Sodium Bicarbonate in the Treatment of Subtypes of Acute Lactic Acidosis: Physiologic Considerations

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Use of bicarbonate to treat lactic acidosis has recently been challenged. Primarily based on animal models of hypoxic and nonhypoxic lactic acidosis, many current reviews and editorials advocate abandonment of sodium bicarbonate as a buffer, suggesting it to be ineffective in normalizing pH and potentially detrimental through promotion of lactic acid production. Similarly, the American Heart Association now recommends that sodium bicarbonate be used only late in the course of cardiopulmonary resuscitation (CPR), if at all. In sharp contrast, other editorials and reviews vigorously defend use of bicarbonate in the treatment of acute lactic acidosis, questioning the validity or applicability of the experimental studies.

Physicians find themselves in the crossfire of these arguments, uncertain as to whether sodium bicarbonate may help or harm patients with acute lactic acidosis. The purpose of this review is to explore current understanding of the physiology of lactic acidosis and extracellular acid-base disturbances in the presence of abnormal ventilation, perfusion, and oxygenation states. Emphasis will be placed on how each of these states influence the effectiveness of sodium bicarbonate as a buffer in an attempt to arrive at physiologically supportable recommendations for its use.

In this review, lactic acidosis, more appropriately termed lactic acidemia, will be defined as a state where arterial lactic acid concentration exceeds 5 mmol/L and arterial pH is less than or equal to 7.25. Such conditions have been associated with high mortality rates in numerous clinical series. Discussion will focus on type A lactic acidosis which, by convention, denotes conditions where tissue mitochondrial function is intact, but oxygen delivery is inadequate to meet aerobic requirements. Type B lactic acidosis wherein apparently adequate oxygen is supplied, yet acidosis occurs on the basis of abnormal carbohydrate metabolism (phenformin intoxication, hepatic failure, diabetes mellitus, fructose ingestion) will not be specifically considered. This classification of lactic acidosis is somewhat artificial as patients with either type of lactic acidosis may develop simultaneous disruptions of both oxygen and carbohydrate metabolism. Because the pathophysiology of lactic acidosis may in a given patient...
sometimes be cloudy, specific guidelines for treatment may also be difficult to establish.

**Pathophysiology of Lactic Acidosis and the Physiologic Effects of Acidemia**

**Lactate Production and Clearance**

Lactate (lactic acid) production occurs in cytosol and can be described by the reaction:

\[ CH_3-\text{CO}^{-}\text{CO}_2^- + [NADH] + [H^+] \xrightarrow{\text{lactate dehydrogenase}} \text{OH} \]

\[ [CH_3-\text{CH-CH}_2\text{CO}_2^-] + [NAD'] \]  

(1)

Applying the law of mass action, the above relationship may be expressed quantitatively as:

\[ [\text{lactate}] = K \cdot [\text{pyruvate}] \cdot [H^+] \cdot \frac{[\text{NADH}]}{[\text{NAD}^+]} \]  

(2)

where K = rate constant of lactate dehydrogenase, [H+] = cytosolic hydrogen ion concentration, [NADH]/[NAD+] = ratio of the cytosolic concentration of these respective reductive and oxidative compounds.

Examination of equation 2 allows an analysis of factors that increase lactate production. Lactate is the end-product of anaerobic glycolysis which is controlled by three unidirectional enzymes: hexokinase, phosphofructokinase, and pyruvate kinase (Fig. 1). The activity of phosphofructokinase is affected by the cytosolic ATP concent-

**Fig. 1. Simplified Glycolytic Pathway.**

Glycolysis is controlled by three unidirectional enzymes: hexokinase, phosphofructokinase (PFK), and pyruvate kinase. The activity of PFK increases when cytosolic ATP levels and/or hydrogen ion concentration decrease, resulting in increased pyruvate production. Pyruvate may be converted to lactate via lactate dehydrogenase, to acetyl-CoA via pyruvate dehydrogenase, or to oxaloacetate via mitochondrial pyruvate carboxylase. See text for details regarding how these steps are affected by elevated lactate, acidosis, ischemia, and pharmacologic agents.
tration. When ATP levels are decreased, as in ischemia or hypoxemia, the rate of entry of glycolytic intermediates is increased, increasing pyruvate and lactate production.\textsuperscript{24,33,35} An additional effect of decreased oxygen availability is impaired conversion of NADH to NAD\textsuperscript{+} within mitochondria. This results in decreased cytosolic [NAD\textsuperscript{+}] which accelerates lactate production.

From equation 2 one might expect intracellular acidosis to also increase lactate production. Actually, it has been shown that increased intracellular hydrogen ion concentration leads to decreased activity of phosphofructokinase\textsuperscript{24,33,36} which slows the rate of intermediate entry. Thus the development of intracellular acidosis tends to slow lactate production. Conversely, alkalization potentiates lactate production. Metabolic alkalosis induced by bicarbonate administration causes substantial augmentation of exercise-induced hyperlactatemia in humans\textsuperscript{36,37} and increases resting lactate production in patients with congestive heart failure.\textsuperscript{38,39} In the hypoxic rat, respiratory alkalosis accelerates the rate of increase of blood lactate.\textsuperscript{40} Thus, attenuation of intracellular acidosis can accelerate lactate production. As discussed below, elevated lactate levels, especially when coupled with acidosis, may have adverse effects upon cardiovascular function.

Liver and renal cortex are the major sites of lactate clearance.\textsuperscript{17,24,30-32,34} The liver normally metabolizes 50–60\%, and kidneys 30\%, of basal lactate loads.\textsuperscript{17,32,34} Lactate, once converted back to pyruvate, may be used as a substrate for gluconeogenesis (requiring ATP) or may undergo aerobic oxidation to CO\textsubscript{2} and water. As both pathways of lactate use depend on adequate (mitochondrial) oxygenation, it might be expected that impaired hepatic and/or renal perfusion should decrease lactate clearance. Indeed, when either the liver or kidneys are hypoperfused or hypoxic, lactate extraction ceases\textsuperscript{41-43} and, in the case of the liver, lactate production can occur. Importantly, hepatic lactate clearance is also impaired by metabolic or respiratory acidosis.\textsuperscript{52,42,44-47} When lactate exceeds 2 mmol/L, the hepatic membrane lactate transporter becomes saturated, whereupon lactate entry is principally by diffusion. Under these conditions the rate-limiting step in lactate clearance (gluconeogenesis) is the conversion of pyruvate to oxaloacetate. This step, mediated by mitochondrial pyruvate carboxylase, is inhibited by intracellular acidosis and depletion of ATP\textsuperscript{24,34,46,47} (fig. 1).

States of sustained or increasing lactic acidosis are almost always due to a simultaneous increase in production and decrease in clearance of lactic acid. Both abnormalities in production and clearance result from inadequate oxygenation at the cellular (mitochondrial) level. This process can become self-sustaining as worsening acidemia leads to further decreases in hepatic lactate clearance.\textsuperscript{24,34}

**Hemodynamic Effects of Acidosis**

The effect of acidosis upon the function of the cardiovascular system has been extensively studied. Concerns regarding the likelihood of significant interspecies differences and use of variable experimental methodologies and forms of acidosis are partly responsible for lack of consensus as to the hemodynamic consequences of acidosis in humans. In vitro data generally demonstrate that either respiratory or metabolic acidosis below pH 7.1 decreases intrinsic myocardial contractility and responsiveness to catecholamines.\textsuperscript{1,48-54} In contrast, some ex vivo data from anesthetized dogs, cats, and sheep suggest there is little discernible effect on contractility or catecholamine responsiveness above an arterial pH of 6.8–6.9.\textsuperscript{55-57} Nonetheless, the great majority of in vivo and clinical data demonstrate impaired contractility and/or altered responses to exogenous catecholamines with progressive metabolic acidosis.\textsuperscript{2,3,5-9,58,59} Hemodynamic deterioration is usually mild above pH 7.2 due to compensatory increases in sympathetic nervous system activity.\textsuperscript{2,58} Attenuation of sympathetic nervous system responses by β or ganglionic blockade increases the detrimental effect of acidosis.\textsuperscript{2,60,61}

Of great clinical importance, the ischemic or hypoxic myocardium has been found to be particularly vulnerable to detrimental effects of acidosis.\textsuperscript{56,57} Consequently, patients with poor contractile function and/or reduction of myocardial sympathetic responsiveness (e.g., chronic left ventricular failure), those treated with β blockers, or those with myocardial ischemia, are thought particularly vulnerable to the adverse effects of acidosis.

Some evidence suggests that at identical values of extracellular pH, respiratory acidosis produces a greater degree, or more rapid onset of myocardial dysfunction than metabolic acidosis.\textsuperscript{49,50,62} This is believed due to the ability of CO\textsubscript{2} to freely diffuse across cellular membranes and exacerbate intracellular acidosis to a greater extent than extracellular metabolic acids.\textsuperscript{53,61-64} An important observation was made by Ng et al., studying the effect of extracellular acid-base changes upon myocardial performance using an isolated denervated isovolemic left ventricle preparation.\textsuperscript{64} There was consistent reduction in left ventricular systolic pressure (LVSP) when coronary blood pH fell and arterial P\textsubscript{CO\textsubscript{2}} (P\textsubscript{aco\textsubscript{2}}) rose, and an increase in LVSP when pH rose and P\textsubscript{aco\textsubscript{2}} fell. An increase in both pH and P\textsubscript{aco\textsubscript{2}} by the addition of bicarbonate to the perfusing blood caused a marked but temporary reduction in LVSP. The authors concluded extracellular CO\textsubscript{2} rapidly equilibrated with the intracellular space, whereas bicarbonate (or hydrogen ions) did so more slowly. The result was transient acidification of the intracellular space whenever P\textsubscript{aco\textsubscript{2}} increased regardless of extracellular pH. Clancy et al. made similar observations and conclusions, determin-
bicarbonate equilibration across the myocardial membrane was complete by about 10 min. Shapiro et al. have recently confirmed this effect in brain tissue using 31P NMR. Hence, acute elevation of P\textsubscript{CO\textsubscript{2}}, regardless of net extracellular \(p\text{H}\) change, causes intracellular H\textsuperscript{+} to transiently increase until bicarbonate or H\textsuperscript{+} fluxes can catch up. During the period of intracellular acidification organ function can be expected to be depressed. States of intracellular acidosis, particularly when involving heart or liver will accelerate development of lactic acidosis by exaggerating decreases in tissue oxygen delivery and lactate clearance.

Some data indicate elevated blood lactate may have negative inotropic effects independent of \(p\text{H}\). Furthermore, if lactate cannot be metabolized due to decreased oxygen availability, increased intracellular lactate levels suppress the activity of glycolytic enzymes (fig. 1). This inhibits aerobic glycolysis and so robs the myocardium of its only remaining mode of ATP production. A third mechanism of lactate-induced myocardial dysfunction involves altered adrenergic responsiveness. In an \textit{in vitro} model of lactic acidosis, \(\beta\)-adrenergic receptors were rapidly desensitized and uncoupled. Both excess lactate (16 mmol/l) and low \(p\text{H}\) (7.1) were required for full expression of the defects. Thus, particularly in the presence of acidosis, elevated lactate levels may impair myocardial performance.

Extracellular Acid-Base Dynamics and Carbon Dioxide Metabolism

The Bicarbonate Buffer System

The dynamics of the bicarbonate/carbon dioxide buffer system can be described by the Henderson-Hasselbalch equation:

\[
pH = pK' + \log \left( \frac{[HCO_3^-]}{\Omega \cdot P_{CO_2}} \right)
\]

where \(pK' = 6.1\) at 37\textdegree C, \(\Omega\) = solubility coefficient of CO\textsubscript{2} in plasma = 0.03 mmol\cdot l\textsuperscript{-1}\cdot mmHg\textsuperscript{-1} (37\textdegree C), \(P_{CO_2}\) = partial pressure of carbon dioxide in the system (mmHg), \(HCO_3^-\) = serum bicarbonate concentration (mmol/l).

The key concept in equation 3 is that \(p\text{H}\) is not related to the absolute value of either bicarbonate concentration nor \(P_{CO_2}\), but rather to their ratio.

When exogenous bicarbonate is administered during acidemia, bicarbonate reacts with hydrogen ions to form carbonic acid. Physicochemical equilibrium is shifted, favoring dissociation of carbonic acid to CO\textsubscript{2} and water. CO\textsubscript{2} partial pressure increases. The degree of alkalinization resulting from increased \([HCO_3^-]\) is limited by the rise in P\textsubscript{CO2}. In (open) systems where increases in P\textsubscript{CO2} are prevented (by ventilation) alkalinization occurs. When CO\textsubscript{2} cannot be eliminated, the \(p\text{H}\) of the system is only minimally changed. Ostrea and Odel demonstrated \textit{in vitro} that when isotonic sodium bicarbonate was added to whole blood in a (closed) system where generated CO\textsubscript{2} could not escape, P\textsubscript{CO2} increased and \(p\text{H}\) was unchanged. Only when CO\textsubscript{2} was eliminated was the system alkalinized.

Similarly, Steichen and Kleinman noted in hypoxic acidotic dogs that administration of 2 mEq/kg of sodium bicarbonate over 3 min when ventilation was unchanged resulted in no net change in arterial \(p\text{H}\), although P\textsubscript{CO2} rose from 46 to 61 mmHg. If CO\textsubscript{2} elimination cannot keep pace with increased CO\textsubscript{2} generation, administration of bicarbonate during acidemia produces hypercarbia (respiratory acidosis) with little net improvement in \(p\text{H}\).

Clearance of Carbon Dioxide from Tissues

Carbon dioxide elimination depends upon uptake at the tissue level and subsequent delivery to and clearance from the alveolus. The amount of CO\textsubscript{2} delivered to the pulmonary capillary bed is the product of pulmonary arterial blood flow (cardiac output) and the CO\textsubscript{2} content of mixed venous blood. The amount of CO\textsubscript{2} delivered to the pulmonary capillary bed must also be the sum of whole body CO\textsubscript{2} production and CO\textsubscript{2} delivered to the tissue in arterial blood. Thus:

\[
\text{cardiac output} \times \text{mixed venous CO}_2 \text{ content (ml/l)} = \text{net CO}_2 + \text{cardiac} \times \text{arterial CO}_2 \text{ content (ml/l)}
\]

It follows that:

\[
\text{mixed venous CO}_2 \text{ content} = \frac{\text{net CO}_2 \text{ production}}{\text{cardiac output}} + \text{arterial CO}_2 \text{ content}
\]

As blood carbon dioxide content is proportional to its partial pressure, equation 5 can be approximated by:

\[
P_{VCO_2} \propto \frac{\text{net (whole body) CO}_2 \text{ production}}{\text{cardiac output}} + P_{A CO_2}
\]

where \(P_{VCO_2}\) = partial pressure of CO\textsubscript{2} in mixed venous blood.

From equation 6 it can be concluded: 1) If net CO\textsubscript{2} production and P\textsubscript{A CO2} remain constant, as cardiac output decreases, P\textsubscript{V CO2} must rise and become progressively less dependent on P\textsubscript{A CO2} (sample calculations are shown in table 1); and 2) If cardiac output and P\textsubscript{A CO2} remain
TABLE 1. Calculated Carbon Dioxide Content and Mixed Venous Carbon Dioxide Partial Pressure as a Function of Cardiac Output at Constant Tissue Carbon Dioxide Production and Arterial Carbon Dioxide Partial Pressure in an Average Adult*  

<table>
<thead>
<tr>
<th>Cardiac Output (l/min)</th>
<th>Arterial CO₂ (mL/l)</th>
<th>Tissue CO₂ Production (mL/min)</th>
<th>Venous CO₂ Content (mL/l)</th>
<th>P&lt;sub&gt;CO₂&lt;/sub&gt; (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>40</td>
<td>494</td>
<td>180</td>
<td>530</td>
</tr>
<tr>
<td>3.75</td>
<td>40</td>
<td>494</td>
<td>180</td>
<td>542</td>
</tr>
<tr>
<td>2.5</td>
<td>40</td>
<td>494</td>
<td>180</td>
<td>566</td>
</tr>
<tr>
<td>1.25</td>
<td>40</td>
<td>494</td>
<td>180</td>
<td>638</td>
</tr>
</tbody>
</table>

* Calculations are for a 70-kg adult (body surface area = 1.7 m²), with standard values of CO₂ production (180 mL/min) and cardiac index (3.1 m²·min⁻¹) using equation 5, and standard CO₂ dissociation curves, correcting for the Haldane effect. P<sub>CO₂</sub> = arterial carbon dioxide partial pressure. P<sub>VO₂</sub> = mixed venous carbon dioxide partial pressure. As cardiac output decreases, P<sub>VO₂</sub> increases.

The constant, increases in net CO₂ production result in increased P<sub>VO₂</sub>.

Equation 6 can also be applied to individual organs:

\[
\text{organ venous } P_{CO₂} = \frac{\text{organ CO₂ production}}{\text{organ perfusion}} + P_{CO₂}
\]  

(7)

Equation 7 shows CO₂ clearance from tissue beds to depend on perfusion. High levels of perfusion relative to CO₂ production result in tissue and venous P<sub>CO₂</sub> approximating the arterial level. If organ perfusion decreases, CO₂ is not cleared as rapidly. Tissue P<sub>CO₂</sub> levels rise, producing an intracellular respiratory acidosis, reflected by an elevated venous P<sub>CO₂</sub>. Hence as individual organ and/or whole body perfusion decreases, tissue (intracellular) respiratory acidosis occurs, reflected by progressive elevations of tissue venous and mixed venous P<sub>CO₂</sub>, respectively. CPR, a state of severe hypoperfusion where "cardiac output" is 20–25% of normal is associated with severe mixed venous respiratory acidosis. The calculations in table 1 are in close agreement with the observations of Weil et al. who measured an average P<sub>VO₂</sub> of 74 mmHg during CPR in humans.

CLEARANCE OF CARBON DIOXIDE FROM THE ALVEOLUS

Whole body CO₂ clearance is achieved via alveolar ventilation. In abnormal ventilation/perfusion states as net alveolar gas exchange efficiency is decreased, less of the total tidal volume (V<sub>T</sub>) appears involved in CO₂ exchange. That fraction of the V<sub>T</sub> not involved in gas exchange is the physiologic dead space (V<sub>D</sub>). The physiologic dead space to tidal volume ratio (V<sub>D</sub>/V<sub>T</sub>) is a measure of efficiency of CO₂ elimination. Normal V<sub>D</sub>/V<sub>T</sub> in humans is equal to 0.3. In dogs, as cardiac output decreases V<sub>D</sub>/V<sub>T</sub> increases. Similarly, patients with chronic low output congestive heart failure (cardiac index ≤ 2.0 l·m⁻²·min⁻¹, left ventricular ejection fraction ≤ 0.22) have been found to have considerably elevated V<sub>D</sub>/V<sub>T</sub> ratios (V<sub>D</sub>/V<sub>T</sub> = 0.52). As V<sub>D</sub>/V<sub>T</sub> increases, total ventilation must increase greatly if CO₂ elimination is to equal its production (table 2).

Pulmonary CO₂ elimination efficiency will worsen under conditions of increased alveolar pressures (e.g., positive pressure ventilation) and/or either increased (e.g., acute pulmonary hypertension and right ventricular failure) or decreased pulmonary arterial pressures (e.g., hypotension, hypovolemia). Such conditions create alveoli that are ventilated but not perfused (zone 1 of West), resulting in further increases in net V<sub>D</sub>/V<sub>T</sub>. If total ventilation cannot be increased to compensate for an elevated V<sub>D</sub>/V<sub>T</sub> arterial respiratory acidosis occurs. This will result in an increase in any preexisting tissue (intracellular) respiratory acidosis (see equations 6 and 7).

CARBON DIOXIDE PRODUCTION FROM BICARBONATE ADMINISTRATION

Several studies indicate that, at least acutely, approximately 10–15% of administered bicarbonate is immediately converted to CO₂. If 1 mEq/kg of bicarbonate is given to a 70-kg person, then 7–10 mmol of CO₂ will be generated. Assuming CO₂ to be an ideal gas, 7–10 mmol of CO₂ will occupy 150–200 ml in the gas phase. As normal resting CO₂ production is equal to 180 ml/min in an average adult, administration of 1 mEq/kg of bicarbonate will produce the rough equivalent of 1 min worth of carbon dioxide. If given over 1 min, ventilation must double (4.9–9.5 l/min) to avoid elevation of P<sub>CO₂</sub>. Required increases in ventilation will be less if sodium bicarbonate is given over a longer period of time. As shown in table 3, under conditions of increased V<sub>D</sub>/V<sub>T</sub> even greater increases in total ventilation are required for CO₂ elimination to equal production (i.e., P<sub>CO₂</sub> to remain normal) when CO₂ production is increased. If

TABLE 2. Calculated Ventilatory Requirements to Maintain P<sub>CO₂</sub> Equal to 40 mmHg in an Average Adult*  

<table>
<thead>
<tr>
<th>Dead Space/Tidal Volume Ratio (V&lt;sub&gt;D&lt;/sub&gt;/V&lt;sub&gt;T&lt;/sub&gt;)</th>
<th>Total Ventilation (l/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 (normal)</td>
<td>4.9 (normal)</td>
</tr>
<tr>
<td>0.4</td>
<td>5.7 (1.2 × normal)</td>
</tr>
<tr>
<td>0.5</td>
<td>6.8 (1.4 × normal)</td>
</tr>
<tr>
<td>0.6</td>
<td>8.6 (1.7 × normal)</td>
</tr>
<tr>
<td>0.7</td>
<td>11.4 (2.3 × normal)</td>
</tr>
</tbody>
</table>

* Calculations are for a 70-kg adult with standard values of CO₂ production (180 mL/min) and dead space to tidal volume ratio (0.3). Effective alveolar ventilation must equal 3.4 l/min in order to maintain P<sub>CO₂</sub> equal to 40 mmHg at this rate of CO₂ production. Total ventilation includes dead space and alveolar ventilation. As V<sub>D</sub>/V<sub>T</sub> increases total ventilation must increase in order to maintain arterial normocarbia.
TABLE 3. Calculated Ventilatory Requirements and Mixed Venous CO\textsubscript{2} Tension at Varies V\textsubscript{D}/V\textsubscript{T} Ratio, Cardiac Output, and Rates of CO\textsubscript{2} Production* 

<table>
<thead>
<tr>
<th>Total CO\textsubscript{2} Production (mL/min)</th>
<th>Total Ventilation (liters/min) to Achieve P\textsubscript{a\textsubscript{CO}2} Equal to 40 mmHg at V\textsubscript{D}/V\textsubscript{T}</th>
<th>P\textsubscript{a\textsubscript{CO}2} (mmHg) at P\textsubscript{a\textsubscript{CO}2} Equal to 40 mmHg at Varies Percent of Normal Cardiac Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>0.3</td>
<td>0.4 0.5 0.6 0.7 100 75 50 25</td>
</tr>
<tr>
<td>350</td>
<td>4.9</td>
<td>5.7 6.8 8.6 11.4 43 45 51 73</td>
</tr>
<tr>
<td>1 mEq/kg sodium bicarbonate/min</td>
<td>9.5</td>
<td>11.1 13.3 16.6 22.2 50 54 68 120</td>
</tr>
<tr>
<td>265</td>
<td>7.2</td>
<td>8.4 10.1 12.6 16.8 46 50 58 100</td>
</tr>
<tr>
<td>1 mEq/kg/2 min</td>
<td>6.4</td>
<td>7.5 9 11.3 19 45 49 55 88</td>
</tr>
<tr>
<td>237</td>
<td>6.4</td>
<td>7.5 9 11.3 19 45 49 55 88</td>
</tr>
<tr>
<td>1 mEq/kg/4 min</td>
<td>6</td>
<td>7 8.4 10.5 14.1 44 47 53 85</td>
</tr>
<tr>
<td>222</td>
<td>6</td>
<td>7 8.4 10.5 14.1 44 47 53 85</td>
</tr>
<tr>
<td>1 mEq/kg/5 min</td>
<td>5.8</td>
<td>6.8 8.1 10.2 13.6 44 47 52 85</td>
</tr>
</tbody>
</table>

* Calculations are for a 70-kg adult (body surface area = 1.7 m\textsuperscript{2}) with standard values of CO\textsubscript{2} production (180 mL/min)\textsuperscript{96} and cardiac index (3.1 m\textsuperscript{3} min\textsuperscript{-1})\textsuperscript{70} using equation 5 and standard CO\textsubscript{2} dissociation curves,\textsuperscript{75-76} correcting for the Haldane effect. One milliequivalent per kilogram sodium bicarbonate will produce approximately 170 mL of CO\textsubscript{2}. Total carbon dioxide production is the sum of tissue CO\textsubscript{2} production and that produced by bicarbonate administration. As total CO\textsubscript{2} production and/or V\textsubscript{D}/V\textsubscript{T} increases, total ventilation must increase to maintain P\textsubscript{a\textsubscript{CO}2} equal to 40 mmHg. As cardiac index decreases and/or CO\textsubscript{2} production increases, P\textsubscript{a\textsubscript{CO}2} increases.

these requirements cannot be met, arterial respiratory acidosis will occur.

Even if P\textsubscript{a\textsubscript{CO}2} is maintained at normal levels, increased CO\textsubscript{2} production results in mixed venous hypercapnia, the severity of which increases as cardiac output decreases (equation 6 and table 3). In low cardiac output states, P\textsubscript{v\textsubscript{CO}2} is enormously increased during rapid bicarbonate administration.\textsuperscript{95,96} The calculations in table 3 are in extremely close agreement with the findings of Falk et al.\textsuperscript{95} and Guerci et al.\textsuperscript{98} who noted a P\textsubscript{v\textsubscript{CO}2} of 110–130 mmHg after rapid bicarbonate administration during CPR. Inspection of table 3 suggests, however, that if bicarbonate is given slowly, and the cardiac index is greater than or equal to 50% of normal (1.5 m\textsuperscript{3} min\textsuperscript{-1}) mixed venous hypercapnia can be minimized.

Equation 3 shows mixed venous pH does not depend solely upon P\textsubscript{v\textsubscript{CO}2}, but upon [HCO\textsubscript{3}\textsuperscript{-}] as well. Despite elevation of P\textsubscript{v\textsubscript{CO}2}, mixed venous pH cannot be made more acidic by the addition of alkali, simply because lactic acid is stronger than carbonic acid and protons will always be buffered by bicarbonate in these circumstances. It is also important to appreciate that elevation of P\textsubscript{CO}2 in the central veins resulting from bicarbonate administration does not reflect, nor necessarily create, an elevation of P\textsubscript{CO}2 at the tissue (intracellular) level. As shown by equation 7 tissue CO\textsubscript{2} tension depends on arterial, not venous P\textsubscript{CO}2. The physiologic significance of an acute elevation P\textsubscript{v\textsubscript{CO}2} in the face of an unchanged arterial and tissue P\textsubscript{CO}2 is currently unknown.

**Models of Acute Lactic Acidosis**

Employing the physiologic principles discussed above, type A lactic acidosis (i.e., due to inadequate tissue oxygen supply) can be considered the result of three different pathophysiologic states, each having a different response to bicarbonate administration: 1) Tissue hypoxia resulting from a low flow state despite adequate arterial oxygen content (clinical correlate: CPR). 2) Tissue hypoxia secondary to low arterial oxygen content despite increased perfusion (clinical correlate: hypoxemia). 3) Tissue hypoxia due to inadequate but potentially remediable cardiac output with adequate arterial oxygen content (clinical correlate: myocardial dysfunction due to ischemia, failure, or acidosis).

**CARDIOPULMONARY RESUSCITATION**

During CPR, endotracheal intubation and ventilation with 100% oxygen will often provide near maximal arterial oxygen content.\textsuperscript{78,97-99} However, systemic perfusion is extremely low (20–25% of normal)\textsuperscript{75,77} and is inadequate to meet tissue oxygen delivery requirements despite maximal tissue oxygen extraction.\textsuperscript{76,90} The resulting lactic acidosis during CPR is often severe.\textsuperscript{78,97} Systemic perfusion ("cardiac output") in this setting is dependent neither on inotropic state nor pH but rather on the mechanics of CPR and, in practice, cannot be substantially improved.

During CPR the efficiency of pulmonary CO\textsubscript{2} elimination is markedly impaired due to low pulmonary blood flow and high alveolar pressures. Based on the difference between end-tidal and P\textsubscript{a\textsubscript{CO}2}, V\textsubscript{D}/V\textsubscript{T} during CPR appears to be approximately 0.6–0.7.\textsuperscript{95,100-104} Unless ventilation is increased 1.5–2 times, normal arterial hypercapnia will result. Even if P\textsubscript{a\textsubscript{CO}2} is maintained at normal levels, due to the low flow state, P\textsubscript{v\textsubscript{CO}2} will be markedly elevated, reflecting poor clearance of CO\textsubscript{2} from the tissue beds and tissue respiratory acidosis. This results in a major dispar-
ity between arterial and mixed venous CO₂ tensions, PₐCO₂ not reflecting the status of the tissues (table 3). During CPR administration of bicarbonate cannot improve systemic perfusion or tissue oxygen delivery. Due to CO₂ which it generates, and the inefficiency of alveolar ventilation, bicarbonate has significant potential to elevate PₐCO₂, exacerbating respiratory acidosis at the tissue level. Depending on V_D/V_T and the rate of administration (table 3), ventilation must increase by yet another factor of 2–4 to avoid elevations of PₐCO₂, if bicarbonate is to be given.

A critical question is whether bicarbonate administration can improve tissue (intracellular) pH and/or increase the likelihood of defibrillation during CPR. One can apply the relationships in equation 7 to hydrogen ions in general:

\[
\text{venous } [H^+] \propto \frac{\text{tissue } H^+ \text{ production}}{\text{tissue perfusion}} + \text{arterial } [H^+] \quad (8)
\]

Equation 8 implies tissue (intracellular) hydrogen ion concentration (pH), as reflected by venous pH, will depend upon the ratio of tissue pH production to perfusion. In states of decreased perfusion, tissue pH will become progressively less affected by arterial pH and more affected by the rate of H⁺ production. Any improvement in arterial pH due to bicarbonate administration will have less than a normal effect upon tissue pH in low flow states. As a consequence, although the intravascular space may be rapidly alkalized by bicarbonate administration, it is unclear how rapidly the remaining extra- and intracellular spaces may be alkalized.

In two experimental studies of defibrillation, neither respiratory nor metabolic acidosis affected defibrillation threshold. Similarly, Niemann et al. found arterial pH to have no relation to success of defibrillation during CPR, although central venous pH did. One may conclude that tissue acid-base state is not reflected nor affected by arterial pH during CPR.

During CPR one can expect very limited benefit from use of bicarbonate, although exacerbation of tissue (intracellular) acidosis by arterial hypercapnia is a very real possibility. Even if arterial respiratory acidosis is avoided, as shown in table 3, administration of bicarbonate will elevate PₐCO₂ to very high levels. Although such elevations have been associated with decreased survival in one model of CPR, whether this is cause or effect cannot currently be determined. During CPR, acid-base management is probably optimized by achieving best possible systemic perfusion through good CPR technique and ventilating with 100% oxygen, maximizing tissue oxygen delivery. Wiklund et al. have shown improved pulmonary CO₂ elimination and subsequent increased rates of survival when epinephrine was used in experimental CPR. Presumably, epinephrine administration during CPR (as recommended by the American Heart Association) increases pulmonary perfusion pressure, decreases V_D/V_T, and improves CO₂ clearance.

**Hypoxemia**

The model of hypoxemic lactic acidosis developed by Arieff et al. which has been influential in discouraging the use of bicarbonate, will be reviewed. Dogs were ventilated with 8% oxygen to produce P_aO₂ of 25–50 mmHg. This resulted in progressive lactic acidosis with P_H₄ near 7.15, arterial lactate 7–8 mmol/l, and cardiac index 150% of control. Ventilation was unchanged throughout the experiment at a level that initially produced PₐCO₂ of 36 ± 6 mmHg. Hepatic intracellular pH and lactate extraction were markedly reduced from normal controls. Under these conditions animals received either no treatment or 1 M sodium bicarbonate or 1 M sodium chloride at 2.5 mmol·kg⁻¹·h⁻¹ for 60 min. At 60 min there was no difference in arterial pH (7.06) or P_aO₂ between groups, although animals treated with bicarbonate had higher arterial and hepatic lactate levels, and lower cardiac output, mean arterial pressure, hepatic vein flow, and hepatic intracellular pH than animals treated with hypertonic saline. In the bicarbonate group elevations in PₐCO₂ and hepatic portal vein PₐCO₂ (55 ± 16 mmHg) were associated with progressive decreases in hepatic intracellular pH, hepatic blood flow, and diminished lactate clearance. Elevated lactate levels (12.6 mmol/l) in the face of progressive acidosis (P_H₄ 7.06) were associated with decreased cardiac output despite unchanged loading conditions. Thus, bicarbonate appeared to accelerate the rate of lactate accumulation and consequent hemodynamic deterioration.

In this model of hypoxemic lactic acidosis, arterial oxygen content was reduced from 18.9 to 6.6 ml/dl. The only mechanism whereby tissue oxygen requirements could be met was by increased blood flow or cardiac output. Increased cardiac output in turn increases myocardial oxygen demand, which must be satisfied by increased coronary blood flow. If coronary flow cannot be sufficiently enhanced (e.g., coronary atherosclerosis) or if maximally increased coronary flow does not satisfy myocardial oxygen demand due to low arterial oxygen content (e.g., anemia or hypoxemia), cardiac output will be less than normoxic maximal. Thus, in the face of decreased arterial oxygen content, the upper limit of cardiac output may be limited by available coronary arterial oxygen supply and/or coronary arterial vasodilatory reserve to the point that net tissue oxygen delivery is inadequate. In these experiments, the maximum increase in cardiac output was only 130% of control, achieving an average total oxygen delivery of 8 ± 1 ml of O₂·kg⁻¹·min⁻¹. This is below
the threshold of minimum tissue oxygen delivery requirements in anesthetized dogs (10 ml·kg\(^{-1}\)·min\(^{-1}\)).\(^{111}\) Thus, in this model it was impossible for the heart to increase its output sufficiently to meet systemic oxygen requirements and avoid progressive lactic acidosis, regardless of pH.

Bicarbonate administration resulted in venous hypercarbia most marked in the portal system. Hepatic pH decreased, leading to an impairment of hepatic lactate clearance and acceleration of the rate of rise of lactate. Hyperlactataemia, acidemia, and hypoxemia lead to a deterioration in contractile state and cardiac output. Importantly, the authors noted a correlation with \(pH_a\) and cardiac output, such that when \(pH_a\) was normalized so too was cardiac output.\(^{13}\) However, because lactic acidosis was unavoidable in this model as acidemia recurred, cardiac output fell.

In practice, if lactic acidosis occurs solely on the basis of hypoxemia, and the heart and sympathetic nervous system are otherwise intact, a \(pH_a\) of 7.1–7.2 should not greatly compromise myocardial performance. As Arieff \textit{et al.} have shown,\(^{13}\) if \(pH_a\) drops below this level, particularly if lactate levels are elevated or there is pre-existing myocardial dysfunction, the globally hypoxic heart will become unresponsive to the high levels of catecholamines that have supported its function,\(^{56,57}\) and deterioration of myocardial performance may be abrupt. In such cases, administration of bicarbonate to raise \(pH_a\) to greater than or equal to 7.2 may be necessary in an attempt to maintain hemodynamic stability.\(^{57}\) In so doing several considerations must be kept in mind. 1) Bicarbonate dosage calculations (mEq/kg) based upon calculated extracellular base deficits (mEq/l) which assume base deficits to be limited to the extracellular space (~0.2 l/kg) underestimate total body deficits.\(^{92}\) Nevertheless, this calculated dose is likely excessive as initial therapy. The clinical objective is not complete normalization of intra-and extracellular pH, but rather, re-establishment of a pH allowing maximal cardiovascular function. Accordingly, an appropriate starting dose is probably one-third to one-half of the calculated dose with supplements given based upon serial changes in \(pH\) and cardiovascular function. 2) Bicarbonate should be administered slowly so as to minimize any increase in \(PCO_2\) which, although probably correlating poorly with hepatic \(PCO_2\), may serve as a guide in an attempt to avoid any further decrease in portal vein and hepatic \(pH\) and lactate clearance. 3) Minute ventilation must increase appropriately so as to eliminate generated \(CO_2\) and avoid arterial respiratory acidosis, which would be expected to (at least transiently) adversely effect myocardial performance.\(^{61,64,65}\) 4) As discussed earlier, in the face of a continued stimulus for lactate production (i.e., hypoxemia), attenuation of acidosis may accelerate lactate production. Very high lactate levels may have independent adverse effects upon the hypoxic myocardium and/or impair adrenergic responsiveness.\(^{1,2,4,66}\) Bicarbonate administration is a temporizing measure but may allow time for interventions to improve oxygenation.

**LOW OUTPUT STATE**

A common clinical circumstance is that in which arterial oxygen content is near maximal, but cardiac output is insufficient to deliver adequate oxygen to the periphery. Lactic acidosis that develops in this case is the result of both increased production and decreased clearance of lactate. The therapeutic goal, to improve cardiac output, can at times be achieved by optimization of cardiac rate, rhythm, and ventricular loading conditions. If these attempts are inadequate, improvement in inotropic state may be required via the use of exogenous catecholamines. Because the presence of acidemia (\(pH \leq 7.2\)) can impair and/or alter catecholamine responses, particularly in states of myocardial hypoxia, normalization of extracellular \(pH\) may be required.

As of yet there are no controlled clinical data nor appropriate experimental models from which one may establish either the appropriate starting dose and rate of administration of bicarbonate, nor whether or not bicarbonate is effective in this situation. Furthermore, what constitutes “adequate” blood pressure and cardiac output and at what \(pH\) it may be achieved, if at all, will vary among patients and clinical circumstances. These difficulties notwithstanding, if bicarbonate is to be given, the traditional starting dose of one-third to one-half of the calculated extracellular bicarbonate deficit would seem a reasonable starting point. The following considerations must be kept in mind. 1) If pump failure is the result of myocardial ischemia, regional myocardial \(PCO_2\) will be elevated due to impaired clearance of acid metabolites and \(CO_2\), and the buffering of metabolic acids with \(HCO_3^-\).\(^{112-114}\) Elevation of tissue \(CO_2\) is thought to reflect and contribute to myocardial intracellular acidosis.\(^{62,114}\) Any increase in \(P_{aCO_2}\) would be expected to worsen myocardial \(pH\) (equation 8) and performance,\(^{61,64}\) particularly so in the regions of ischemia. Thus, as repeatedly stressed in this review, ventilation must increase appropriate to the rate of bicarbonate administration so as to avoid even transient increases in \(P_{aCO_2}\). 2) The required increase in ventilation may be marked due to an increase in \(V_D/V_T\) which occurs in low cardiac output states.\(^{84-86}\) Although a spontaneously ventilating patient may be able to increase his/her total ventilation to compensate for an increased \(V_D/V_T\), increased \(CO_2\) production associated with bicarbonate administration may exceed the patient’s ventilatory ability.\(^{58,86,115}\) Thus, in some cases bicarbonate could precipitate ventilatory failure. In the intubated patient, end-tidal \(CO_2\) can be continuously measured and ventilation
increased during bicarbonate administration in an attempt to avoid hypercarbia. However, in states of increased \( V_{D}/V_T \) end-tidal \( CO_2 \) will underestimate alveolar and arterial \( P_{CO_2} \). 116 Thus although useful in detecting trends, end-tidal \( CO_2 \) monitoring cannot substitute for blood gas analysis. 3) Attempts to achieve a \( pH_a \) of 7.4 may be unnecessary and, in fact, undesirable. When charged intermediate metabolites such as lactate are converted to uncharged substances (e.g., glucose or \( CO_2 \) and water), protons are taken up. 34 With restoration of adequate systemic oxygen delivery improvements in lactate production and clearance lead to spontaneous resolution of acidemia. If a near normal \( pH \) is achieved before lactate clearance is complete, subsequent lactate metabolism may result in an alkaline \( pH \), a phenomenon called rebound alkalinization. Recently, Bersin et al. have demonstrated metabolic alkalinosis (\( pH_a = 7.51 \)) to result in impaired myocardial and systemic oxygen delivery in patients with severe coronary disease and chronic ventricular dysfunction. 39 Such patients appear to be critically dependent upon compensatory alterations of oxygen-hemoglobin binding which facilitate oxygen off loading. Leftward shifts in hemoglobin \( P_{50} \) induced by alkalinosis lead to decreased myocardial oxygen and lactate consumption and further impairment of contractility. Likewise, metabolic alkalinosis (\( pH > 7.55 \)) has been associated with subsequent mortality in survivors of CPR. 117

### Other Therapies

Based on the discussion above it would appear desirable to have a buffer that does not generate \( CO_2 \) as increases in \( CO_2 \) appear to limit the effectiveness of bicarbonate. Tris-(hydroxymethyl) aminomethane, abbreviated either TRIS or THAM, does not generate \( CO_2 \) and has been investigated as a buffer, in both animals and humans. 118 A complete discussion of the actions and complications of this buffer are beyond the scope of this review. With controlled ventilation, venous and tissue \( P_{CO_2} \) appear to decrease with administration of THAM, in contrast to bicarbonate. 118,119 Nonetheless, in clinical and experimental models of metabolic acidosis or CPR, THAM has not consistently been shown to be a better buffer than bicarbonate. 120,121 In fact, in recent experimental models, intracellular \( pH \) appeared to be more favorably improved by bicarbonate than THAM. 122 Carbicarb\(^\text{®} \), a mixture of sodium carbonate and bicarbonate, holds great promise as the buffer of the future. Because of \( CO_2 ^2 \) ion Carbicarb\(^\text{®} \) does not raise \( P_{CO_2} \) when injected into blood 118,119 and may, under some conditions, actually lower \( P_{CO_2} \). Carbicarb\(^\text{®} \) has the capacity to generate \( HCO_3^- \) not only from the carbonate ion but from \( CO_2 \) either in the blood or in reservoirs of supply of \( CO_2 \) accessible to blood, (e.g., the \( CO_2 \) stores in poorly perfused tissues). 123,†† Bersin et al., studying the effects of Carbicarb\(^\text{®} \) in a dog model of hypoxic lactic acidosis, found it to result in an improvement in \( pH_a \), mean arterial pressure, cardiac output, and hepatic lactate clearance, whereas an equivalent dose of bicarbonate lead to deterioration in these variables. 13 In contrast to bicarbonate, administration of Carbicarb\(^\text{®} \) did not increase mixed venous \( P_{CO_2} \) nor decrease hepatic intracellular \( pH \). Sun et al., using a similar model in rats, made comparable observations. 124

Although not a buffer, dichloroacetate (DCA) has received attention as a possible treatment for lactic acidosis. By enhancing the activity of pyruvate hydrogenase, 125 DCA accelerates conversion of pyruvate to acetyl-CoA and thereby the metabolism of lactate and pyruvate by the tricarboxylic acid cycle (fig. 1). In the hypoxic dog model, DCA improved hepatic lactate clearance and intracellular \( pH \) and attenuated the rise of blood lactate. 10 Although blood pressure and cardiac output were not significantly improved, a subsequent investigation by Abu-Romeh using hypoxic rats found hemodynamic performance to be better preserved in animals given DCA compared with those given saline. 126 In a study of nine patients undergoing cardiac catheterization, DCA enhanced myocardial lactate consumption and increased cardiac output primarily via afterload reduction. 127 The two largest human series wherein hypotensive critically ill patients with various etiologies of shock and lactic acidemia were treated with DCA have shown marked but inconsistent responses. 128,129 Unfortunately, no other therapies were compared with DCA. Of all patients treated, 26% were without metabolic or hemodynamic improvement. Responders had a 74% decrease in lactate levels and normalization of \( pH_a \), but required 6–18 h to achieve these endpoints. In responders as a group there was no consistent improvement in hemodynamics although some individual patients had significant immediate improvements in blood pressure and cardiac output. Median survival in nonresponders was 26 h compared with 60 h in those that did respond. The authors were unable to determine clinical or metabolic variables that could predict the likelihood of response to DCA. It appears the numerous pathophysiology leading to lactic acidosis respond to DCA therapy in variable and, at present, unpredictable ways. A prospective randomized study of DCA versus other therapies may help to better define the role of this potentially useful agent.


Conclusions

Until new agents are more completely investigated and proven to be superior, bicarbonate should not be completely abandoned in the treatment of lactic acidosis. The weight of experimental and clinical evidence supports the conclusion that acidosis impairs cardiovascular function and responses to the potentially beneficial effects of exogenous or endogenous catecholamines. In practical terms bicarbonate is effective as an alkalinizing agent only when generated CO₂ is eliminated from the body. For this reason, the efficacy of bicarbonate depends upon the pathophysiologic basis by which lactic acidosis occurs.

In states of severe hypoperfusion, such as CPR, CO₂ elimination is impaired both at the tissue level and at the lung. Bicarbonate administration increases the CO₂ load to the lung, leading to further increases in arterial and intracellular PCO₂ if ventilation is not appropriately increased. Even if PaCO₂ is kept normal, current data suggest tissue (intracellular) pH and likelihood of defibrillation is minimally affected by pH₄ during CPR. Hence, there appears to be little to no role for bicarbonate in this setting.

Myocardial performance and maximal systemic oxygen delivery under hypoxicemic conditions is maintained, with an otherwise healthy heart, at a pH₄ of 7.1–7.2 via increased sympathetic nervous system activity. Further decrements of pH, especially in the presence of elevated lactate, may lead to severe hemodynamic deterioration. Small titrated doses of bicarbonate are used in this situation as a temporizing measure to achieve a pH compatible with cardiovascular responsiveness while attempts to improve oxygenation are continued. Elevation of PaCO₂ must be avoided to prevent intracellular acidosis, which even though transient, may prove detrimental.

In acidemic states where cardiac output is insufficient to meet systemic oxygen requirements and is unimproved by catecholamines, partial correction of pH₄ may be necessary in order to restore adequate hemodynamics. Bicarbonate administration may lead to ventilatory failure and arterial hypercapnia in patients with compromised pulmonary function and could be anticipated to worsen the clinical situation unless appropriate respiratory management is undertaken. As in hypoxicemic states, complete correction of pH₄ is probably unnecessary. The goal is improved myocardial performance, not an arbitrary pH₄. Creation of alkalemia has the potential to adversely affect myocardial performance in certain patients.

With a clear appreciation of the heterogeneous nature of states of lactic acidosis and how abnormalities of cardiac, pulmonary, and hepatic function may influence its effectiveness and potential for toxicity, bicarbonate continues, for the present, to have a role in the treatment of lactic acidosis.

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