generated and delivered to the systemic circulation. The consequence of a primary imposed increase in arterial CO_2 pressure will be acute respiratory acidosis, and the slower adaptation will produce a secondary metabolic alkalosis that reduces the extent of the primary acidosis due to CO_2 retention.[2]

regulation of proton secretion, titration of luminal buffers such as phosphate and ammonia ('net acid excretion'), and *de novo* generation of bicarbonate that is delivered to the blood side of renal epithelial cells. This schema provides a physiological framework to understand the primary acid–base disturbances, and the secondary compensations to those disturbances.[2,4] When AKI develops, net acid excretion is limited and external buffering becomes necessary to maintain acid–base homeostasis.

Hypercapnic acidosis: physiological compensatory mechanisms

Acute hypercapnia acidifies body fluids and titrates non-bicarbonate buffers, with an immediate increase in plasma bicarbonate that can be readily estimated.[2] Sustained hypercapnia causes an additional, larger increase in plasma bicarbonate concentration by stimulating net renal acid excretion and generation of 'new bicarbonate' (Figure 1); a new steady state is reached within 3–5 days in dogs, but the response pattern has not been as well defined in humans.

Hypercapnia stimulates the central drive to respiration. Exposure to an 8 mm Hg increase in end-tidal $PaCO_2$ increases the ventilatory chemosensitivity to acute hypoxia[8] and plasma bicarbonate will be secondarily elevated by *de novo* renal bicarbonate generation. Peripheral and central chemoreceptors are primarily stimulated by H^+; rapid diffusion of CO_2 across the blood–brain barrier permits changes in the arterial dissolved CO_2 tension ($PaCO_2$) to translate into rapid changes in the pH at the central respiratory chemoreceptor.[9]

Respiratory failure and AKI

Respiratory acidosis accompanies alveolar hypoventilation during acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). The annual estimates in the US are 190,600 cases of ALI, associated with 74,500 deaths and 3.6 million hospital days.[10] The ratio of partial pressure of oxygen to the fraction of inspired oxygen (paO_2/FiO_2 ratio) decreases to <300 in ALI and <200 in ARDS.[11] ALI and ARDS often require mechanically assisted ventilation,[10,12] and pulmonary edema can develop even in the 'normal' range of pulmonary capillary pressure owing to increased capillary and alveolar permeability, and alterations in the clearance of intra-alveolar fluid.[13]

The prevalence of AKI is similar to that of ARDS.[14,15] When AKI complicates ARDS, the mortality risk is increased because of severe inflammation,[16] fluid overload,[13] multiple electrolyte disorders, and metabolic and respiratory acidosis.[17] Bicarbonate infusion may transiently control acidemia, but associated risks include worsened hypoxemia from volume overload, and intracellular acidosis induced by rapid intracellular diffusion of CO_2.[18] Early initiation of renal replacement therapy may be required to manage fluid overload[13] and severe systemic acidosis,[17,19,20] but the choice of modalities has an impact on the management of acid–base disorders.

Management of ALI and hypercapnic acidosis

The landmark ARDS Network study[21] of low tidal volume ventilation and low plateau end inspiration showed reduced mortality and decreased number of days of ventilator support. A subsequent comparison by the ARDS Network trial comparing higher and lower levels of positive end-expiratory pressure and low tidal volumes demonstrated a mortality of 26%, similar to 30% mortality seen in the low tidal volume trial.[22] On the basis of these studies, ARDS patients are currently managed with initial lower tidal volumes (4 to 6 ml/kg of predicted body weight) and a plateau pressure $\leqslant 30$ cm of water, modulating positive end-expiratory pressure and fraction of inspired oxygen to maintain adequate oxygenation while 'permitting' CO_2 retention.[23–25] This strategy is associated with respiratory acidosis, but minimizes barotrauma, decreases inflammation, and increases the number of ventilator-free days and survival.[26] During low tidal volume respiration, $PaCO_2$ increased by 8.9 kPa (66.5 mm Hg) and pH decreased to 7.2, levels that were generally 'well tolerated' as long as tissue perfusion and oxygenation were preserved.[27] This approach is now nearly universal in the critical care setting and presents an opportunity to consider the physiopathology and management of hypercapnic acidosis, especially for patients with concurrent AKI who receive CRRT.

Hypercapnic acidosis: controversies

Acute HCA appears to be well tolerated,[27,28] but robust neuroendocrine responses are required to compensate for the direct negative inotropic and vasodilating effects of elevated $PaCO_2$.[28,29] Mechanisms to defend intracellular pH must also be intact, particularly in critical organs such as the brain and heart.[28,30] Cerebral autoregulation is impaired in septic

shock, and thus hypotension can cause severe cerebral hypoperfusion, especially in patients with hypercapnia, which has raised concerns about increased capillary permeability and cerebral water content, and worsening encephalopathy in septic patients exposed to permissive hypercapnia.[31] Thus, in sepsis and AKI, hypercapnia may set the stage for worsened encephalopathy, and HCA should be avoided in cases of intracranial pathology or when increased intracranial pressure is present.[32]

Concerns have also recently been raised regarding the frequent use of paralytic agents,[25] the risk of decreased neuromuscular function,[33] and the theoretical potential for hypercapnia to cause intracellular acidosis, myocardial depression, pulmonary and intracranial hypertension, and increased catecholamine secretion.[5] The anti-inflammatory effects of HCA may impair host defenses.[29] Furthermore, acidosis may reduce alveolar fluid clearance by inducing endocytosis of alveolar epithelial cell Na^+/K^+ ATPase.[34–37] These latter concerns are especially important in view of recent studies demonstrating the importance of minimizing alveolar fluid accumulation.[11,13]

In spite of these theoretical concerns, clinical studies suggest that HCA has very few detrimental effects[38] and improves arterial and tissue oxygenation.[27] Although the average $PaCO_2$ in the low tidal ventilation arm of the ARDS Network study was only 5 mmHg higher than in the conventional arm,[21] additional clinical studies support the safety of more severe HCA in ARDS[39,40] even among patients randomized to higher tidal volume ventilation.[40] Although experimental studies suggest that hypercapnia may delay weaning from ventilation,[41] the ARDS Network studies actually demonstrate increased number of ventilator-free days among hypercapnic patients.[21,22]

The study design of the original tidal volume ARDS Network trial permitted bicarbonate administration to buffer acidosis to a plasma $pH \geqslant 7.2$.[21] More recent evidence questions this approach, and suggests that the acidosis may be beneficial *per se*. HCA reduces oxidative stress and generation of reactive oxygen species in experimental endotoxin-induced lung injury via multiple processes, including antioxidant effects,[42] and attenuates the expression of nuclear factor-κB, a key regulator of the expression of multiple genes involved in cytokine cascades and inflammatory responses.[27,41,43]

Barotrauma is associated with AKI in experimental animals,[44–46] and recent studies have suggested that lung-protective ventilation may also protect against AKI.[17] In the ARDS Network trial,[21] patients ventilated with low tidal volume strategies appeared to require less intermittent hemodialysis, but this needs to be confirmed in prospective trials with more sensitive and less subjective outcome measures than initiation of dialysis.

The results of clinical and experimental models of ALI and sepsis indicate that, although controversial, HCA may be beneficial but may not be appropriate for all critically ill patients: among patients with advanced age and multiple comorbidities, the use of lung-protective strategies could have detrimental effects.[29] It is unclear whether patients with compromised cardiovascular, renal, and cerebral function will realize a net benefit because the strong neurosympathetic activation and cardiovascular responses invoked by HCA can cause imbalanced myocardial oxygen delivery, renal vasoconstriction, oliguria, pulmonary hypertension, and worsening acidemia.[27,29]

Bicarbonate in the management of respiratory acidosis: friend or foe?

The usual mode of administration of sodium bicarbonate (via systemic infusion) may worsen existing hypercapnia whenever the compensatory respiratory reflexes or alveolar ventilation are compromised, or in mechanically ventilated patients. Low tidal volume protocols provide guidance for balancing risk/benefit between lung-protective ventilatory strategies and the treatment of hypercapnic acidosis; the subject is extensively reviewed by Kallet *et al.*[25] The question whether HCA should be treated to a $pH \geqslant 7.2$ is controversial.[25,47–50] Early studies[48] using sodium bicarbonate infusion to correct acidosis showed multiple adverse effects including hyperosmolality, congestive heart failure with volume expansion, decreased ionized calcium plasma concentration, and intracellular acidosis.[51] Bicarbonate buffering did not improve hemodynamic variables, tissue oxygen delivery, or uptake,[47–50,52] and enormous amounts of bicarbonate may be needed to produce small increases in arterial pH.[32] This phenomena has been described as an increased bicarbonate 'space' or volume of distribution, and probably represents titration of intracellular and intraosseous buffer stores during systemic acidosis.[53]

Extracorporeal techniques and acid–base disorders

Renal replacement therapy can be used to correct systemic acidemia; however, with high-efficiency intermittent hemodialysis, the rapid flux of bicarbonate from dialysate to patient can generate excess CO_2, requiring hyperventilation to maintain the acid–base balance, especially if overt metabolic alkalosis is the result.[54] This concern may not apply to CRRT because the rate of buffer delivery is much slower than that with intermittent hemodialysis. Case reports have described the successful use of CRRT to correct combined respiratory and metabolic acidosis in the setting of AKI.[55]

Total CO_2 can be removed by convective hemofiltration,[3] if at the same time the ultrafiltered fluid is replaced by a bicarbonate-free solution. In a proof-of-concept model in sheep, Cressoni *et al.*[56] used venovenous hemofiltration with replacement fluid containing NaOH. Half of the metabolic production of CO_2 was removed, permitting a 50% reduction in minute ventilation while maintaining the $PaCO_2$ level in the range of 35 to 38 mm Hg, stable blood pH (pH decreased only by 0.1 unit), and mild metabolic acidosis (average plasma bicarbonate level 20 mmol/l). Strategies using trisodium citrate in the prefiltered, bicarbonate-free replacement

fluid, both as a source of alkali base and as anticoagulant,[57,58] may add additional advantages to the device design and acid–base control during CRRT. Concerns about the use of citrate have been described,[59] and are addressed later in this review. These exciting studies indicate that CO_2 removal by hemofiltration may be—with further refinement—an effective adjunctive treatment of systemic acidosis for patients with respiratory failure.[3] This development represents another example of the use of CRRT techniques for 'overall patient support', rather than just replacement of compromised renal function.[60]

Alternative extracorporeal approaches to severe hypercapnia include a venovenous circuit in which a CO_2-removing cartridge and a hemofilter are placed in series, performing extracorporeal CO_2 removal.[61] When used in the clinical setting, the device removes CO_2 and controls $PaCO_2$ and plasma pH in spite of hypoventilation. Another approach provides CO_2 control by arteriovenous CO_2-removal devices[62] that do not have a blood pump, reducing the potential for hemolysis and the complexity of the extracorporeal circuit. Limitations of these devices include lack of extracorporeal blood flow control and risk of bleeding and limb ischemia.[56,61] Development of more efficient devices capable of removing a substantial amount of CO_2 production (30–100%) with blood flows of 250–500 ml/min is foreseeable. Future ARDS management may include a minimally invasive extracorporeal CO_2 removal circuit associated with non-invasive ventilation, and thus avoid intubation, minimize sedation, and prevent ventilator-induced ALI and nosocomial infections.[63]

Summary and conclusions: hypercapnic acidosis

Contemporary pulmonary-protective management strategies have demonstrated a reduction in mortality among patients with ALI/ARDS. The resulting hypercapnic acidosis is generally considered an acceptable side effect among selected patients as long as arterial pH can be maintained at a safe level ($\geqslant 7.2$). Central infusion of bicarbonate is associated with complications including volume overload or hypertonic challenge, worsening hypercapnia and lactic acidosis, and is not currently recommended unless metabolic or mixed acidosis coexist. Early initiation of CRRT may be considered for AKI and combined respiratory and metabolic acidosis, and by its continuous nature will lessen the adverse effects of bicarbonate administration. Newer extracorporeal techniques, enabling acid–base control by removal of CO_2 from the extracorporeal circuit, may be valuable options to facilitate lung-protective strategies while managing the consequences of hypercatabolism, systemic acidosis, and fluid overload.

METABOLIC ACIDOSIS

Gunnerson and Kellum[5] reviewed the prevalence of metabolic acidosis in the intensive care setting, and concluded that metabolic acidosis was far more common than lactic acidosis. Since that time, the use of CRRT, especially with citrate anticoagulation, has become much more common and essentially provides a continuous source of bicarbonate (or citrate as a bicarbonate equivalent) so that the prevalence and/or severity of hyperchloremic acidosis may well be reduced among patients receiving CRRT. If the prevalence of hyperchloremic acidosis is lessened by CRRT, then the occurrence of anion-gap metabolic acidosis, such as lactic acidosis, will be relatively more common.

Lactic acidosis

Lactic acidosis is associated with a high mortality,[64,65] and lactate levels predict outcome.[66] Improving hemodynamic and oxygen delivery improved the survival of patients with severe sepsis and lactic acidosis, and a significant benefit for early lactate clearance was shown for mortality in severe sepsis.[67,68] Therapy was directed at global tissue hypoxia rather than at lactate levels *per se*, and did not demonstrate any utility of management targeted at the lactate levels rather than simply optimizing overall hemodynamic status. Nevertheless, the Surviving Sepsis Campaign[69] regards sepsis with lactate level $\geqslant 4$ mmol/l as an indication for aggressive treatment protocols.

A randomized, controlled study[70] showed decreased morbidity using lactate-directed strategies, but results were limited to postcardiac surgery patients. Recently, Jansen *et al.*[71] examined whether intensive care patients with lactate levels $\geqslant 3$ mmol/l benefited from therapies aimed at reducing lactic acid levels by 20% within 2 h, compared with standard management. When adjusted for predefined risk factors, hospital mortality was reduced by 40%, disease severity was lower, ionotropes were stopped earlier, and patients weaned from mechanical ventilation and discharged from the intensive care unit sooner, suggesting benefit from initial lactate monitoring and intervention. However, the lactate-managed group did not have more rapid reductions in serum lactate than control patients.[71] This study underscores the importance of lactate as a prognosis indicator that can signal underlying deterioration, prompt more aggressive management, and also help to avoid unnecessary treatment when the condition stabilizes.

Pathophysiology

Pyruvate is the precursor of lactate and is produced in the cytoplasm from glucose metabolism via glycolysis by the Embden–Meyerhof pathway.[72] A healthy 70-kg adult produces $\sim$1300 mmol lactate a day.[64,66] Skeletal muscle, brain, red blood cells, and renal medulla are responsible for the majority of lactate production. Both the liver and kidney are important lactate-consuming organs, and under normal conditions the liver takes up $\sim$60% of the circulating lactate.[73] Lactate can be metabolized by the kidney, where filtered lactate is almost completely reabsorbed in the proximal convoluted tubule and metabolized.[74]

Pyruvate normally undergoes oxidative decarboxylation by mitochondrial pyruvate dehydrogenase (PDH) to acetyl-coenzyme A, and then ultimately to CO_2 and H_2O. This process results in the synthesis of 36 mol of adenosine triphosphate (ATP) and requires oxidized nicotinamide

adenine dinucleotide (NAD^+). Pyruvate can also enter the Cori cycle in the liver and renal cortex and be converted back to glucose. Oxidative phosphorylation, ATP synthesis, and reoxidation of NADH are inhibited during hypoxia, leading to increased NADH/NAD^+ ratio and conversion of pyruvate to lactate, with synthesis of 2 molecules of ATP, rather than 36 molecules generated via the tricarboxylic acid cycle. The overall result of anaerobic metabolism is hyperlactacidemia, elevated lactate/pyruvate ratio, greater glucose utilization, and lower energy production.

Lactic acidosis occurs whenever production of lactate exceeds its utilization. In most cases of clinically significant lactic acidosis, there is evidence of defective utilization, as well as increased production, depending on the etiology of lactic acidosis. Severe acidosis, by itself, has been shown to impair lactate uptake by the liver in experimental animals.[75] When exposed to severe hypoxia, liver lactate clearance is decreased, whereas kidney lactate clearance continues. The ability of the kidney to remove lactate is increased by acidosis: although acidosis inhibits hepatic metabolism, it increases lactate uptake and utilization by stimulating the activity of phosphoenolpyruvate carboxykinase.[74,76]

Traditionally, lactic acidosis has been characterized by impaired mitochondrial oxidative capacity in the setting of tissue hypoxia (Type A) or dysregulation of cell metabolism rather than hypoxia (Type B).[73,77–82] Type B lactic acidosis is divided into Type B1 (related to underlying diseases like malignancies or liver disease), Type B2 (related to the effect of drugs and toxins), and Type B3 (associated with inborn errors of metabolism).[66] The commonest drugs associated with Type B2 lactic acidosis include biguanides, reverse-transcriptase inhibitors, aspirin, propofol, and linezolid[83–85] among others.[66,86,87] In critically ill patients, the clinical distinction between Type A and Type B lactic acidosis may not hold; patients can have dysregulation of cellular metabolism as well as hypoxia.[88]

Lactic acidosis and sepsis

Sepsis is a common cause of lactic acidosis in the intensive care unit, traditionally classified as Type A lactic acidosis because of inadequate oxygen supply and amplified anaerobic metabolism. However, the lack of response to increased oxygen delivery, the absence of tissue hypoxia, and normal tissue ATP levels suggest that lactate formation during sepsis is due to dysregulation of cellular metabolism.[77,82,89]

The source of lactic acid in sepsis is controversial. Decreased clearance of lactate rather than increased production has been demonstrated in sepsis.[90] In addition, increased pyruvate production, decreased PDH activity, regional differences in lactate production, and decreased clearance of lactate have also been implicated as possible contributors to lactic acidosis.[91–94] Decreased muscle PDH activity has been shown in sepsis, and its restoration by dichloroacetate, an activator of PDH,[95,96] suggested that lactic acidosis during sepsis may be due to functional inhibition of PDH, with enhanced conversion of pyruvate to lactate.

Treatment of lactic acidosis

Traditional sodium bicarbonate infusion therapy. Clinical studies do not currently support the routine use of sodium bicarbonate infusion to treat lactic acidosis.[65] Central administration of sodium bicarbonate may increase lactate production, decrease portal vein flow, lower intracellular pH, and worsen cardiac output.[18,47,97,98] Bicarbonate infusion can increase extracellular pH only if ventilation removes the excess CO_2; otherwise, hypercapnia lowers intracellular pH and impairs cellular function, with myocardial[51] and cerebral[48] intracellular acidosis. Bicarbonate can worsen tissue oxygen delivery if arterial pH increases more than intracellular pH, with a leftward shift in the oxyhemoglobin dissociation curve. If tissue hypoxia is present, the use of bicarbonate can stimulate glycolysis mediated by the pH-sensitive, rate-limiting enzyme phosphofructokinase, and increase lactate production.[99]

A recent survey[100] highlighted the uncertainty about infusing bicarbonate during metabolic acidosis, and showed significant differences between critical care and nephrology specialists. For example, 40% of the intensivists would not give bicarbonate unless pH was <7.0, but only 6% of nephrologists would wait until pH was that low. Current consensus is that unless efforts are focused on reversing the underlying defects responsible for the acidosis, bicarbonate infusion will not be beneficial.[101] The Surviving Sepsis Campaign[69] recommended holding bicarbonate for lactic acidosis unless systemic pH <7.15; others have recommended an even lower threshold of $\leqslant 7.0$.[59]

Sodium bicarbonate infusion has been studied in two randomized trials in patients with sepsis-induced lactic acidosis. Cooper *et al.*[48] infused sodium bicarbonate to 14 critically ill patients, without any improvement in cardiac hemodynamics, and with decreased ionized serum calcium and increased $PaCO_2$. Mathieu *et al.*[52] randomized 10 critically ill patients to sequential infusion of either sodium bicarbonate or sodium chloride, without any significant differences in measures of lactate production or O_2 delivery. Bicarbonate therapy can improve systemic pH if ventilation and arterial oxygenation are adequate, and shock has been reversed.[25]

Carbicarb, an equimolecular mixture of sodium bicarbonate and sodium carbonate, has a buffering capacity similar to sodium bicarbonate but generates less carbon dioxide because its pH and buffer poise is higher than a pure bicarbonate solution. In animal models of hypoxic lactic acidosis, Carbicarb reduced circulating lactate and improved tissue and blood acid–base status compared with sodium bicarbonate.[102–105] Controlled studies with Carbicarb in patients with metabolic studies are lacking.

Other treatments. Dichloroacetic acid stimulates the activity of mitochondrial PDH enzyme complex indirectly through inhibition of the PDH kinase, and hence decreases lactate production.[95] dichloroacetic acid also exerts a positive inotropic effect that has been attributed to improvement in myocardial glucose use and high-energy phosphate production.

Data from animal studies[99] and one placebo-controlled double-blind clinical trial[106] have shown that dichloroacetic acid improved acid–base status, but the magnitude of change was small, without any improvement in hemodynamics nor survival.

CRRT and lactic acidosis. Small observational studies using CRRT with bicarbonate-based solutions showed efficient management of severe Type A lactic acidosis in hemodynamically unstable patients.[107–112] Levraut *et al.*[113] used continuous venovenous hemodiafiltration in 10 critically ill patients with stable lactic acidemia. Hemofilter lactate clearance and endogenous total plasma lactate clearance were measured; the median total plasma lactate clearance was 1379 ml/min, whereas the median hemofilter lactate clearance was <40 ml/min. The use of lactate-buffered fluids is not helpful, and in some cases leads to further increases in serum lactate levels. Conversely, bicarbonate-buffered replacement fluids allow correction of acidosis without exacerbation of lactic acidosis.[74] CRRT offers several practical and theoretical advantages over traditional intermittent dialysis support and central bicarbonate infusions that are worth emphasizing: bicarbonate (or citrate, as a bicarbonate equivalent) can be given in a prefilter solution with concurrent ultrafiltration so that fluid overload is avoided; systemic acidosis is treated with continuous titration of the added bicarbonate in the extracorporeal circuit rather than central infusion; and maintenance of normal ionized calcium in the setting of effective bicarbonate addition. Evidence supporting this approach is anecdotal at best; and prospective controlled trials are worth considering.

Drug-induced lactic acidosis. Metformin inhibits hepatic gluconeogenesis.[114] The association of metformin with lactic acidosis has been object of much debate.[115] At therapeutic doses, metformin alone does not elevate plasma lactate levels,[116] and serum levels are not reliable predictors of metformin-related toxicity.[117] Metformin-associated lactic acidosis is associated with increased intestinal lactic acid production, impaired gluconeogenesis, glycogenolysis, mitochondrial respiration, and oxidative phosphorylation,[118] especially in the setting of shock and overdose.[119] Metformin-associated lactic acidosis has been associated with mortality rates $>30\%$,[117,120,121] especially when complicated by multiple organ failure.[122]

Pharmacokinetic studies have demonstrated that metformin is exclusively eliminated by the kidneys.[123] Metformin has a molecular weight of 165 Da, and is highly water soluble. Hemodialysis and CRRT[124–136] have been used successfully in the treatment of metformin-associated lactic acidosis by correcting the acidosis and removing metformin from plasma.[116,118,137]

Another biguanide, phenformin, was withdrawn from the market because it was associated with lactic acidosis in 40 to 64 cases per 100,000 patient years.[121] Severe lactic acidosis was associated with abnormally low systemic O_2 consumption, despite normal or increased O_2 delivery.[138]

Lactic acidosis due to reverse-transcriptase inhibitors is caused by mitochondrial toxicity leading to impaired pyruvate oxidation and increased lactate accumulation.[139] Discontinuation of the causative agent is the mainstay of management. Investigations on the use of riboflavin, thiamine, and L-carnitine in improving mitochondrial function are ongoing.[139–141] Treatment has included intensive supportive therapy with intravenous bicarbonate, ventilator support, and dialysis. Case reports have demonstrated successful treatment of NRTI-induced lactic acidosis with dialysis and CRRT.[142–147]

Summary and conclusions: lactic acidosis

Elevated serum lactate levels are useful for identifying critically ill patients. There are well-documented associations between lactic acidosis and adverse outcomes, but a convincing benefit of bicarbonate infusion therapy has not been demonstrated. Management of lactic acidosis should be geared toward the causative mechanisms. In the setting of AKI, extracorporeal techniques are useful in treating cases of uncontrollable acidemia complicated by multiple organ failure, and assist in the removal of causative toxins such as metformin.

CRRT AND REGIONAL CITRATE ANTICOAGULATION

Regional citrate anticoagulation is increasingly used for CRRT because it can provide effective anticoagulation of the extracorporeal circuit and improve filter patency while minimizing the risk of systemic bleeding.[57,148] However, regional citrate anticoagulation has been associated with significant acid–base derangements including both metabolic alkalosis and metabolic acidosis.

Citrate ($C_6H_7O_7$, molecular weight 191 Da) is a small negatively charged tricarboxylic acid that functions as the first intermediate in the Krebs cycle. It is metabolized to *cis*-aconitate, and then to D-isocitrate and α-ketoglutarate. All three-carbon molecules are liberated as CO_2, which can be converted to bicarbonate, facilitated by carbonic anhydrase. Citrate can also be transported out of the mitochondria into the cytoplasm and broken down to acetyl CoA for fatty-acid synthesis. Mitochondria-rich tissues such as liver, skeletal muscles, and kidney possess a higher capacity for citrate generation and elimination. As the highest pKa of citrate is below physiological pH, citrate predominantly circulates as a trivalent anion. Plasma levels of total citrate are normally low, averaging 0.1 mmol/l, and most of the circulating citrate is complexed with calcium, magnesium, and sodium.[149]

When used as an anticoagulant for CRRT, citrate is infused into the blood at the beginning of the extracorporeal circuit and provides anticoagulation by chelating ionized calcium (iCa^{++}). Optimal regional anticoagulation occurs when the iCa^{++} concentration in the extracorporeal circuit is below 0.35 mmol/l (0.7 mEq/l).[150,151] The majority of the calcium-citrate complex is freely filtered and lost in the effluent; therefore, a systemic calcium infusion is required to correct the ionized calcium and avoid systemic hypocalcemia. The amount of citrate that is delivered to the systemic circulation is determined by the citrate concentration in the

prefilter infusion ('replacement') solution, the ultrafiltration rate, and the relative flow rates of the replacement fluid and the blood flow in the extracorporeal circuit. Any calcium-citrate complex that returns to the patient is potentially metabolized to bicarbonate by the liver, kidney, and skeletal muscle.

Metabolic alkalosis

Metabolic conversion of citrate delivered from the extracorporeal circuit can result in an excessive alkali load. In addition, citrate is used to prepare blood products, and patients receiving large volumes of blood products, as well as those receiving citrate during CRRT, may develop metabolic alkalosis. Metabolic alkalosis can also be magnified by acetate-containing total parenteral nutrition. During CRRT, metabolic alkalosis can be managed by decreasing the infusion rate of citrate or by using a lowered bicarbonate concentration in the dialysate, as well as by careful monitoring of other sources of alkali. Careful attention to the systemic pH is especially important when patients are being weaned from ventilator support; systemic alkalemia suppresses the central drive to respiration and may impair weaning.

Metabolic acidosis

As citrate is metabolized predominantly in the mitochondria in the liver, skeletal muscle, and kidney, citrate metabolism may be compromised in patients with cardiogenic shock with reduced hepatic and muscle blood flow. Similarly, patients with acute liver failure—particularly fulminant hepatic failure—may be unable to adequately metabolize citrate and can become acidotic because of continued bicarbonate and citrate losses into the effluent of the extracorporeal circuit. Citrate toxicity in the setting of liver failure is characterized by low systemic iCa^{++}, elevated total serum calcium, and metabolic acidosis.[152–155] The accumulation of citrate causes systemic iCa^{++} concentration to decrease, whereas the bound fraction of calcium increases. When calcium is infused to correct the low iCa^{++}, most of the calcium binds to citrate, causing a disproportionate rise in total Ca while iCa^{++} remains low. In this situation, the 'calcium gap' (total Ca minus iCa^{++}) or the 'calcium ratio' (total Ca/iCa^{++}) increases. Citrate toxicity is likely when the ratio of total serum calcium to ionized calcium concentration exceeds 2.5 when both total and ionized calcium are measured in mmol/l, or >10 if total calcium is measured in mg/dl. Citrate excess and toxicity can be corrected with a reduction or discontinuation of citrate infusion, increased dialysate flow rate to increase citrate loss across the dialysis membrane when citrate is being infused in the prefilter circuit, and increased calcium infusion to correct decreased ionized calcium concentration.

CONCLUSION

Using the newer understanding of biochemical processes and melding the sometimes paradoxical findings of basic and clinical research, critical care and nephrology specialists have a key collaborative role in the management of critically ill patients. Important and distinct differences have emerged between potential side-effect profiles associated with traditional bicarbonate infusion and the addition of bicarbonate or citrate as bicarbonate equivalents into the extracorporeal circuit during CRRT. Whether these potential advantages will convey clinical benefit needs to be assessed in a prospective controlled multicentric study. At the very least, we emphasize that these new approaches have altered the traditional view of acid–base disorders in the intensive care unit. We propose that these areas must be revisited and that the usual proscriptions against bicarbonate infusion (via a central line) may not be relevant when patients with respiratory acidosis due to low tidal volume respiration, or severe metabolic acidosis and lactacidemia, are receiving CRRT. A similar approach could be developed with peritoneal dialysis[156] when extracorporeal CRRT is not readily available.

When applying newer concepts and technologies in the management of acid–base disorders in the intensive care unit, the challenge resides in the conceptual integration and interpretation of the interactions between basic science, clinical outcomes research, critical care, nephrology, pharmacology, and innovative extracorporeal technologies. These interactions and collaborations make successful management of such severely ill patients a major yet rewarding challenge, especially with the goal of discharging such complex patients with heightened prospects for returning to '*the free and independent life*.'

DISCLOSURE

All the authors declared no competing interests.

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