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# Alkali Therapy in Lactic Acidosis

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## **Alkali Therapy in Lactic Acidosis**

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## Abstract

This report attempts to frame the debate about clinical administration of sodium bicarbonate in the setting of lactic acidosis in terms of simple questions. Specifically, we address why we develop lactic acidosis in some circumstances, how acute lactic acidosis impairs cardiovascular function and why sodium bicarbonate may have deleterious effects which limit its utility. We also attempt to explore treatment alternatives to sodium bicarbonate

## Keywords

lactic acidosis, sodium bicarbonate, carbicarb

## Introduction

The treatment of lactic acidosis remains controversial. Although many in vitro and animal studies were performed over the past 40 years, there is still a dearth of clinical data addressing simple questions such as whether sodium bicarbonate therapy is deleterious or beneficial or whether alternative buffers such as tris (hydroxymethyl)aminomethane (THAM) or a combination of sodium bicarbonate with disodium carbonate (Carbicarb) offer advantages to patients. In this report we will attempt to highlight the key issues that may be useful in the design of subsequent clinical treatments and studies. To this end, we plan to frame and answer some very simple questions.

## Why do we generate lactic acidosis?

The end product of anaerobic glycolysis is pyruvate, which can be metabolized to carbon dioxide by the energy efficient Krebs cycle in the mitochondria. Alternatively, pyruvate can be metabolized by an energy inefficient pathway by the enzyme lactate dehydrogenase to lactate:



Lactic acidosis, one consequence of the shock state is associated with cellular dysfunction and is a predictor of mortality and morbidity.<sup>1-3</sup> Together with diabetic ketoacidosis, it accounts for approximately 85% of the cases of acute severe metabolic acidosis.<sup>4</sup> The major causes of lactic acidosis are typically divided into disorders associated with tissue hypoxia (type A) and disorders in which tissue hypoxia is absent (type B). Cardiogenic or hypovolemic shock, severe heart failure, severe trauma and sepsis are the most common causes of type A lactic acidosis.<sup>5</sup> Normally, approximately 1400 mmol of lactic acid are produced daily, primarily by skeletal muscle and gut. The production of lactic acid is balanced by the metabolism of an equivalent amount of the compound in the liver, which constitutes the Cori cycle. Other tissues including the kidneys are capable of metabolizing lactate as well. In humans, the kidneys contribute approximately 10-20% of lactate removal.<sup>6</sup> On the other hand, tissue hypoxia results in excessive lactate production which can increase under pathological conditions nearly 100 fold.<sup>6</sup>

Lactate removal takes place via its oxidation to pyruvate by lactate dehydrogenase. Pyruvate may be either oxidized to carbon dioxide producing energy or transformed into glucose through



gluconeogenesis. Pyruvate oxidation requires oxygen supply and the cooperation of pyruvate dehydrogenase, the tricarboxylic acid cycle, and the mitochondrial respiratory chain. Congenital or acquired deficiencies in gluconeogenesis including tissue hypoxia may induce lactate accumulation.<sup>7</sup> Impaired mitochondrial oxidative function, as occurs in hypoxic states, leads to accumulation of pyruvate in the cytosol and thus to increased lactate production. The accumulation of pyruvate in the hypoxic state reflects both overproduction of pyruvate and reduced utilization of pyruvate through its two pathways, the oxidative decarboxylation to acetyl-coenzyme A (acetyl-CoA) and gluconeogenesis.<sup>8</sup>

### **Is the development of acidosis a “bad” thing?**

Clearly there are some “good” things about acidosis. On a tissue level, a moderate degree of acidosis allows for greater delivery of oxygen, the shortage of which often underlies the basic pathophysiology of lactic acidosis (see above). Acidosis also appears to decrease the ongoing rate of lactic-acid generation (or ketoacid generation). This negative feedback attenuates the net degree of acidemia.<sup>9</sup>

However, if we examine the effect of acidosis on the heart and the vascular system, one must conclude that it is generally deleterious. In cardiac cells, the drop in intracellular pH is known to have deleterious effects on myocardial contractile function.<sup>9-11</sup> This has been clearly shown in the isolated perfused rat heart.<sup>12</sup> Schotola, et al studied the effect of incremental dose of the beta agonist isoproterenol on human ventricular trabeculae at pH 7.20 and 7.40. They observed a reduction in cardiac contractility and rightward shift of the isoproterenol dose response curve at pH 7.20.<sup>13,14</sup> In intact animals, compensatory mechanisms related to the neuroendocrine response initially maintain cardiac output, but ultimately cardiac output falls with severe acidosis<sup>15,16</sup> as we discuss below.

Several cellular and functional processes have been implicated in the pathogenesis of cardiac contractile dysfunction in severe acidemia. These include impairment of energy production,<sup>15,17</sup> disturbances in intracellular calcium transport and cycling,<sup>18-24</sup> and impairment of actin-myosin cross-bridge cycling by inorganic phosphate (Pi) and H<sup>+</sup> accumulation.<sup>25</sup> In myocardial cells metabolic acidosis results in increased energy demand that exceeds energy production.<sup>15</sup> This discrepancy between demand and production of energy is evidenced by decreases in creatinine phosphate (PCr) and reciprocal increases in inorganic phosphate (Pi) beyond what would be expected from the calculated increases in [H<sup>+</sup>].<sup>16</sup> The decrease in energy production in the isolated perfused heart appears to be the result of inhibition of the mitochondrial oxidative phosphorylation more than direct effects on glycolysis through allosteric effects on phosphofructokinase.<sup>17</sup>

Intracellular pH also has a considerable impact on the amplitude of the systolic calcium transient and subsequent excitation-contraction coupling pathway. The net impact of intracellular acidosis is an increase in the calcium transient amplitude due to increased sarcoplasmic reticulum calcium content which subsequently affects the excitation-contraction coupling pathway. It was also demonstrated that global acidosis or ischemia modifies Ca<sub>i</sub><sup>2+</sup> cycling in myocytes causing a rise

in the diastolic  $Ca_i^{2+}$  and prolongation of the cellular calcium transient characterizing a potential pro-arrhythmic state.<sup>26</sup>

As mentioned earlier, it is apparent that the sympathoadrenal system constitutes an important aspect of the heart's response to acidosis.<sup>27</sup> Increased release of catecholamines in response to the acidic environment from cardiac nerve endings and adrenal medulla was observed but myocardial responsiveness to catecholamines was found to be altered along with markedly enhanced vagal stimulation.<sup>28-32</sup> Mitchell et al demonstrated that in moderate acidosis (pH > 7.2), there is actually an increase in the maximal rate of left ventricular pressure (max dp/dt) and stroke volume related to the increased catecholamine levels, but with severe acidosis, the contractile state of the left ventricle is significantly depressed.<sup>27</sup> Teplinsky and colleagues showed that experimental lactic acidosis caused a 40% reduction in stroke volume without reducing venous return in animals suggesting impaired myocardial contractility.<sup>33</sup> Davies demonstrated that human beta 2-adrenergic receptors were altered in an in vitro model of lactic acidosis accompanied by resistance to the inotropic and vasoconstrictive effects of infused catecholamines.<sup>34</sup> In another study by Kellum and colleagues, moderate and severe acidosis caused hypotension in animals without affecting plasma levels of inflammatory markers.<sup>35</sup> Conduction abnormalities which predispose to ventricular arrhythmias are often found in animal models of metabolic acidosis. This finding can explain the ventricular irritability observed during myocardial ischemia.<sup>36</sup>

### **If acidosis is “bad,” why isn’t the administration of sodium bicarbonate “good?”**

It is very clear that therapy directed to the specific cause of the acidosis is rational. Clinical outcomes are in fact quite good when such intervention effectively normalizes the production of acid as is the case with diabetic ketoacidosis and some cases of toxic alcohol ingestion where the process of organic acid production can be stopped. On the other hand, conditions presenting with type A lactic acidosis and associated circulatory disturbances and tissue hypoxia as in sepsis or cardiac arrest seem to require addressing the acidosis directly. In fact, given the potential deleterious effects of severe acidosis, some experts recommend intravenous sodium bicarbonate therapy although its value in reducing mortality or improving hemodynamics remains unproven.<sup>5</sup>

Questioning the utility of bicarbonate therapy began in the late 1970s with the observation in experimental lactic acidosis that bicarbonate therapy worsened outcomes. In animal models of lactic acidosis, administration of  $NaHCO_3$  increased lactate production by the splanchnic bed.<sup>37</sup> Graf et al<sup>38</sup> compared the effect  $NaHCO_3$  therapy in dogs with hypoxic lactic acidosis with the effects of sodium chloride or no therapy. Treatment with  $NaHCO_3$  was associated with decreases in cardiac output and blood pressure compared with the other two groups. Moreover and despite the infusion of  $NaHCO_3$ , both arterial pH and bicarbonate concentration decreased by a similar amount in all three groups of dogs. This was postulated to result primarily from a paradoxical intracellular acidosis resulting from the rapid equilibrium of  $CO_2$  across the cell membrane and the delayed equilibration of bicarbonate.<sup>39</sup> Other possible adverse effects of sodium bicarbonate therapy include hypertonicity and delayed metabolic alkalosis,<sup>32,40</sup> but the paradoxical intracellular acidosis is probably the most important. Graf and colleagues measured intracellular liver pH with DMO distribution and found bicarbonate actually lowered this value in their

animal model.<sup>38</sup> This has been confirmed using other methods of intracellular pH determination.<sup>12,15,16,41</sup> To fully understand this, we can look at what happens when the bicarbonate buffer system is open vs. closed.

In an open system (i.e., when tissue perfusion and pulmonary ventilation is adequate), CO<sub>2</sub> tension is controlled by the brain stem through respiratory drive and the CO<sub>2</sub> which is generated from oxidative metabolism of carbon containing organic compounds and the dehydration of H<sub>2</sub>CO<sub>3</sub> by carbonic anhydrase (figure 1) is eliminated by the lungs. This has been shown in both experimental animals<sup>42</sup> and humans<sup>43</sup>. Such a system can be modelled experimentally using an instrument called a tonometer where the CO<sub>2</sub> tension can be held constant.<sup>44</sup> However, when tissue perfusion and/or pulmonary ventilation are compromised as occurs during circulatory shock, the clinical scenario more closely approximates a closed system. A simple model for a closed system is a glass syringe with a gas tight rubber stopper.<sup>45</sup>

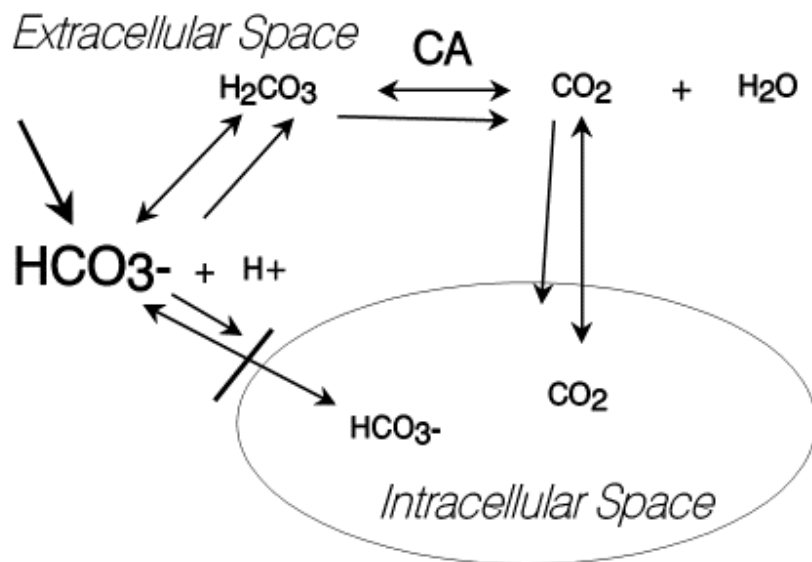


Figure 1

Figure 1: Schematic illustrating effects of sodium bicarbonate (HCO<sub>3</sub><sup>-</sup>) administration into an acidotic milieu. Other abbreviations: H<sup>+</sup> - protons, H<sub>2</sub>CO<sub>3</sub> carbonic acid, CO<sub>2</sub> - carbon dioxide, CA - carbonic anhydrase.

Kimmoun et al<sup>46</sup> investigated the cardiovascular and metabolic effects of an adaptive sodium bicarbonate therapy, including ventilation of CO<sub>2</sub> increase with hyperventilation and ionized calcium decrease with calcium administration. Their strategy normalized extra- and intracellular pH, improved cardiac elastance and improved aortic and mesenteric vasoactivity compared with controls. Small studies have shown promising results when high dose bicarbonate was administered via continuous venovenous hemofiltration to treat acidosis and renal failure.<sup>47,48</sup> The harmful effect of bicarbonate-induced widespread intracellular acidosis on cellular and metabolic function, particularly the heart, suggests that alternative buffers compatible to bicarbonate but without the CO<sub>2</sub> generating potential might offer clinical advantages.

## Alternative Buffers

In an effort to overcome the side effects of sodium bicarbonate, other alkali therapies have been developed. THAM, (tris-hydroxymethyl-aminomethan), dichloroacetate and Carbicarb constitute the most prominent molecules in this context. THAM was first introduced into clinical practice in 1959.<sup>49</sup> 30% of this compound exists in the nonionized form where it can penetrate cells and thereby raise the intracellular pH by buffering protons by virtue of the ammonia moiety.<sup>40</sup> In experimental studies, THAM was found to have a comparable buffering capacity to bicarbonate but without intracellular acidosis.<sup>50</sup> Moreover, THAM was found to have a favorable effect on myocardial contractility when used in dogs with lactic acidosis<sup>51</sup> as well as in perfused isolated heart model during metabolic acidosis<sup>52</sup> (pH=7.0).

Clinical trials assessing THAM in patients with lactic acidosis are limited. Hoste and colleagues showed that administration of THAM to patients in ICU with mild metabolic acidosis was as effective as sodium bicarbonate.<sup>53</sup> Further studies looking at outcome and cardiovascular function are needed to examine the use of THAM in the treatment of acute metabolic acidosis. THAM has considerable side effect profile including hepatic failure and hyperkalemia. Moreover, THAM is excreted by the kidney in its protonated form. Therefore, its usefulness would appear to be limited to acidosis in the presence of significant renal failure.<sup>40</sup>

Dichloroacetate (DCA) is another investigational drug that has been studied in lactic acidosis. DCA exerts multiple effects on pathways of intermediate metabolism resulting in stimulation of peripheral glucose utilization and inhibition of gluconeogenesis.<sup>54</sup> In lactic acidosis, DCA is believed to facilitate the oxidation of lactate by stimulating the activity of pyruvate dehydrogenase. In healthy volunteers during incremental exercise, DCA resulted in the reduction of blood lactate accumulation accompanied by reduction in pulmonary CO<sub>2</sub> output without enhancing exercise tolerance.<sup>55</sup> However, in a randomized controlled trial in patients with lactic acidosis, DCA resulted in statistically significant but clinically unimportant changes in arterial-blood lactate concentrations and pH and fails to alter either hemodynamics or survival.<sup>56</sup> DCA is not currently available in the United States for clinical use.

Carbicarb, a mixture of equimolar quantities of sodium bicarbonate and sodium carbonate was first formulated in 1983 by Filley and Kindig.<sup>57</sup> Sodium carbonate in the mixture reacts with carbonic acid (H<sub>2</sub>CO<sub>3</sub>) to generate bicarbonate via the following reaction.<sup>45,57</sup>



Thus, the carbonate component of Carbicarb consumes CO<sub>2</sub> while the HCO<sub>3</sub><sup>-</sup> component and the newly generated HCO<sub>3</sub><sup>-</sup> will form CO<sub>2</sub> when protons are buffered. At the cellular level, systemic [administration of] Carbicarb to treat severe acidosis resulted in systemic alkalization without major changes in PaCO<sub>2</sub> and intracellular pH in hepatocytes<sup>16</sup>, isolated heart<sup>12,58,59</sup> and brain cells<sup>41</sup> compared with NaHCO<sub>3</sub> therapy which resulted in paradoxical intracellular acidosis. In animals [with lactic acidosis], Carbicarb was found to be superior to NaHCO<sub>3</sub> with improved tissue pH, lactate production and cardiac hemodynamics.<sup>60</sup> In healthy volunteers, Carbicarb was associated with transient decrease in PaCO<sub>2</sub> compared with sodium bicarbonate.<sup>43</sup>

In a study of 36 patients undergoing surgery who developed mild acidosis, Carbicarb was found to be safe and comparable to  $\text{NaHCO}_3$ .<sup>61</sup> Controlled studies of the impact of Carbicarb in patients with severe acidosis have not been reported and the drug is not currently available in the United States.

Carbicarb is an efficient buffer that does not cause intracellular acidosis. It has the potential for treating acute acidosis without impairing cellular and cardiac function. Each molecule of  $\text{CO}_3^{2-}$  will effectively eliminate one hydrogen ion in the blood, thereby directly lowering the proton concentration and raising pH. In addition,  $\text{HCO}_3^-$ , the product of  $\text{CO}_3^{2-}$  buffering is the main component of the sodium bicarbonate solution that is safe in humans and has excellent cellular permeability. On the other hand, Carbicarb can be damaging to the adjacent tissues after injection due to its hypertonic nature and the high level of alkalinity.<sup>62</sup> Moreover, stability problems with the mixture and the proposed delivery syringe have slowed its entry into the clinic. Specifically, the extremely high pH of Carbicarb appears to degrade the rubber stoppers which can safely be used to seal bicarbonate ampules (unpublished observations).

### **Simulations of different combinations of bicarbonate and carbonate:**

As mentioned above, Carbicarb, like THAM, was developed with the aim of avoiding “paradoxical” intracellular acidosis. To examine what changes in  $\text{PaCO}_2$  and pH might be anticipated, we performed the following simulations guided by the observed responses seen with closed and open systems.<sup>45</sup> Specifically, we found in the past that when bicarbonate was added to a closed system, we observed very little change in pH but rather marked increases in  $\text{PaCO}_2$ . In contrast, the addition of carbonate to a closed system resulted in the rapid consumption of  $\text{CO}_2$  as new  $\text{HCO}_3^-$  was generated. Using these principles and the known values for  $\text{CO}_2$  solubility and the equilibrium constant for the  $\text{H}_2\text{CO}_3 - \text{HCO}_3^-$  system, simulations were performed using the programming language Matlab™ (R2014a, the Mathworks, Inc.) using code detailed in Appendix 1.

We first examined the effects of  $\text{NaHCO}_3$  addition in an “open” system where  $\text{PaCO}_2$  was maintained at 40 torr. Bicarbonate caused no changes in  $\text{PaCO}_2$  (by definition, figure 2a) and increase in final pH in proportion to the change in  $\text{HCO}_3^-$  (figure 2b). In such a system, addition of carbonate was twice as potent as bicarbonate as the reaction  $\text{CO}_3^{2-} + \text{CO}_2 \rightarrow 2 \text{HCO}_3^-$  predicted, but no qualitative differences were noted (data not shown). In contrast, when bicarbonate was added to a closed system, increases in  $\text{PaCO}_2$  were seen in proportion to the initial  $[\text{H}^+]$  with essentially no change in pH as we observed in the aforementioned experimental publication<sup>45</sup>, (figures 2c and 2d, respectively). Disodium carbonate however was a very effective alkalinizing agent over a wide range of pH values (figure 3 panel a and b). When we looked at varying the proportion of carbonate to bicarbonate in a mixture, it appeared that  $\text{CO}_2$  neutrality was achieved at relatively low proportions of carbonate, especially when the initial  $\text{PaCO}_2$  was high (figure 4, panels a and b).

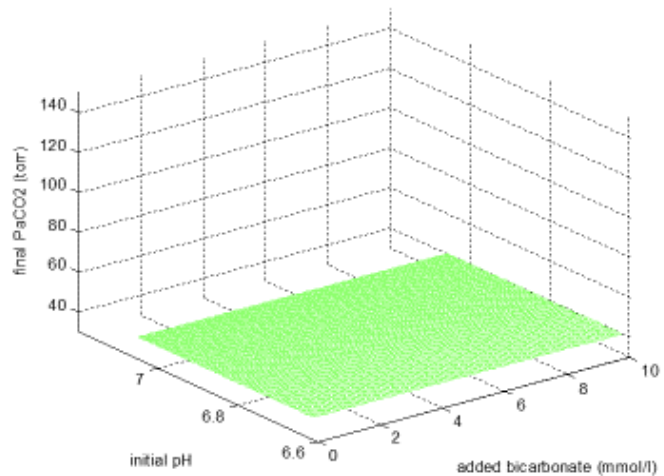


Figure 2a

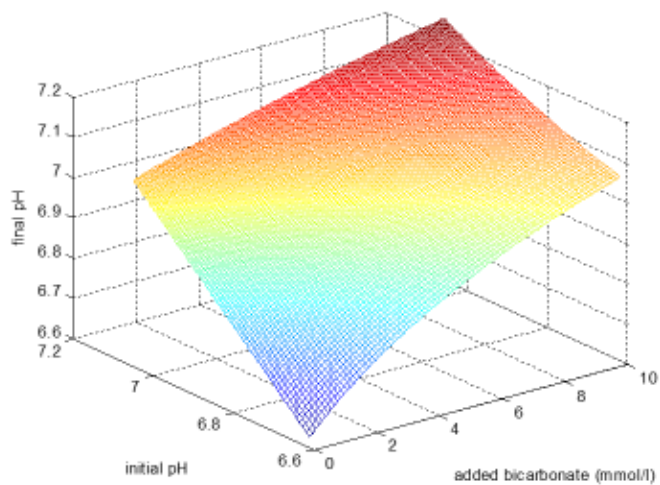


Figure 2b

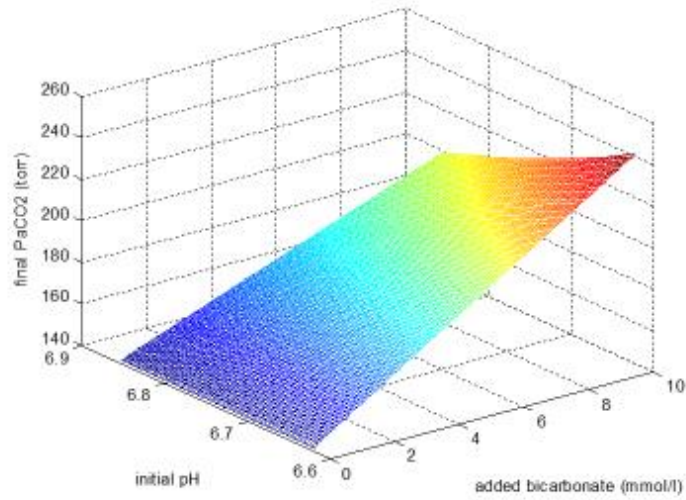


Figure 2c

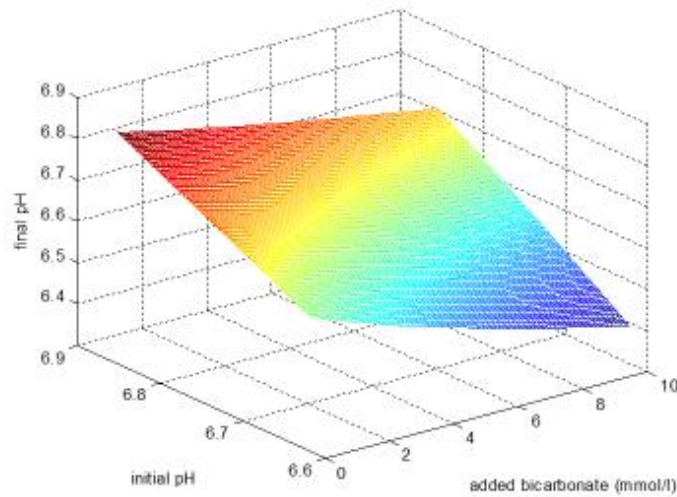


Figure 2d

Figure 2: Simulated changes in PaCO<sub>2</sub> and pH in open and closed system following addition of HCO<sub>3</sub><sup>-</sup> (0 – 10 meq/l) with starting PaCO<sub>2</sub> of 40 torr and initial pH (6.4 to 7.0). Panels 2a and 2b show PaCO<sub>2</sub> and pH (respectively) in open system and Panels 2c and 2d show PaCO<sub>2</sub> and pH (respectively) in closed system.

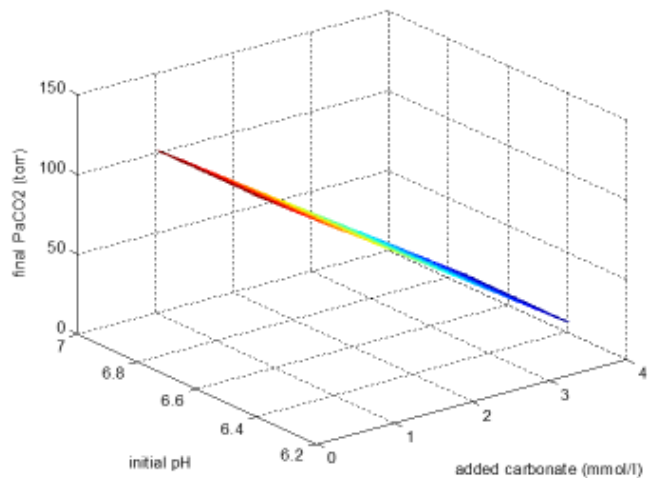


Figure 3a

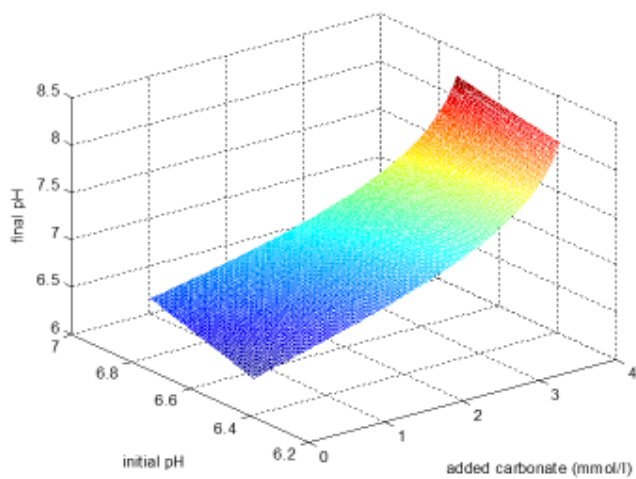


Figure 3b

Figure 3: Simulated changes in PaCO<sub>2</sub> (Panel 3a) and pH (Panel 3b) in a closed system following addition of disodium carbonate (0-4 mmol/l) with initial pH varied between 6.4 and 7 with initial PaCO<sub>2</sub> of 100 torr.



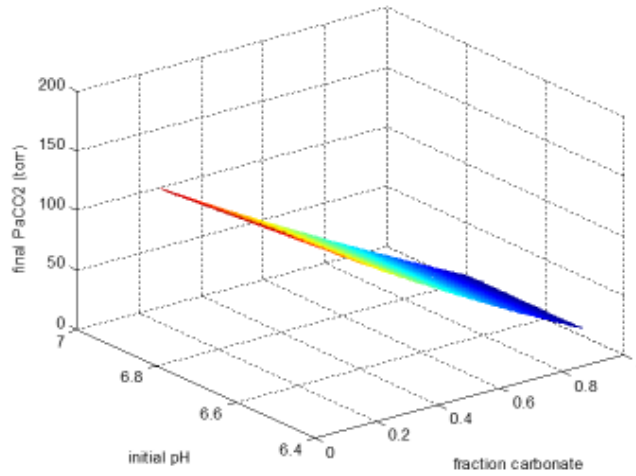


Figure 4a

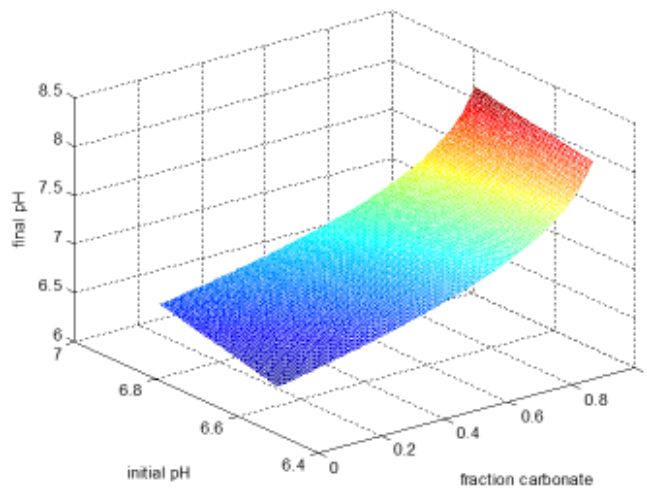


Figure 4b

Figure 4: Simulated changes in PaCO<sub>2</sub> (Panel 4a) and pH (Panel 4b) in a closed system following addition of a mixture of disodium carbonate and sodium bicarbonate (total 2 mmol/l of carbonate + bicarbonate) with initial pH varied between 6.4 and 7 with initial PaCO<sub>2</sub> of 100 torr.

## **Conclusions:**

It is very clear that, while cardiovascular function is embarrassed by acute lactic acidosis, treatment with sodium bicarbonate may have deleterious effects that appear largely related to its propensity to generate CO<sub>2</sub> in a closed system. As there is no accepted methodology for assessing whether the patient's milieu is more closely approximated by a closed or an open system, it is very difficult to advise physicians whether or how to administer sodium bicarbonate in the clinical setting of lactic acidosis. Although some experimental buffers have been developed which appear promising, further clinical proof is necessary before their use can be advocated. Our simulations showed that solutions containing carbonate to bicarb ratios less than 1:1 might be useful in treating lactic acidosis. It needs to be examined if these solutions with different ratios will differ from carbicarb in terms of stability and administration issues.”

## Appendix 1: Matlab™ code

```

%bicarbonate addition simulation open
for i=1:100
    HCO3m(i)=4+i/10;
    aHCO3(i)=i/10;
    pCO20=40;
end
for i=1:100
    for j=1:100
        pH(i,j)=6.1+log10(HCO3m(i)+ aHCO3(j))/1.2;
        pCO2(i,j)=40;
    end
end
mesh(aHCO3,pH(:,1),pH)
axis([0 10 6.6 7.2 6.6 7.2])
xlabel('added bicarbonate (mmol/l)')
ylabel('initial pH')
zlabel('final pH')
figure
mesh(aHCO3,pH(:,1),pCO2)
axis([0 10 6.6 7.2 30 150])
xlabel('added bicarbonate (mmol/l)')
ylabel('initial pH')
zlabel('final PaCO2 (torr)')

%bicarbonate addition simulation open
for i=1:100
    HCO3m(i)=14+i/10;
    aHCO3(i)=i/10;
    pCO20=140;
    pH(i,1)=6.1+log10(HCO3m(i)/(pCO20*0.03));
end
for i=1:100
    for j=1:100
        pCO2(i,j)=((HCO3m(i)+aHCO3(j))*10^-pH(i,1))/(0.03*10^(-6.1));
        pH(i,j)=6.1+log10(HCO3m(i)/(0.03*pCO2(i,j)));
    end
end
mesh(aHCO3,pH(:,1),pH)
%axis([0 10 6.6 7.2 6.6 7.2])
xlabel('added bicarbonate (mmol/l)')
ylabel('initial pH')
zlabel('final pH')
figure
mesh(aHCO3,pH(:,1),pCO2)
%axis([0 10 6.6 7.2 30 150])
xlabel('added bicarbonate (mmol/l)')
ylabel('initial pH')
zlabel('final PaCO2 (torr)')

%carbonate addition simulation closed

```

```

pCO20=140;
keq=1.2/((40e-6)*24);

for i=1:100
    HCO3m(i)=8+i/10;
    CN(i)= i/25;
end
for i=1:100

    for j=1:100
        x=pCO20*0.03;
        a=HCO3m(i)+ 2*CN(j);
        z=6.1+log10(a/x);
        x=x-CN(j);
        z=6.1+log10(a/x);
        x=1000*a*keq*10^-z;
        z=6.1+log10(a/x);
        x=1000*a*keq*10^-z;

        pH(i,j)=z;
        PCO2(i,j)= x/0.03;
    end
end
mesh(CN,pH(:,1),pH)
%axis([0 1.0 6.6 7.2 6.6 8.0])
xlabel('added carbonate (mmol/l)')
ylabel('initial pH')
zlabel('final pH')
figure
mesh(CN,pH(:,1),PCO2)
%axis([0 1.0 6.6 7.2 0 40])
xlabel('added carbonate (mmol/l)')
ylabel('initial pH')
zlabel('final PaCO2 (torr)')

%mixture of carbonate/bicarbonate closed
pCO20=140;
keq=1.2/((40e-6)*24);
d=input('enter dose of bicarbonate/carbonate mixture');

%set up intial bicarb concentrations and fraction of carbonate
for i=1:100
    HCO3m(i)=12+i/10;
    FCN(i)= (i-1)/100;
end

% develop simulations
for i=1:100

    for j=1:100
        % initial H2CO3
        x=pCO20*0.03;

```

```

%reaction of carbonate with CO2 generating new bicarbonate
a=HCO3m(i)+ 2*d*FCN(j);
% new pH
z=6.1+log10(a/x);
% reduction in CO2 tension from carbonate
x=x-2*d*FCN(j);
%new pH
z=6.1+log10(a/x);
%new H2CO3 based on bicarbonate addition
x=1000*a*keq*10^-z;
%new pH
z=6.1+log10(a/x);
%recalculate H2CO3
xx=1000*(a+d*(1-FCN(j)))*keq*10^-z;
%recalculate pH
z=6.1+log10(a/xx);
%enter data into matrices
pH(i,j)=z;
PCO2(i,j)= xx/0.03;
end
end
%plots
mesh(FCN,pH(:,1),pH)
%axis([0 1.0 6.6 7.2 6.6 8.0])
xlabel('fraction carbonate')
ylabel('initial pH')
zlabel('final pH')
figure
mesh(FCN,pH(:,1),PCO2)
%axis([0 1.0 6.6 7.2 0 40])
xlabel('fraction carbonate')
ylabel('initial pH')
zlabel('final PaCO2 (torr)')

```

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