IN-DEPTH REVIEW

Use of Base in the Treatment of Severe Acidemic States

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- Severe acidemia (blood pH < 7.1 to 7.2) suppresses myocardial contractility, predisposes to cardiac arrhythmias, causes venoconstriction, and can decrease total peripheral vascular resistance and blood pressure, reduce hepatic blood flow, and impair oxygen delivery. These alterations in organ function can contribute to increased morbidity and mortality. Although it seemed logical to administer sodium bicarbonate to attenuate acidemia and therefore lessen the impact on cardiac function, the routine use of bicarbonate in the treatment of the most common causes of severe acidemia, diabetic ketoacidosis, lactic acidosis, and cardiac arrest, has been an issue of great controversy. Studies of animals and patients with these disorders have reported conflicting data on the benefits of bicarbonate, showing both beneficial and detrimental effects. Alternative alkalinizing agents, tris-hydroxymethyl aminomethane and Carbicarb, have shown some promise in studies of animals and humans, and reevaluation of these buffers in the treatment of severe acidemic states seems warranted. The potential value of base therapy in the treatment of severe acidemia remains an important issue, and further studies are required to determine which patients should be administered base therapy and what base should be used.

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INDEX WORDS: Bicarbonate; metabolic acidosis; tris-hydroxymethyl aminomethane (THAM); Carbicarb.

For more than 100 years, bicarbonate administration has been considered the cornerstone of therapy for patients with severe acidemia associated with acute metabolic acidosis. The administration of bicarbonate in this situation appeared logical because acute acidemia was shown to have a deleterious impact on organ function. It was assumed that bicarbonate administration would normalize extracellular pH, as well as intracellular (pHi), and restore organ function to normal. Results of several studies have suggested this thesis is overly simplistic. Thus, not only may acidemia per se be injurious, but its presence may induce adaptive processes that are not rapidly reversed or, paradoxically, themselves can be injurious to cells. Moreover, bicarbonate administration under certain circumstances can have adverse consequences.

In this review, we summarize the literature currently available concerning benefits and complications of bicarbonate therapy in the treatment of the most common causes of severe acidemia observed clinically, with the hope that this information will assist clinicians in deciding on the...
value of bicarbonate (or another base) in these situations.

**REQUIREMENT FOR THE REGULATION OF pH, AND EXTRACELLULAR pH**

It has been postulated that cell pH is maintained at approximately 7.2 in the mammalian organism for several reasons: (1) to ensure that the large number of important metabolic intermediates are in the ionized state and therefore have little tendency to escape from the cell; (2) a large number of intracellular enzymes, such as phosphofructokinase (the rate-limiting enzyme of glycolysis), that take part in cellular metabolism have a pH optimum close to this value; and (3) DNA, RNA, and protein synthesis are highly pH-dependent processes, and their synthesis is facilitated at this or a slightly higher pH. In addition, pH is maintained relatively constant by the activity of various plasma membrane hydrogen/base transporters, including the Na⁺/H⁺ exchanger, H⁺-adenosine triphosphatase (ATPase), Na⁺HCO₃⁻ cotransporter, Cl⁻-HCO₃⁻ exchanger, sodium-dependent Cl⁻-HCO₃⁻ exchanger, K⁺-HCO₃⁻ cotransporter, and H⁺-K⁺-ATPase. In response to acute acidemia, specific plasma membrane H⁺/HCO₃⁻ transporters that return pH toward its original value are activated. The nature of the transporters that primarily accomplish this task varies among different organ systems.

Maintenance of blood pH at approximately 7.4 is important to stabilize pH at its normal value. Regulation of extracellular pH independent of its effect on pH might also be important. Thus, binding of some hormones to their receptors, such as insulin and catecholamines, is altered by changes in extracellular pH and this effect might contribute to the adverse consequence of metabolic acidosis. Moreover, in some studies, acidemia had a negative impact on organ function without a detectable change in pH. Although normalization of pH is important for proper cellular function, under certain conditions, some transport processes contributing to the normalization of pH can paradoxically have adverse consequences on cellular function. One of the best characterized examples is the response of the heart to intracellular acidosis occurring in the setting of ischemia. Several studies have shown that intracellular acidosis arising with ischemia increases the activity of the Na⁺/H⁺ exchanger NHE1. Stimulation of this antiporter augments not only proton efflux, but also sodium influx. The increased sodium is initially transported out of the cell through Na⁺,K⁺-ATPase to maintain a low intracellular sodium concentration. However, with continuing ischemia, the enhanced adenosine triphosphate (ATP) production necessary to support Na⁺,K⁺-ATPase activity is constrained. Increased cell sodium concentrations decrease the activity of the Na⁺/Ca²⁺ exchanger, thus increasing intracellular calcium levels. Elevated intracellular calcium concentrations and low ATP levels can contribute to electrical instability of the myocardium and the generation of arrhythmias, cellular necrosis, and impaired myocardial function. Treatment with etohisopropylamiloride, an inhibitor of the Na⁺/H⁺ exchanger, has been shown to protect against cardiac ischemia and reperfusion and significantly reduce infarct size in various experimental models. Theoretically, a similar sequence of events might occur in some types of metabolic acidosis if ATP generation by tissues is impaired in the presence of intracellular acidosis, although this possibility remains to be examined.

**IMPACT OF ACIDEMIA ON CARDIAC FUNCTION**

Severe acidemia is rarely lethal in the absence of cardiac dysfunction. Thus, complication-free survival has been observed in previously healthy individuals, even with severe lactic acidosis (blood pH < 6.8) after strenuous exercise. In addition, patients with other causes of severe acidemia have survived blood pH values as low as 6.5. Although the duration of exposure to the severe acidemia in these reports was limited. Conversely, severe acidemia can have profound effects on the function of various organs and contribute to increased morbidity and mortality. Although several organs are affected by severe acidemia, the impact on cardiac function is most critical to patient survival. Therefore, the majority of experimental and clinical studies have focused on the effect of acidemia on cardiovascular function. Major clinical sequelae of acidemia are listed in Table 1.
Table 1. Adverse Clinical Effects of Acidemia

<table>
<thead>
<tr>
<th>Cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased cardiac output</td>
</tr>
<tr>
<td>Anormias</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Resistance to vasoressors</td>
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<tr>
<td>Venous constriction with centralization of blood volume</td>
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<td>Central nervous system</td>
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<tr>
<td>Decreased sensorium</td>
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<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Gastric atony</td>
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<tr>
<td>Hepatic</td>
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<tr>
<td>Reduced hepatic blood flow</td>
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<tr>
<td>Metabolic</td>
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<tr>
<td>Increased binding of oxygen to hemoglobin with reduced oxygen delivery</td>
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<tr>
<td>Insulin resistance</td>
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Myocardial Contractility

In 1910, Jerusalem and Starling were among the first investigators to describe negative inotropic effects of acidemia associated with changes in PCO₂. Subsequent in vitro studies using isolated cardiac muscle and heart preparations also showed a reduction in contractile force with exposure to an acidic milieu caused by a decrement of bicarbonate concentration. To determine the level of pH at which alterations in cardiac function occurred, stepwise decrements of extracellular pH were produced by using either a bicarbonate- or non-bicarbonate-based solution. Left ventricular pressure decreased slightly (5% to 10%) when extracellular pH was reduced from 7.4 to 7.2. However, there was a greater decrease (15%) if pH was reduced to levels less than 7.2. Conversely, if extracellular pH was reduced to 7.2 by increasing PCO₂ (acute respiratory acidosis), the decrease in left ventricular pressure was substantially greater (25% to 30%). Further reductions in extracellular pH to 6.7 caused left ventricular pressure to decrease by 30%. The decrement was greater when pH was decreased to the same degree by increasing PCO₂ (80%). The lesser impact of changes in extracellular pH with acute metabolic compared with acute respiratory acidosis was also associated with a smaller decrease in pH. Other in vitro studies confirmed the greater impact of acute respiratory compared with acute metabolic acidosis on cardiac function.

However, it should be noted that not all studies examining the impact of metabolic acidosis showed a decrease in myocardial pH. Studies performed in intact rats by Zahler et al and Bettice et al did not find a significant decrease in pH in the myocardium during acute metabolic acidosis. Reasons for the differences among studies are not obvious.

A similar correlation between the severity of acidemia and degree of cardiac depression was noted in whole animal experiments. In the intact animal, detectable depression of cardiac function was only apparent when blood pH was decreased to less than 7.2. The contractile force of the left ventricle increased as blood pH was reduced from 7.4 to 7.2 and remained elevated as long as blood pH was not decreased further. The initial increase in cardiac contractile force appeared to be mediated in part by sympathoadrenal factors because blockade of adrenergic responses by pretreatment with propranolol abolished the positive inotropic response. Furthermore, there was a more precipitous decrease in cardiac output in animals administered propranolol when blood pH was decreased to less than 7.2. Decreases in cardiac output with some forms of acute metabolic acidosis may be even greater: cardiac output decreased by as much as 50% during lactic acidosis.

The response of the heart to changes in extracellular pH is schematically shown in Fig 1.

Thus, in vitro and in vivo studies have documented profound reductions in cardiac function when extracellular pH decreased to less than 7.2. Furthermore, it appears that a change in pH is the most important factor determining the response of the heart to acute acidosis given that respiratory acidosis has a more profound impact on cardiac function than metabolic acidosis. However, a role for changes in extracellular pH per se cannot be excluded.

Cellular processes responsible for impairment of cardiac contractility during severe acidemia are incompletely understood. Several factors have been implicated, including an acidemia-related reduction in high-energy phosphate metabolic intermediates of the myocardial cell, reduction or elevation in intracellular calcium levels, change in the availability of calcium for binding to troponin-myosin complex, or impairment of actin-myosin cross-bridge cycling by monovalent phosphate.
Normals
Cardiac Blood pH

Fig 1. Schematic showing nature of changes in cardiac output noted in response to acute metabolic acidosis. With mild reductions in blood pH from 7.4 to 7.2, a small increase in cardiac output may be observed as a result of stimulation by catecholamines. As blood pH decreases to less than 7.2, depression of cardiac contractility leads to a decrease in cardiac output to an extent approximately correlated with the severity of acidemia. Administration of β-blockers modifies the response, accentuating the depression of cardiac function and thus decreasing cardiac output even with mild reductions in blood pH. Similarly, a greater decrease in cardiac output might be observed at lesser degrees of acidemia in the presence of severe cardiac disease.

Electrical Stability of the Myocardium

Experimental and clinical studies have shown acidemia can contribute to the generation of cardiac arrhythmias in both the presence and absence of myocardial ischemia. Gerst et al evaluated the ventricular fibrillation threshold in dogs made acidemic by reducing base concentration or increasing PCO₂. Even minor reductions in blood pH to 7.3 associated with acute metabolic acidosis caused a decrease in the ventricular fibrillation threshold. The threshold was reduced further when blood pH was reduced to less than 7.1. Conversely, acidemia associated with acute respiratory acidosis had no impact on the ventricular fibrillation threshold, but produced abnormalities in myocardial repolarization in humans, indicating that it could predispose to arrhythmia development. Examination of the relationship between acidemia and the appearance of arrhythmias in various clinical studies has not shown a strong correlation. Arrhythmias were noted in some patients with severe acidemia, and in one study, post-myocardial infarction ventricular tachycardia and atrial fibrillation resolved after correction of acidemia. Conversely, the presence of arrhythmias in patients with myocardial infarction in a separate study was related more strongly to the presence of hypoperfusion, rather than the acidemia itself. Theoretically, individuals with cardiac disease should be more sensitive to the depressive and arrhythmogenic effects of acidemia, but this possibility remains to be examined.

When arrhythmias develop, they are caused in part by a direct effect of acidemia on the heart to increase the diastolic depolarization rate. Other factors that might contribute include alterations in serum and intracellular concentrations of calcium, magnesium, and potassium and the increased sympathetic discharge noted with acidosis.

Acidemia can have other deleterious effects on the myocardium. Using a cell-culture model, it was shown that a lower pH is important to the apoptotic cell death of myocardial cells in response to hypoxia or ischemia. Thus, apoptosis occurred in myocytes exposed to hypoxia only when extracellular pH was decreased, but not when a decrease in pH was prevented. Therefore, acidemia, if present, could potentially modify the extent of myocardial damage after coronary artery occlusion.

Peripheral Vascular Resistance

Acute metabolic acidosis causes a decrease in peripheral vascular resistance from a direct vasodilatory effect. However, because arterial vasoconstriction is enhanced by the increased sympathetic discharge noted with acute metabolic acidosis, the severity of the decrease in peripheral resistance will depend on the interplay of these countervailing forces. Patients administered β-blockers can have a more dramatic decrease in blood pressure because they lack some of the compensatory mechanisms required for adaptation to the decrease in peripheral resistance. The response of the vasculature to both α- and β-adrenergic stimulation is also reduced in the presence of a low blood pH, theoretically making patients with hypotension relatively resistant to pressors administered to increase blood pressure. The type of metabolic acidosis might have an impact on the resistance to administered agents. In an in vitro model of lactic acidosis, β-adrenergic receptors were rapidly desensitized and uncoupled. Full expression of this effect
required both an elevated lactate concentration and low pH (<7.1).34

Although total peripheral vascular resistance decreases during acute metabolic acidosis, the response of the vasculature is not uniform in all vascular beds.9 For example, cerebral circulation is exquisitely sensitive to changes in blood pH, and metabolic and respiratory acidosis cause a decrease in cerebral vascular resistance and increase in cerebral blood flow.9 Some experiments indicated that renal vascular resistance increased, whereas others showed dilatation of these vessels. Effects of acute metabolic acidosis on myocardial blood flow are complex because the acidemia accompanying metabolic acidosis can affect myocardial blood flow directly and possibly indirectly by altering myocardial oxygen consumption.35 Both an increase and decrease in coronary blood flow have been observed during acute metabolic acidosis.80.61 However, if alterations in blood flow to the heart and central nervous system are present, they might contribute in part to changes in cardiac and cerebral function observed with metabolic acidosis.

Low blood pH is also associated with venoconstriction9 caused by augmented sympathetic stimulation. This constriction of the venous system displaces blood into the central circulation, leading to elevated pulmonary vascular volume and pressure.

In summary, the acidemia that accompanies metabolic acidosis, if severe, alters cardiovascular function by suppressing myocardial contractility, potentially inducing arrhythmias, and decreasing total peripheral vascular resistance and blood pressure. The magnitude of the reduction in blood pressure also depends on the impact of catecholamines released during acute metabolic acidosis, which tend to favor vasoconstriction and increased cardiac output. Therefore, administration of β-blockers can modify the response to metabolic acidosis. Acidemia also produces venoconstriction, which, in combination with the depression of cardiac function, can predispose patients to the development of congestive heart failure.

Oxygen Delivery

Additional metabolic and physiochemical effects have been documented that alter the transport and delivery of oxygen to peripheral tissues independent of hemodynamic changes. A decrease in pH reduces the affinity of hemoglobin for oxygen within minutes, thus enhancing the delivery of oxygen to tissues (Bohr effect). However, glycolysis is reduced over the ensuing 12 to 36 hours, thus depleting red blood cells of such important glycolytic intermediates as 2,3-diphosphoglyceric acid (DPG).52.63 Because DPG decreases the affinity of hemoglobin for oxygen, reducing this moiety favors increased oxygen binding to hemoglobin. Thus, acute acidemia facilitates oxygen delivery, whereas more chronic acidemia hampers oxygen delivery. A chronically acidemic patient often has normal tissue oxygen delivery because of counterbalancing effects of these two processes. Rapid correction of chronic acidemia theoretically might impair oxygen delivery by suppressing the Bohr effect in the presence of low DPG levels.63

Electrolyte Abnormalities

Acute acidemia has complex effects on various serum electrolyte levels, which can modify the response of the cardiovascular system during severe metabolic acidosis. An increase in serum potassium concentration can be observed during acidemia as a result of enhanced cellular potassium efflux. The increase in serum potassium concentration is more frequent with hyperchloremic acidosis and is often absent with organic acidoses, eg, acute lactic acidosis in patients undergoing electroshock therapy.64 Although metabolic acidosis initially is associated with a reduction in urinary excretion of potassium, it leads to an increment in kaliuresis as the acidosis is prolonged.64.65 Thus, hypokalemia is frequently observed with acute metabolic acidosis. The serum potassium concentration found with metabolic acidosis depends on the interaction of these effects.

Changes in total and ionized calcium levels occur during acute metabolic acidosis as a consequence of several mechanisms. Ionized calcium level may increase immediately because of a pH-related decrease in the binding of free calcium to albumin.66.67 Subsequently, total serum and ionized calcium levels might be altered by changing the concentrations and/or biological activities of vitamin D and parathyroid hormone, stimulating the release of calcium from bone.
and enhancing urinary excretion of calcium.\textsuperscript{68} The final impact of metabolic acidosis on serum and ionized calcium values will depend on several factors, including the severity of metabolic acidosis, its duration, and level of renal function. Most importantly, these alterations in calcium level can have an important impact on cardiovascular function. Studies of humans have shown a direct correlation between ionized calcium concentration and cardiac contractility: an increase in ionized calcium level enhances cardiac contractility and a reduction in ionized calcium level depresses cardiac contractility.\textsuperscript{67,69}

**CORRECTION OF METABOLIC ACIDOSIS**

**Endogenous Mechanisms for the Correction of Acidemia in Acute Metabolic Acidosis**

Processes that operate normally to correct acidemia in the two types of metabolic acidosis, high anion gap and normal (hyperchloremic) anion gap, are listed in Table 2. In high anion gap metabolic acidosis, with the exception of renal failure, the increase in the unmeasured anion gap is primarily caused by an increase in organic anion concentrations.\textsuperscript{70,71} After the metabolic abnormality producing the acidosis has been corrected, these anions are rapidly converted to bicarbonate in the tissues, as seen in the rapid restoration of plasma bicarbonate concentration after the cessation of strenuous exercise or discontinuation of electroshock therapy (disorders causing lactic acidosis).\textsuperscript{39,72} Conversely, in normal anion gap metabolic acidosis, the concentration of chloride, a nonmetabolizable anion that cannot be converted to bicarbonate, is increased. Thus, rapid correction of metabolic acidosis by metabolic conversion of anions to bicarbonate cannot occur.

The second endogenous process that contributes to the normalization of serum bicarbonate concentrations in both high and normal anion gap metabolic acidosis is renal generation of new bicarbonate, primarily from \(\alpha\)-ketoglutarate (derived from glutamine metabolism). This process begins immediately, but may take several days to reach its maximal rate.\textsuperscript{73} Because some disorders causing metabolic acidosis are associated with abnormal renal function, renal generation of new bicarbonate may be impaired. This is especially important in normal anion gap metabolic acidosis, in which renal bicarbonate generation is the only endogenous mechanism available to correct systemic acidemia independent of administering exogenous bicarbonate.

**Exogenous Bicarbonate Therapy: Benefits and Complications**

The rationale given by some clinicians for the administration of sodium bicarbonate in patients with severe acidemia is that it increases arterial pH and pHi, thus eliminating potential adverse effects of acidemia on cardiac function, hepatic uptake of lactate, tissue perfusion, tissue oxygenation, and pHi.\textsuperscript{2,3,5} Conversely, the opposing view is that bicarbonate therapy should be withheld even in the treatment of patients with severe acidemia (blood pH < 7.1) because the administration of sodium bicarbonate not only does not benefit the patient, but paradoxically, can lead to deterioration in systemic hemodynamics, in addition to producing volume overload, hyperosmolality, paradoxical cerebral spinal fluid (CSF) acidosis, increased organic acid production, and reduced pHi.\textsuperscript{14-16,22,25,74}

It should be emphasized that the controversy regarding the appropriateness of bicarbonate therapy in the treatment of severe acidemia has centered on three clinical disease states: (1) type A lactic acidosis, (2) metabolic acidosis and hypercarbia associated with cardiac arrest, and (3) diabetic ketoacidosis.\textsuperscript{2,3,14} The majority of

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**Table 2. Processes Contributing to the Correction of Metabolic Acidosis**

<table>
<thead>
<tr>
<th>High Anion Gap</th>
<th>Normal Anion Gap</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism of organic anions</td>
<td>—</td>
<td>Process takes minutes to hours</td>
</tr>
<tr>
<td>Renal synthesis of (\text{HCO}_3^-)</td>
<td>Renal synthesis of (\text{HCO}_3^-)</td>
<td>Magnitude of increase in plasma (\text{HCO}_3^-) concentration depends on quantity of circulating organic acid anions</td>
</tr>
<tr>
<td>Process begins immediately, but may take several days to reach maximum</td>
<td>Rate of (\text{HCO}_3^-) generation reduced with renal failure</td>
<td></td>
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</tbody>
</table>
both experimental and clinical studies assessing the risks and benefits of bicarbonate therapy in the treatment of severe acidemia examined these three disorders. The emphasis on these three disorders undoubtedly occurs because collectively, they account for greater than 90% of patients with severe acidemia observed in the United States.\textsuperscript{75} Thus, we focus our analysis on these three disorders in evaluating the risks and benefits of bicarbonate therapy.

\textit{Diabetic Ketoacidosis}

In patients with diabetic ketoacidosis and high anion gap metabolic acidosis, rapid restoration of normal acid-base balance theoretically can be achieved by the administration of insulin and appropriate fluids, primarily as a consequence of the stoichiometric conversion of organic acid anions to bicarbonate. However, acidemia can contribute to insulin resistance, thus retarding the correction of ketoacidosis and hyperglycemia and exposing the patient to adverse effects of these metabolic abnormalities for a longer period.\textsuperscript{32,33,76} Therefore, several studies were performed to determine whether bicarbonate therapy might (1) increase the rate of correction of acidemia and hyperglycemia, and (2) reduce morbidity and/or mortality in these patients.

\textit{Animal studies.} Few studies have addressed these issues in animals. Whittaker et al\textsuperscript{33} examined insulin sensitivity in rats with streptozotocin-induced diabetes and ketoacidosis. Responsiveness to insulin was reduced in acidemic rats and directly correlated with blood pH. When blood pH was less than 6.9, there was little or no response. This effect was mimicked by acidemia produced by ammonium chloride administration. Moreover, correction of acidemia by bicarbonate administration reversed the insulin resistance.

Okuda et al\textsuperscript{174} assessed the effect of bicarbonate-rich perfusate on hepatic production of ketones using an in situ liver preparation. Perfusate with this solution increased ketone production by the liver substantially, to twice the basal level, indicating that bicarbonate therapy stimulated ketone production by the liver, theoretically exacerbating ketoacidosis.

Beech et al\textsuperscript{180} examined the response of rats with diabetic ketoacidosis that were anesthetized and placed on fixed ventilation. Rats were administered saline, sodium bicarbonate, or Carbicarb, along with conventional insulin therapy. Treatment with either bicarbonate or Carbicarb caused a decrease in blood pressure, elevation in blood lactate concentration, and decrease in ratios of myocardial phosphocreatinine and ATP to phosphate despite an increase in myocardial pH, measured by nuclear magnetic resonance spectroscopy.

\textit{Studies of humans.} Lever and Jaspan\textsuperscript{77} retrospectively compared recovery rates of plasma glucose and plasma bicarbonate concentrations, arterial pH, and level of consciousness in 52 patients with diabetic ketoacidosis treated with bicarbonate and 21 patients treated with only insulin, potassium, and saline (conventional therapy). Initial values for blood pH and plasma bicarbonate in the bicarbonate-treated group averaged 6.98 and 4.0 mEq/L, and 6.96 and 3.5 mEq/L in the conventionally treated group, respectively. Mean changes in pH and plasma bicarbonate concentration (0.4 and 1.0 mEq/L/h) were not different from those in the conventionally treated group (0.36 and 1.2 mEq/L/h, respectively). Also, the rate of decrease in blood glucose level was not different. Most importantly, no mortality or increased morbidity occurred in the conventionally treated group. Hale et al\textsuperscript{178} compared the benefit of bicarbonate therapy in patients with diabetic ketoacidosis and mild lactic acidosis randomly assigned to the administration of either bicarbonate or saline, along with insulin. Arterial pH increased more rapidly in patients administered bicarbonate; however, blood glucose levels decreased at the same rate with or without bicarbonate therapy. Also, there was a delay in decreases in both blood lactate concentration and lactate-pyruvate ratio in patients administered bicarbonate. No adverse effects were noted with bicarbonate treatment.

Assal et al\textsuperscript{179} evaluated bicarbonate therapy in 9 patients with severe diabetic ketoacidosis and impaired mental status. Bicarbonate therapy neither augmented the rate of decline in blood glucose levels nor decreased ketone levels in the blood. Morris et al\textsuperscript{180} evaluated 21 adults with severe diabetic ketoacidosis (blood pH, 6.9 to 7.14) randomly assigned to the administration of insulin with or without bicarbonate. During treatment, there was no difference between groups in rates of decline of blood glucose or ketone levels.
or increase of plasma bicarbonate or blood pH values.

Gamba et al.\(^{81}\) studied 20 patients with severe ketoacidosis and plasma pH less than 7.15 (range, 6.9 to 7.14) in a double-blind randomized study. Patients were treated similarly except for the administration of bicarbonate or sodium chloride. Although plasma bicarbonate levels and pH increased more rapidly in the bicarbonate-treated group, there was no difference in the rate of return of blood glucose to normal levels. Furthermore, \(\text{PaCO}_2\), \(\text{PaO}_2\), blood pressure, and mental status were similar in both groups. There were no deaths in either group. Viallon et al.\(^{82}\) evaluated the use of bicarbonate in patients with severe ketoacidosis; blood pH varied between 6.83 and 7.03. There was no significant difference in recovery rates or complications between those administered bicarbonate and those administered conventional treatment. However, the group administered bicarbonate required greater quantities of potassium.

Okuda et al.\(^{74}\) examined the recovery of hyperglycemia and resolution of ketonemia in three patients with severe ketoacidosis (plasma pH, 6.98; plasma bicarbonate, 2.1 mEq/L) administered bicarbonate in addition to insulin and fluids and four patients with less severe disease (plasma pH, 7.27; plasma bicarbonate, 14.2 mEq/L) administered insulin and fluids alone. Decrements in plasma glucose levels were similar in both groups. However, although the absolute and percentage increases in plasma pH and bicarbonate concentration were greater in the bicarbonate-treated group, plasma concentrations of ketone bodies actually rose. Conversely, plasma ketone levels decreased in the group administered insulin and fluids alone. These data indicate that rather than enhancing the rapidity of recovery of ketoacidosis, bicarbonate therapy might extend the period of ketoacidosis.

In one of the larger series, Green et al.\(^{83}\) retrospectively examined the use of bicarbonate in 147 children with severe diabetic ketoacidosis. Fifty-seven children were treated without bicarbonate; 9 of these patients had blood pH values less than 7.00, and 1 patient had a pH of 6.73. Complications were similar between the groups, although the bicarbonate-treated group required a longer period of hospitalization.

In summary, although amelioration of aci-

demia with bicarbonate therapy improves insulin sensitivity in studies of experimental animals, bicarbonate therapy in studies of humans (Table 3) does not appear to speed the recovery from ketoacidosis or hyperglycemia or prevent complications in patients with diabetic ketoacidosis. Although studies in the literature do not support a role for bicarbonate in the treatment of diabetic ketoacidosis, it is important to recognize some of their limitations. These studies did not specifically evaluate patients with deficient endogenous mechanisms for the correction of acidemia, such as those with a low level of circulating metabolizable organic anions and patients with significant renal impairment, who potentially would be exposed to adverse effects of acidemia for a more prolonged time. Moreover, they also did not examine patients with significant cardiovascular disease, who might be more susceptible to the arrhythmogenic and depressive effects of acidemia. Further studies might be worthwhile to determine whether these groups of patients experience more complications during ketoacidosis, and if so, does bicarbonate therapy reduce the rate of complications.

**Potential morbidity of bicarbonate therapy.** In addition to the lack of apparent benefit of bicarbonate therapy in diabetic ketoacidosis, complications of therapy have been described in patients with diabetes. In 1961, Posner and Plum\(^{84}\) reported the association between exacerbation of CSF acidosis and impaired brain function in patients with diabetic ketoacidosis administered bicarbonate. The investigators hypothesized that bicarbonate therapy suppressed ventilation; however, the administered bicarbonate did not easily cross the blood-brain barrier. Subsequent studies have shown the presence of similar CSF acidosis in patients administered insulin and saline, but not bicarbonate.\(^{79,85}\) In nine patients with severe ketoacidosis and impaired mental status, blood pH increased from 7.06 ± 0.03 to 7.41 ± 0.04, whereas CSF pH paradoxically decreased from 7.27 ± 0.01 to 7.15 ± 0.03 within 4 hours after the administration of bicarbonate. Despite the decrease in CSF pH, mental status markedly improved in all patients. Moreover, in a group of similar patients administered only insulin and saline, a similar decrease in CSF pH was observed within hours of treatment.\(^{79}\) These studies confirm that some worsening of CSF acidosis is...
Table 3. Comparison of Conventional Therapy With and Without Bicarbonate in Diabetic Ketoacidosis

<table>
<thead>
<tr>
<th>Patients</th>
<th>Mean Initial Blood pH/\text{HCO}_3^- (mEq/L)</th>
<th>Blood Glucose Recovery Rate</th>
<th>Acidosis Recovery Rate</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective study of 52 patients treated with NaHCO₃ versus 21 patients without</td>
<td>7.0/4.3 versus 7.07/4.2</td>
<td>No difference</td>
<td>No difference</td>
<td>Similar level of consciousness after treatment; no difference in morbidity or mortality</td>
<td>77</td>
</tr>
<tr>
<td>Prospective study of 16 patients with DKA and LA treated with NaHCO₃ and 16 patients without</td>
<td>7.05/7 versus 7.06/7</td>
<td>No difference</td>
<td>More rapid recovery in NaHCO₃-treated group</td>
<td>Delay in decrease in lactate level in NaHCO₃-treated group, no difference in complications</td>
<td>78</td>
</tr>
<tr>
<td>Retrospective analysis of 9 patients treated with NaHCO₃ versus 6 patients without</td>
<td>7.06/12 versus 7.05/11.0</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference in level of consciousness, but lower CSF pH in HCO₃-treated group</td>
<td>79</td>
</tr>
<tr>
<td>Randomized prospective study of 10 patients treated with NaHCO₃ versus 11 patients without</td>
<td>7.3/7.4 versus 7.27/7.7</td>
<td>No difference</td>
<td>No difference in time to reach pH &gt; 7.3</td>
<td>No difference in decline in serum ketone or glucose levels, no difference in rates of change in CSF pH and HCO₃ between groups</td>
<td>80</td>
</tr>
<tr>
<td>Randomized double-blind study of 9 patients treated with NaHCO₃ versus 11 patients without</td>
<td>7.05/2.87 versus 7.04/2.55</td>
<td>No difference</td>
<td>More rapid increase in pH and [HCO₃^-]p in NaHCO₃-treated group</td>
<td>No difference in mental status, blood pressure, or complications after treatment between groups</td>
<td>81</td>
</tr>
<tr>
<td>Retrospective study of 24 patients treated with NaHCO₃ versus 15 patients without</td>
<td>6.93/3.1 versus 7.04/4.5</td>
<td>No difference</td>
<td>No difference in time to normalize values</td>
<td>No difference in complications, K requirement greater in NaHCO₃ group</td>
<td>82</td>
</tr>
<tr>
<td>Retrospective study of 147 children with severe DKA; 90 treated with NaHCO₃ versus 57 without</td>
<td>pH &lt; 7.15 for all patients</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference in complications</td>
<td>83</td>
</tr>
<tr>
<td>3 Patients treated with NaHCO₃ versus 4 patients without</td>
<td>6.98/2.1 versus 7.27/14.2</td>
<td>No difference</td>
<td>Greater absolute increase in pH and [HCO₃^-]p in HCO₃-treated group</td>
<td>Delay in decrease in serum ketones in NaHCO₃-treated group</td>
<td>74</td>
</tr>
</tbody>
</table>

Abbreviations: DKA, diabetic ketoacidosis; LA, lactic acidosis; [HCO₃^-]p, plasma bicarbonate concentration; K, potassium.

Observed with treatment, but for the most part, these changes do not appear to have a clinical impact on the outcome of the patient. Exacerbation of hypokalemia also was reported with bicarbonate therapy, but the clinical relevance of this observation is unclear. Factors
regulating serum potassium concentration in diabetic ketoacidosis are complex (ie, changes in transcellular potassium transport and altered renal potassium excretion). Bicarbonate therapy may unmask a potassium deficit caused by combined effects of osmotic diuresis and excretion of nonreabsorbable ketone bodies on renal potassium excretion. The recognition that patients with diabetic ketoacidosis are usually significantly potassium depleted should readily allow for correction of potassium depletion with treatment.

Volume expansion, with potential precipitation of congestive heart failure or exacerbation of hypertension, has been reported with the administration of sodium bicarbonate. Volume expansion might also be a consequence of the sodium chloride routinely administered to these patients. However, the majority of patients have modest to severe volume deficits caused by vomiting or the osmotic diuresis accompanying hyperglycemia. It therefore is less likely that substantial volume expansion will occur, and if it does, it can be managed easily by the administration of diuretics, or if severe renal impairment is present, the initiation of dialysis.

Hypernatremia and hypertonicity also have been reported with the administration of the typical hypertonic sodium bicarbonate ampules, which contain 44 mEq of sodium bicarbonate in 50 mL of solution (880 mEq/L). This problem can be avoided by carefully following up serum sodium concentrations to detect the development of hypernatremia and providing free water as needed.

Metabolic alkalosis (overshoot alkalalemia) can result from excessive bicarbonate therapy because a patient with ketoacidosis has endogenous sources of bicarbonate (metabolic conversion of organic anions into bicarbonate with insulin therapy). The potential for this problem depends largely on the quantity of circulating organic acid anions. In some organic acids normally associated with a high anion gap, such as diabetic ketoacidosis, concentrations of circulating organic acid anions reflected by the delta serum anion gap may vary despite the presence of continued hypobicarbonatemia and acidemia. A normal anion gap can occur at the time of presentation in volume-repleted patients or as a result of saline administration to patients with an initial high anion gap who are volume depleted. The serum anion gap in organic acidosis is determined not only by the rate of organic acid anion generation, but also the rate of their renal excretion and conversion to bicarbonate. In non-volume-depleted patients with ketoacidosis, glomerular filtration rate is sufficiently preserved to allow enhanced renal organic acid excretion with sodium, favoring the development of a normal anion gap. In the presence of low levels of circulating ketone bodies, rapid generation of bicarbonate from the metabolism of ketone bodies is attenuated. As a consequence, these patients are at low risk for overshoot alkalosis. Conversely, they might also be subject to the adverse consequences of acidemia for a more prolonged period.

On the other hand, patients with high circulating organic anion levels are more prone to the development of overshoot alkalosis because of the dominance of endogenous mechanisms (ie, metabolism of organic anions into bicarbonate). The rate of recovery from ketoacidosis is more rapid in patients with elevated organic acid anion levels than those with low organic acid anion levels. Calculation of the serum anion gap and careful administration of base, taking into account these endogenous sources, will prevent significant alkalosis from occurring.

Finally, bicarbonate therapy can paradoxically increase the production of several organic acids, including acetoacetic acid, β-hydroxybutyric acid, and lactic acid. As a consequence, bicarbonate therapy under certain circumstances might delay recovery from ketoacidosis or lactic acidosis. The mechanism underlying this effect has not been completely elucidated, but may be caused in part by intracellular alkalization.

In summary, although bicarbonate therapy potentially can have such adverse consequences as volume expansion, hypernatremia, exacerbation of hypokalemia, development of overshoot metabolic alkalosis, and stimulation of organic acid production, most of these can be avoided by administering bicarbonate cautiously and carefully following up the patient’s acid-base and electrolyte profiles. Studies of humans have not shown a significant negative impact of bicarbonate therapy on cardiovascular status. However, a single study by Beech et al in rats, cited previously, showed a negative impact of bicarbonate
treatment. This result emphasizes the importance of designing additional studies of humans to examine the effect of bicarbonate therapy in patients with significant comorbid conditions.

**Lactic Acidosis**

Two forms of lactic acidosis are known. Type A lactic acidosis is the most common form observed clinically and usually arises in the course of cardiac arrest, severe hypoxemia, or states of markedly impaired tissue perfusion. Type B lactic acidosis is less common and presents without overt clinical evidence of impaired perfusion. This type of lactic acidosis occurs primarily because of abnormal carbohydrate metabolism, e.g., phenformin intoxication. Because acidemia was shown in experimental situations to reduce hepatic blood flow, theoretically impairing the clearance of lactate, and depress cardiac output, thus contributing to reduced tissue perfusion, it appeared logical to postulate that bicarbonate therapy would be beneficial in the treatment of lactic acidosis.\(^3\,^5\,^37\) Therefore, experimental studies performed in animals and clinical studies in humans were designed to determine whether bicarbonate therapy (1) facilitates recovery from lactic acidosis, (2) improves cardiovascular function, (3) affects lactate production, and (4) reduces mortality.

**Animal studies (Table 4).** Arieff et al\(^21\) first developed several animal models of types A and B lactic acidosis to examine the effect of bicarbonate therapy on metabolic profile, cardiovascular status, and mortality of lactic acidosis. In one

<table>
<thead>
<tr>
<th>Experimental Model of Lactic Acidosis</th>
<th>HCO(_3^-) Dose</th>
<th>Hemodynamic Status</th>
<th>pH, Lactate Production</th>
<th>Mortality</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenformin-induced in dogs</td>
<td>1 mol/L at 1 mL/min</td>
<td>↓ CO</td>
<td>↓</td>
<td>↑</td>
<td>Not different in HCO(_3^-)-treated and NaCl-treated group</td>
<td>No ↑ [HCO(_3^-)]p</td>
</tr>
<tr>
<td>Hypoxia-induced in dogs</td>
<td>1 mol/L at 2.5 mEq/kg/h</td>
<td>↓ CO</td>
<td>↓</td>
<td>↑</td>
<td>Marked ↑ lactate production</td>
<td>22</td>
</tr>
<tr>
<td>Lactic acid infusion in rats</td>
<td>1 mol/L at 0.1 mL/min</td>
<td>↓ BP</td>
<td>U</td>
<td>NA</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Hypoxia-induced in rats</td>
<td>270 μg/kg/min</td>
<td>↓ CO</td>
<td>NA</td>
<td>NA</td>
<td>Prolonged survival ~20 min</td>
<td>49</td>
</tr>
<tr>
<td>Lactic acid infusion in pigs</td>
<td>1 mol/L at 3.5 mL/min</td>
<td>No change in CO or Emax</td>
<td>NA</td>
<td>NA</td>
<td>Very large amount of bicarbonate administered</td>
<td>↓ BP w/o ↑ CO</td>
</tr>
<tr>
<td>Hemorrhagic shock in pigs</td>
<td>7.5% at 0.05 mEq/kg/min</td>
<td>NA</td>
<td>↑ Serum lactate in HCO(_3^-)-treated group</td>
<td>NA</td>
<td>Slower recovery of tissue PO(_2) in NaHCO(_3)-treated group</td>
<td>89</td>
</tr>
<tr>
<td>Hypovolemic shock in rats</td>
<td>1 mol/L at 3-6 mEq/kg</td>
<td>↑ BP</td>
<td>U</td>
<td>NA</td>
<td>↑ BP similar in NaCl- and HCO(_3^-)-treated groups</td>
<td>91</td>
</tr>
<tr>
<td>Hemorrhagic shock in dogs</td>
<td>1 mol/L at 2 mL/kg</td>
<td>↑ CO</td>
<td>NA</td>
<td>↑</td>
<td>↑ BP and ↓ CO despite ↑ tissue CO(_2)</td>
<td>92</td>
</tr>
</tbody>
</table>

Abbreviations: NA, data not available; U, unchanged; Pi, phosphocreatinine; CO, cardiac output; [HCO\(_3^-\)]p, plasma bicarbonate concentration; BP, blood pressure; Pi, phosphate; Emax, slope of left ventricular end systolic pressure-volume relationship; w/o, without.
study, type B lactic acidosis was produced by infusing phenformin into diabetic dogs with pancreatectomies. Animals were intubated, and ventilation was fixed to produce a \( P_{\text{CO}_2} \) of 36 mm Hg. The mean lactate level achieved was greater than 5 mEq/L, arterial pH was less than 7.2, and plasma bicarbonate concentration was less than 12 mEq/L. After lactic acidosis was established, the animals were administered either no treatment, equimolar quantities of sodium chloride, or sodium bicarbonate at a rate of 1 mL/min for approximately 90 minutes. Animals then were monitored for an additional 4 hours. Those treated with bicarbonate manifested a decrement in cardiac output, decrease in hepatic and red blood cell pH, increased gut lactate production, and decreased portal vein blood flow. Conversely, these parameters were not changed with sodium chloride administration. Surprisingly, neither arterial pH nor plasma bicarbonate concentration increased with bicarbonate therapy. Most importantly, mortality rates with sodium chloride or bicarbonate administration were high (83%) and not different from each other.

In another study from the same laboratory, a similar degree of lactic acidosis was produced in intubated anesthetized dogs by ventilation with a mixture of 8% oxygen and 92% nitrogen to simulate the hypoxic lactic acidosis observed in humans. Arterial \( P_{\text{O}_2} \) was kept at 25 to 30 mm Hg, and arterial \( P_{\text{CO}_2} \), 35 mm Hg. After lactic acidosis was established, animals were administered either isotonic fluid, 1 mol/L of sodium bicarbonate at 2.5 mEq/kg of body weight per hour, or 1 mol/L of sodium chloride at the same dosage. Decreases in arterial pH and plasma bicarbonate concentration, increments in gut lactate production, and increases in serum lactate levels were greatest in the bicarbonate-treated group. Moreover, sodium bicarbonate therapy also was associated with the greatest decrease in blood flow to the liver and gut and a decrease in liver pH. Also, cardiac index and blood pressure declined significantly more in dogs administered bicarbonate than in those administered saline. No data for mortality were provided because the duration of observation was little more than an hour.

Halperin et al theorized that organ dysfunction in lactic acidosis arises primarily as the result of an inadequate rate of ATP regeneration in vital organs. These investigators postulated that a large quantity of bicarbonate would have to be administered to maintain a normal ATP regeneration rate and improve survival. They examined hemodynamic profiles and survival times of rats with hypoxic l-lactic acidosis, a model similar to that studied by Arieff et al in dogs. Rats were administered extremely large quantities of sodium bicarbonate (≈12 mEq) to maintain plasma bicarbonate concentrations greater than 20 mEq/L; no infusion; or an equivalent quantity of sodium as chloride. As noted previously, cardiac output decreased dramatically (close to 50%) in animals administered bicarbonate. However, cardiac output returned toward baseline values despite continuing bicarbonate administration after 20 to 30 minutes. In contrast to the studies of Arieff et al, survival was prolonged in animals administered bicarbonate (50% survival at 50 minutes versus 50% survival at 20 minutes for the control group). Conversely, after more than 70 minutes had elapsed, the majority of animals administered bicarbonate also died. Therefore, bicarbonate therapy prolonged survival to only a limited degree. Results of this study are provocative. The quantity of bicarbonate administered is far in excess of that currently recommended and presumably would be difficult to administer to patients with type A lactic acidosis, who usually have reduced renal function. However, bicarbonate could be administered while concomitantly removing fluid, either by administering diuretics or initiating dialysis. Moreover, dialysis also could serve as a vehicle to provide substantial quantities of bicarbonate. As discussed later, dialysis has been used with limited success in a small group of patients.

Other reports of lactic acidosis in animals also showed various adverse effects of bicarbonate. In a model of hemorrhagic shock, piglets administered bicarbonate with hemastarch had greater blood lactate levels, and tissue \( P_{\text{O}_2} \) levels recovered slower than those in controls administered hemastarch alone. Interestingly, bicarbonate administration did not depress cardiac output or blood pressure. Cooper et al measured hemodynamics and left ventricular mechanics in anesthetized atrially paced pigs with lactic acidosis induced by lactic acid infusion. \( P_{\text{CO}_2} \) was kept constant by adjusting ventilation. Bicarbonate
administration reduced mean arterial pressure, but did not alter cardiac output, measured by the slope of the end-systolic pressure-volume relationship.

Beech et al.21 examined the effect of bicarbonate administration on hemodynamic status and skeletal muscle pH in rats with hypovolemic shock. There was no difference in skeletal muscle pH despite a significant increase in PaCO₂ in the bicarbonate-treated group. Moreover, in contrast to other models of lactic acidosis, blood pressure increased with bicarbonate treatment to a similar degree as in saline-treated controls. Unfortunately, measurements of cardiac output or hemodynamic parameters were not obtained. Klepper et al.22 examined the effect on hemodynamic parameters of administering 1 mol/L of sodium bicarbonate to dogs with hemorrhagic shock that were hypoxic and had mild hypercapnia (pH, 7.13; PaCO₂, 42.5 mm Hg). Bicarbonate administration increased PaCO₂ and pulmonary venous PCO₂, but blood pressure and cardiac output both increased significantly.

In summary, many, but not all, reported studies of animals with hypoxic lactic acidosis administered bicarbonate showed a decrease in cardiac output. Concomitant with these hemodynamic alterations, venous PCO₂ increased and pH, of the liver and/or myocardium decreased. Conversely, a decrease in cardiac output was not observed when bicarbonate was administered to animals with lactic acidosis caused by shock; cardiac output increased, presumably because of the accompanying volume expansion. Survival of animals with lactic acidosis administered bicarbonate has been examined in only two reported studies. Conditions of these studies differed dramatically, and the impact on survival was diametrically opposite: survival was unchanged in one study and prolonged in the other, although for a very short time. Further studies examining survival using different types of lactic acidosis are needed to determine the true impact of bicarbonate therapy on mortality.

As listed in Table 5, several explanations have been proposed for the adverse effects of sodium bicarbonate administration on cardiac function, including a decrease in high-energy phosphate levels,35 decrease in intracellular pH,13 reduction in blood ionized calcium levels,60,67 and increase in intracellular calcium levels.18

Zahler et al.35 used the model of lactic acidosis produced by lactic acid infusion in rats to assess the impact of bicarbonate administration. Lactic acidosis produced in this fashion led to decreases in blood pH and ratios of phosphocreatinine and ATP to inorganic phosphate without a significant decrease in myocardial pH. Subsequent bicarbonate administration for 30 minutes caused a further reduction in these ratios, but myocardial pH was not altered. Saline administration did not change these parameters. These investigators postulated that bicarbonate administration interfered with energy production, but not through changes

<table>
<thead>
<tr>
<th>Table 5. Putative Factors Causing Decrease in Cardiac Output in Response to Bicarbonate Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Decreased pH,</td>
</tr>
<tr>
<td>Decreased blood ionized calcium</td>
</tr>
<tr>
<td>Decrease ratio of phosphocreatinine and ATP to Pi</td>
</tr>
<tr>
<td>Increased myocardial calcium concentration</td>
</tr>
</tbody>
</table>

Abbreviation: Pi, phosphate.
in pH. The precise mechanism was not determined.

Numerous in vitro experiments using several different cell types have shown that the addition of bicarbonate to extracellular fluid can cause an increase in extracellular pH, but a decrease in pH. The reduction in pH occurs because the titration of bicarbonate by protons produces carbon dioxide and water. Because carbon dioxide permeates cellular membranes more rapidly than bicarbonate, intracellular carbonic acid concentration increases, transiently reducing pH. Conversely, in these in vitro studies, if dissipation of carbon dioxide generated from bicarbonate administration is facilitated, the addition of bicarbonate leads to an increase in pH. Similarly, even when large quantities of bicarbonate are administered to animals or humans with metabolic acidosis with well-preserved cardiovascular and pulmonary function, little change in PaCO₂ occurs. However, in the presence of conditions that retard the rapid removal of carbon dioxide from tissues, such as hypoperfusion, an increase in tissue carbon dioxide level (best identified in mixed venous blood gases) and decrease in pH, occur. The decrease in pH has been shown to occur in myocardium, brain, liver, skeletal muscle, and red blood cells.

A decrease in ionized calcium level is observed after extracellular pH is increased because this causes enhanced binding of free calcium to albumin. Studies by Cooper et al. showed that the administration of bicarbonate to humans with lactic acidosis reduced ionized calcium levels by 10%. A decrease in ionized calcium levels produced by the administration of calcium binders or dialysis against a low calcium bath leads to marked reductions in cardiac contractility and cardiac output, whereas an increase in ionized calcium levels causes an increment in contractility. The mechanism of this effect has not been completely elucidated. Thus, it is very likely that changes in ionized calcium levels could contribute to the myocardial depressive effects of bicarbonate administration.

The administration of fluid with a pH greater than 7.4 during reperfusion of previously ischemic myocardium increases intracellular calcium levels. Conversely, the increase in intracellular calcium levels is attenuated if the fluid is acidic. The explanation given for this phenomenon is that reperfusion with an alkaline fluid enhances cellular sodium influx through the plasma membrane Na⁺-H⁺ exchanger at a time when low intracellular ATP concentration results in inhibition of cellular sodium efflux through Na⁺,K⁺-ATPase. The net effect is an increase in intracellular sodium concentration, which decreases the efflux of calcium through the plasma membrane Na⁺-Ca²⁺ exchanger, leading to an increase in intracellular calcium concentration. If ATP production is reduced in some forms of lactic acidosis, suggested by some investigators, it theoretically is possible that a similar sequence of events might be observed. This possibility remains to be examined.

Enhanced activity of the Na⁺-H⁺ exchanger might have other consequences on the myocardial cell than just increasing intracellular calcium concentration. Bicarbonate therapy has been proposed as a possible contributor to the development of cerebral edema in diabetic ketoacidosis. It was suggested that increased activity of the Na⁺-H⁺ exchanger after bicarbonate administration increases intracellular sodium concentration and causes swelling of cells. Support for a potentially important role for changes in intracellular sodium levels after base administration comes from studies showing that improvement in cardiac function after the administration of Carbicarb to animals with metabolic acidosis was attenuated if cytosolic sodium concentration increased.

Studies of humans. Although bicarbonate administration has been a mainstay of treatment of lactic acidosis for more than 50 years, surprisingly few clinical studies examining the impact of bicarbonate administration to patients with lactic acidosis have been published (Table 6). Initial uncontrolled anecdotal reports or uncontrolled investigations showed little benefit from bicarbonate. Luft et al. reviewed more than 300 cases of biguanide-induced lactic acidosis reported in the literature. Survival of patients administered bicarbonate was no better than in those treated with supportive care. Similarly, Stacpoole et al. reported 13 patients with hypotension-induced lactic acidosis eventually treated with dichloroacetate. Administration of up to 650 mmol of sodium bicarbonate did not substantially increase blood pH or improve hemodynamic situations. Conversely, Hilton et al.}
Table 6. Effect of Sodium Bicarbonate Administration on Hemodynamics, Acid-Base Parameters, and Mortality in Patients With Lactic Acidosis

<table>
<thead>
<tr>
<th>Patients Description</th>
<th>Hemodynamics</th>
<th>Acid-Base Parameters</th>
<th>Mortality</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective uncontrolled study of 300 patients with biguanide-induced lactic acidosis</td>
<td>NA</td>
<td>NA</td>
<td>Similar in NaHCO₃- and conventionally treated group</td>
<td>Analysis from literature</td>
<td>101</td>
</tr>
<tr>
<td>13 Patients in study of effectiveness of dichloroacetate</td>
<td>NA</td>
<td>No significant increase in HCO₃⁻-treated group</td>
<td>NA</td>
<td>Administration of up to 550 mmol/L of NaHCO₃ did not improve patients</td>
<td>102</td>
</tr>
<tr>
<td>177 Patients with septic shock and lactic acidosis</td>
<td>Improvement in hemodynamic and clinical conditions</td>
<td>Increase in blood pH and [HCO₃⁻]p</td>
<td>Reduction in mortality from expected in HCO₃⁻-treated group</td>
<td>HCO₃⁻ administered during hemofiltration with resolution of lactic acidosis in 45% of patients</td>
<td>103</td>
</tr>
<tr>
<td>Randomized blinded crossover study of 14 patients administered NaCl or NaHCO₃</td>
<td>Improvement in cardiac output in both groups</td>
<td>Increase in blood pH and [HCO₃⁻]p in NaHCO₃-treated group</td>
<td>NA</td>
<td>Increase in cardiac output despite increase in PO₂</td>
<td>98</td>
</tr>
<tr>
<td>40 Patients undergoing surgery with decrease in [HCO₃⁻]p administered either NaCl or NaHCO₃</td>
<td>No change with either solution</td>
<td>Increase in blood pH and [HCO₃⁻]p in NaHCO₃-treated group</td>
<td>NA</td>
<td>No change in cardiac output despite increase in PO₂</td>
<td>106</td>
</tr>
<tr>
<td>10 Patients with sepsis and lactic acidosis administered NaCl or NaHCO₃ and observed for 60 min</td>
<td>No significant change in cardiac output or blood pressure with NaHCO₃</td>
<td>Increase in blood pH and [HCO₃⁻]p in NaHCO₃-treated group</td>
<td>NA</td>
<td>No change in hemodynamic parameters despite increase in PO₂ and venous blood CO₂</td>
<td>107</td>
</tr>
<tr>
<td>10 Patients with class III or IV CHF with low ejection fractions</td>
<td>Administration of NaHCO₃ did not alter average cardiac output, but 2 of 10 patients had decrease in cardiac output</td>
<td>Mean [HCO₃⁻]p, 23-24 mEq/L before treatment, with little change after administration of NaHCO₃</td>
<td>NA</td>
<td>Slight increase in plasma lactate level and decrease in PO₂</td>
<td>105</td>
</tr>
</tbody>
</table>

Abbreviations: NA, data not available; [HCO₃⁻]p, plasma bicarbonate concentration; CHF, congestive heart failure.

examined the effect of bicarbonate-based hemofiltration in 177 patients with lactic acidosis seen over 7 years. Although the mortality rate remained high (71%), in the majority of cases, blood pH and plasma bicarbonate concentration could be increased from means of 7.16 and 11.9 mEq/L to 7.41 and 24 mEq/L within 12 hours of initiation of treatment, respectively. Moreover, lactic acidosis resolved in 45% of patients, although half these patients eventually died. Similar resolution or marked improvement of metabolic acidosis without hemodynamic compromise was reported in 2 patients with lactic acidosis and sepsis treated by ultrafiltration and the admin-
istration of large quantities of bicarbonate, although both patients eventually died.\textsuperscript{104}

Four controlled studies examining the impact of sodium bicarbonate administration on lactic acidosis have been published. Cooper et al.\textsuperscript{88} performed a randomized, blinded, crossover study of 14 patients with lactic acidosis (mean plasma bicarbonate, 17 mEq/L; mean plasma lactate, 7.8 mmol/L) in the intensive care unit. Thirteen of 14 patients required catecholamines to maintain blood pressure. Each patient sequentially was administered either sodium bicarbonate, 0.9 mol/L, at a rate of 2 mmol/kg over 15 minutes, or an equivalent quantity of sodium chloride. Sodium bicarbonate infusion increased blood pH, bicarbonate concentration, and \textit{Paco}_2 and reduced ionized calcium level. However, in contrast to hemodynamic effects observed in animal studies, cardiac output increased by 18% and 16%, respectively, and pulmonary capillary wedge pressure increased to a similar degree with both solutions.

Bersin et al.\textsuperscript{105} examined the impact of sodium bicarbonate administration on cardiac hemodynamics, blood gas analysis results, lactate levels, and oxygen consumption in 10 patients with stable class III or IV congestive heart failure caused by ischemic cardiac disease and cardiomyopathy who had ejection fractions of 10% to 34% and presumed tissue hypoperfusion. Baseline plasma bicarbonate concentrations were 23 to 24 mEq/L, and plasma lactate levels averaged 1.0 mEq/L. Bicarbonate administration did not alter the mean cardiac output of the group; however, 2 of 10 patients experienced a large decrease in cardiac output of 25% to 50% with bicarbonate administration. Mean oxygen consumption and \textit{Pao}_2 of the group decreased, whereas serum lactate levels increased slightly to 1.5 mEq/L.

Mark et al.\textsuperscript{106} studied 40 well-oxygenated patients undergoing major surgery who developed mild reductions in plasma bicarbonate concentrations intraoperatively (mean, 21 ± 2 mEq/L). Half the patients were assigned to the administration of up to 88 mEq of sodium bicarbonate, and half were administered an equivalent quantity of saline as an intravenous bolus. Bicarbonate administration increased plasma bicarbonate concentrations from 21 to 25 mmol/L and \textit{Paco}_2 from 41 to 44 mm Hg. Cardiac output, ejection fraction, stroke volume, and blood pressure were not statistically different from baseline values in either group.

Finally, Mathieu et al.\textsuperscript{107} studied 10 critically ill patients with lactic acidosis primarily caused by sepsis (8 of 10 patients). Patients were administered either 1 mmol/kg of sodium bicarbonate or an equivalent quantity of sodium chloride and observed for 60 minutes. With bicarbonate administration, blood pH, plasma bicarbonate concentration, \textit{Paco}_2, and mixed venous blood \textit{Pco}_2 increased. There was no effect of bicarbonate administration on serum lactate levels, cardiac output, blood pressure, or other hemodynamic variables.

In summary, most patients treated with conventional doses of bicarbonate showed no increase in cardiac output or decrease in morbidity or mortality. However, those treated with large doses of bicarbonate and concomitant dialysis appeared to have a decrease in mortality. These studies, although limited in nature, could support the thesis of Halpierin et al.\textsuperscript{108} that administration of large quantities of bicarbonate might prolong survival sufficiently to allow treatment of the underlying cause of lactic acidosis. Furthermore, depression of hemodynamic status with bicarbonate administration appears to occur only in a small subgroup of patients with mild acidosis and severe underlying cardiovascular disease. These results indicate that bicarbonate therapy might be more deleterious in patients with severe cardiovascular disease and show the need for further studies in this group of patients.

\textbf{Cardiac Arrest}

Bicarbonate had been used for more than 30 years to treat acidemia accompanying cardiac arrest. Treatment with bicarbonate was believed to ameliorate acidemia, thus improving cardiac function. However, analysis of changes in blood and myocardial acid-base parameters during cardiac arrest showed that a decrease in myocardial pH preceded a significant decrease in extracellular pH. Thus, after 5 minutes of cardiac arrest, although arterial pH was within normal range and mixed venous pH was 7.26, intramyocardial pH decreased from 7.2 to 6.95.\textsuperscript{20,23} Moreover, within 2 minutes after the onset of cardiac arrest, cardiac venous \textit{Pco}_2 increased from 40 to 165 mm Hg, and myocardial \textit{Pco}_2 to values exceeding 400 mm Hg, with minimal changes in myo-
cardiac bicarbonate concentration. From these data, it was inferred that the dominant determinant of pH, with cardiac arrest is increased tissue carbon dioxide level, rather than a reduction in bicarbonate concentration. The increased tissue carbon dioxide level is a composite of both enhanced metabolic carbon dioxide production and reduced tissue removal of carbon dioxide caused by hypoperfusion. Thus, although reduced cardiac output can lead to lactic acidosis, this might not be the most important acid-base disorder affecting immediate survival. Data suggesting that: (1) the increase in myocardial carbon dioxide tension, by reducing pH, has an important role in determining cardiac function; (2) bicarbonate administration can exacerbate the increase in myocardial carbon dioxide tension; and (3) bicarbonate administration might provide little improvement in the success of cardiac resuscitation were some of the factors that contributed to abandoning the routine use of sodium bicarbonate for treatment of cardiac arrest. Presently, the American Heart Association recommends that bicarbonate not be routinely used in the treatment of patients with cardiac arrest.

Studies of humans. Limited human studies have examined the benefits of bicarbonate therapy in cardiac arrest, with most published before 1990. Interestingly, Vukmir et al analyzed all studies published before 1996 and found that six of nine studies showed some prolongation of survival time and two studies showed no effect. In a single study, outcome was worsened by bicarbonate administration. In this study, there was an inverse correlation between the amount of bicarbonate infused and survival, ie, a negative effect on long-term survival was observed when more than 1 mEq/kg was administered. Because most studies were uncontrolled, the efficacy of bicarbonate administration in these reports cannot be evaluated.

Animal studies. In contrast to the dearth of data in humans, a substantial number of studies were performed in animals to examine the utility of bicarbonate in the treatment of cardiac arrest. These studies analyzed various outcome measures, such as defibrillation success, survival, or neurological outcome. Importantly, it is worth noting that there were often subtle differences among the studies in such important factors as duration of cardiac arrest, timing and dosage of buffer administration, and concomitant use of epinephrine or other measures affecting tissue perfusion.

In general, those studies in which vasopressors were administered in addition to bicarbonate to improve cardiac perfusion pressure have shown the most benefit from bicarbonate administration. Vukmir et al examined the impact of sodium bicarbonate on recovery from ventricular fibrillation-induced cardiac arrest for 5 or 15 minutes. The bicarbonate-treated group was administered 1 mmol/kg initially, followed by continual administration to maintain plasma bicarbonate concentrations within 5 mEq/L of baseline, whereas the control group was administered lactated Ringer’s solution. In addition, a high dose of epinephrine (0.1 mg/kg) was administered to both groups. Minute ventilation was increased to maintain an end-tidal carbon dioxide level of 3.5% to 4.5%. A 60% increase in minute ventilation was necessary in the bicarbonate-treated group to reach this goal. Survival in the brief-cardiac-arrest protocol (5 minutes) was similar in the presence and absence of bicarbonate administration, but it was greater in the prolonged-arrest group (15 minutes) administered bicarbonate. Moreover, neurological deficits after resuscitation were less in the bicarbonate-treated group. Of note, plasma pH was greater in the bicarbonate-treated group, but surprisingly, venous and arterial PCO2 were not different between the groups.

Bar-Joseph et all studied the resuscitation of adult dogs subjected to cardiac arrest induced by ventricular fibrillation. Animals were treated with chest massage, epinephrine administration, and 1 mmol/kg of sodium bicarbonate or 0.9% sodium chloride every 10 minutes for 40 minutes or until the return of spontaneous circulation. Of note, dogs were ventilated with a tidal volume of 15 mL/kg, fraction of inspired oxygen of 1.0, and frequency of 25 respirations/min to induce slight hyperventilation. Bicarbonate-treated animals had greater coronary perfusion pressures and rates of resuscitation and shorter times to resuscitation compared with those administered sodium chloride (7 of 9 versus 2 of 10 dogs). Moreover, plasma bicarbonate and pH values increased to a greater degree in the bicarbonate-treated group than in animals administered saline. Pulmonary
venous PCO₂ transiently increased after bicarbonate administration, but quickly returned to previous levels.

Redding and Pearson also showed that the administration of sodium bicarbonate with epinephrine improved resuscitation from cardiac arrest. Conversely, Federiuk et al. examined the resuscitation of swine subjected to ventricular fibrillation for 15 to 20 minutes that were administered either epinephrine and bicarbonate or epinephrine and saline. Arterial and venous pH and venous PCO₂ were greater in the bicarbonate-treated group, but the success of defibrillation was similar between the groups. Guerci et al. examined recovery from ventricular fibrillation–induced cardiac arrest in dogs administered saline or bicarbonate 18 minutes after resuscitation had started. The administration of bicarbonate did not improve or impair the ability to defibrillate the animals despite an increase in mixed venous PCO₂. Studies by Minuck and Sharma also found no benefit from bicarbonate compared with placebo in the success of resuscitation from cardiac arrest.

In summary, some studies showed an increased rate of resuscitation when bicarbonate was administered to animals with electrically induced cardiac arrest, whereas others showed no benefit. Those studies that showed an improved rate of resuscitation with bicarbonate administration shared common characteristics: in all studies, cardiac perfusion pressure was maintained by the administration of epinephrine, and in some studies, animals were hyperventilated to prevent the significant carbon dioxide accumulation associated with bicarbonate administration.

It is important to recognize some of the limitations of experiments evaluating bicarbonate therapy in the treatment of cardiac arrest. All studies described used animals in which the myocardium was healthy before the onset of cardiac arrest, and arrest was solely the consequence of ventricular fibrillation. It is more common in the clinical situation of cardiac arrest for patients to have some degree of heart disease, most commonly ischemic heart disease. In this regard, as noted previously, reperfusion of ischemic myocardium with a solution that has an elevated extracellular pH accentuates the increase in intracellular calcium levels and contributes to the electrical instability genesis of arrhythmias and postischemic dysfunction. Further studies are needed to examine the utility of bicarbonate in affecting the success of cardiac resuscitation, particularly in animals and individuals with underlying cardiac disease.

ALTERNATIVES TO BICARBONATE THERAPY

As described previously, bicarbonate administration often increases extracellular pH, but also increases carbon dioxide concentrations in blood and tissues, causing a transient decrease in pH in several vital organs, including the heart.

Because the decrease in pH has been implicated as a factor important in the decrease in cardiac function observed after bicarbonate administration, investigators have focused on the development of agents that could increase both extracellular pH and PCO₂. Two agents studied extensively are Carbicarb and tris-hydroxymethyl aminomethane (THAM).

Carbicarb

Carbicarb, a solution containing equimolar quantities of sodium bicarbonate and sodium carbonate, was first formulated in 1983 by Filley and Kindig. By virtue of its pK, it was postulated that sodium carbonate would be used as a buffer in preference to sodium bicarbonate, thus reducing or even obviating the generation of carbon dioxide and increasing extracellular pH without decreasing pH. The discovery of this agent therefore initially generated a great deal of enthusiasm as a potential buffer effective in the treatment of metabolic acidosis.

Animal Studies

Initial studies performed in dogs with HCl-induced metabolic acidosis showed that 60 seconds after a bolus injection of Carbicarb, PCO₂ and end-tidal carbon dioxide values increased minimally, whereas with sodium bicarbonate, PCO₂ and end-tidal carbon dioxide values increased by 80%. Subsequent studies of rats with mixed metabolic and respiratory acidosis (pH 7.17) produced by asphyxia showed that the administration of sodium bicarbonate increased blood pH minimally (0.03 units) and markedly elevated both PCO₂ (19.1 mm Hg) and lactate concentration. Conversely, Carbicarb caused PCO₂ to increase by only 1.9 mm Hg and did not
change lactate concentration. In an additional study, rats were made acidic by feeding ammonium chloride or inducing hypercapnia. Administration of bicarbonate to rats with metabolic acidosis resulted in an increase in $\text{Paco}_2$ and decrease in brain pH despite an increase in extracellular pH. Conversely, administration of Carbicarb caused an increase in extracellular pH and brain pH, without a change in $\text{Paco}_2$. Similarly, administration of Carbicarb to rats with ammonium chloride–induced metabolic acidosis led to an increase in blood pH, plasma bicarbonate concentration, and pH, of the liver without changes in cardiac output or blood pressure. Conversely, administration of bicarbonate led to a decrease in cardiac output and liver pH. 

In a study of 28 dogs with hypoxic lactic acidosis, Carbicarb administration led to an increase in extracellular pH and liver pH, no change in mixed venous $\text{PCO}_2$, improved lactate use by gut and liver, and stable cardiac output. Conversely, sodium bicarbonate administration led to deterioration in all these parameters. Similar results were obtained by Rhee et al in mongrel dogs with hypoxic lactic acidosis. Carbicarb led to increases in extracellular pH, stroke volume index, and cardiac index without a change in serum lactate concentration. Again, bicarbonate administration led to an increase in $\text{Paco}_2$, but no change in cardiac index. Surprisingly, myocardial pH was not different with the administration of Carbicarb or bicarbonate.

Benjamin et al compared the effects of Carbicarb, hypertonic saline, and sodium bicarbonate on cardiac index, blood pressure, and oxygen delivery in dogs with hemorrhagic shock. The administration of Carbicarb or sodium bicarbonate caused blood pH and bicarbonate concentrations to increase more than with saline. However, blood pressure, cardiac index, and oxygen dynamics increased to a similar extent in all three groups. Beech et al compared the effects of Carbicarb, sodium bicarbonate, and sodium chloride on blood pressure, acid-base parameters, and pH of skeletal muscle using nuclear magnetic resonance in rats with hypovolemic shock. Blood pH and bicarbonate concentration increased with either alkali, but there was no effect on pH. Blood pressure increased equally in all groups. Similarly, Klepper et al compared hemodynamic responses of dogs with hemorrhagic shock to bicarbonate or Carbicarb. Mixed venous carbon dioxide and $\text{Paco}_2$ increased significantly with bicarbonate administration, but was unchanged by Carbicarb. Cardiac output increased within minutes to an equal degree with both solutions.

Thus, in studies using models of ammonium chloride–induced metabolic acidosis or hypoxic lactic acidosis, the administration of Carbicarb, in contrast to bicarbonate, increased extracellular pH, pH, and liver pH, and improved hemodynamics. Conversely, both bases had a similar effect on blood pH, bicarbonate concentration, and hemodynamics when administered to animals with either hypovolemia or hemorrhagic shock.

The value of Carbicarb compared with sodium bicarbonate in the treatment of cardiac arrest has been evaluated in several animal studies. Gazmuri et al showed that Carbicarb administration reduced blood $\text{PCO}_2$, whereas bicarbonate administration increased it. Both agents increased coronary blood pH and bicarbonate concentration, but did not alter coronary vein $\text{PCO}_2$ or change the success rate of resuscitation from cardiac arrest of pigs. Conversely, Bar-Joseph et al examined the impact of Carbicarb compared with bicarbonate on hemodynamics and resuscitation after 10 minutes of cardiac arrest. These investigators showed that neither sodium bicarbonate nor Carbicarb altered arterial or mixed venous $\text{PCO}_2$. Resuscitation was improved compared with controls, but was not different from the bicarbonate-treated group.

Kette et al also compared Carbicarb with sodium bicarbonate in ventricular fibrillation–induced cardiac arrest in pigs. Three minutes after cardiac arrest, precordial compression was initiated, and Carbicarb or bicarbonate was administered. Defibrillation was instituted 11 minutes later. Carbicarb increased blood and cardiac venous pH, but decreased mixed venous $\text{PCO}_2$; bicarbonate increased blood and cardiac venous pH, but also increased mixed venous $\text{PCO}_2$. However, myocardial pH was not different in the presence or absence of either buffer, indicating that both buffers had little impact on intramyocardial acidosis. The number of animals resuscitated was slightly greater in the group administered Carbicarb compared with those administered bicarbonate, but was no different from the control group administered saline.
Studies examining potential benefits of Carbicarb in the treatment of cardiac arrest have shown equivocal results, with only a single study suggesting increased survival or enhanced resuscitation compared with bicarbonate. Thus, although there is a strong theoretical basis for beneficial effects of Carbicarb in the treatment of cardiac arrest, evidence to date is not convincing. Further studies are necessary to delineate the precise role for Carbicarb in the treatment of cardiac arrest.

**Studies of Humans**

Only a single study has been published examining the use of Carbicarb in humans in the treatment of either lactic acidosis or cardiac arrest. Leung et al. studied the effect of Carbicarb compared with sodium bicarbonate on hemodynamics in well-oxygenated patients who developed mild metabolic acidosis during surgery. Carbicarb administration caused an increase in extracellular pH, but did not affect hemodynamic parameters of the group as a whole. However, in a small subset of patients, cardiac output increased by approximately 10% 60 minutes after treatment.

**THAM**

THAM, a biologically inert amino alcohol, was first introduced as an in vitro titrating agent in 1946. In 1959, it was introduced into clinical medicine for the treatment of metabolic and respiratory acidosis. More than 2,200 articles have appeared in the medical literature concerning its use in various disorders, and there remains a group of individuals who champion its use for the treatment of these disorders.

The pK of THAM at 37°C is 7.8; therefore, it is a more effective buffer than bicarbonate in the physiological pH range. It penetrates cells easily and therefore is an effective intracellular buffer. In studies of dogs and rats with apneic hypercapnia, THAM was shown to reduce PaCO₂ levels. In dogs with metabolic acidosis, the administration of THAM resulted in an increase in extracellular pH from 7.34 to 7.47, and in pHᵢ from 7.08 to 7.27. Importantly, despite producing a similar increase in plasma bicarbonate and blood pH values as bicarbonate, it reduced PaCO₂ concentration of the CSF. Studies using a blood-perfused isolated heart preparation exposed to an acidemic milieu (pH 7.0) showed that the administration of THAM improved myocardial contractility, whereas it was transiently worsened by bicarbonate administration. Sun et al. showed that global myocardial ischemia during cardiac arrest is often followed by myocardial dysfunction after successful resuscitation, which can contribute to increased mortality in the days after resuscitation. To determine whether THAM, Carbicarb, or bicarbonate might improve myocardial function and prolong survival after successful resuscitation, they examined the administration of these agents during cardiopulmonary resuscitation in rats with ventricular fibrillation. Carbicarb and THAM administration attenuated the postresuscitation decrease in myocardial pressure, prevented an increase in venous PCO₂, and prolonged survival time far longer than the administration of bicarbonate.

In the treatment of septic shock, the administration of THAM was associated with less mortality than predicted, blood pH and bicarbonate values increased without increasing PCO₂. It has been also used to maintain blood pH and ameliorate depressive effects of the increase in PCO₂ on the myocardium in individuals on controlled hypercapnia. Also, some older studies of diabetic ketoacidosis showed correction of metabolic acidosis and hyperglycemia without obvious toxicity. Conversely, the intra-arterial infusion of THAM into coronary arteries of dogs with ischemic myocardium increased pH and bicarbonate concentration without increasing PCO₂, whereas infusion of an equivalent amount of bicarbonate increased pH, bicarbonate concentration, and PCO₂. However, there was no improvement in myocardial contractility in either group.

Other uses of THAM include treatment of elevated intracranial pressure after head injury and respiratory distress syndrome. Some of the interest in THAM has been tempered by complications associated with its use, including respiratory depression, hypoglycemia, hypokalemia, venous irritation, and sclerosis. As a result of these complications, THAM is rarely used for the treatment of pediatric disorders associated with metabolic acidosis or respiratory distress.

THAM remains an intriguing compound that might have some value in the treatment of severe
metabolic acidosis and cardiac arrest and thus might be worthwhile reevaluating.

CONCLUSION

It is apparent from examination of the literature that normal acid-base balance is beneficial to the organism and acute severe acidemia potentially is deleterious. However, many studies have shown little or no benefit from rapid correction with bicarbonate of acidemia accompanying severe metabolic acidosis or cardiac arrest. As a consequence, in the past decade, the pendulum has swung in favor of those who would abandon the use of bicarbonate or other base therapy. A potential factor in the adoption of this global approach to treatment is the failure to recognize that patients with severe acidemia are not identical. It is important to stress that severe acidemia rarely occurs without the presence of comorbid conditions that can potentially modify not only the effect of acidemia on cellular and organ function, but also the response to bicarbonate or other forms of base. Therefore, relatively rapid correction of acidemia with base administration might be beneficial in some situations, but detrimental in others.

It is our contention that much research still remains to be done to further elucidate mechanisms by which acidemia affects organ function and examine the effect of bicarbonate or other base therapy on organ function, complication rates, and survival in the most frequent causes of severe acidemia: diabetic ketoacidosis, cardiac arrest, and lactic acidosis. Suggested potentially fruitful areas for future research include the following. (1) Examination of the impact of bicarbonate therapy or another base in the treatment of patients with significant underlying cardiovascular disease. This would be of great value because many patients with diabetic ketoacidosis, cardiac arrest, or lactic acidosis have underlying cardiovascular disease. (2) Exploration of the value of dialysis in conjunction with the administration of large quantities of bicarbonate in the treatment of lactic acidosis. These studies seem important because animal studies by Halperin et al.\(^{49}\) and limited clinical studies of humans in which large quantities of bicarbonate were administered in conjunction with dialysis\(^{103,104}\) showed some improvement in survival. (3) Assessment of potential benefits on cardiovascular function of maintaining an elevated ionized calcium concentration constant during bicarbonate administration. This clinical strategy might be valuable in attenuating a deleterious effect of bicarbonate or other base on cardiac output, given the known positive correlation between ionized calcium and cardiovascular function. (4) Evaluation of a possible role for hyperventilation in ameliorating the depression of cardiac output caused by excess carbon dioxide production noted with bicarbonate therapy. Hyperventilation could be a valuable strategy in patients who are intubated despite the reduced pulmonary blood flow often observed in patients with hypoperfusion. (5) Reexploration of a role for bicarbonate or alternative bases, such as THAM or Carbicarb, in the treatment of cardiac arrest. These studies seem necessary given that some animal studies showed increased rates of resuscitation under certain conditions. Results of the proposed studies should provide further information to allow the clinician to decide, when approaching patients with severe acidemic states, whether to treat or not to treat with base.

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