

## Sodium Bicarbonate in Cardiac Arrest: A Reappraisal

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The routine use of sodium bicarbonate in patients with cardiac arrest has been discouraged, without the benefit of outcome evaluation. Current recommendations include an elaborate stratification of circumstances in which bicarbonate is to be used. The physiological and clinical aspects of bicarbonate administration during cardiopulmonary resuscitation in animal and human studies were reviewed. The onset of significant acidemia or alkalemia is associated with adverse system-specific effects. The administration of bicarbonate may mitigate the adverse physiological effects of acidemia, improve response to exogenously administered vasopressor agents, or simply increase venous return due to an osmolar effect, resulting in increased coronary perfusion pressure. Likewise, bicarbonate may have adverse effects in each of these areas. The preponderance of evidence suggests that bicarbonate is not detrimental and may be helpful to outcome from cardiac arrest. An objective reappraisal of the empirical use of bicarbonate or other buffer agents in the appropriate "therapeutic window" for cardiac arrest patients may be warranted. (*Am J Emerg Med* 1996;14:192-206. Copyright © 1996 by W.B. Saunders Company)

The significance of cardiac arrest as a major cause of morbidity and mortality in society today is self-evident. A primary myocardial event or sudden cardiac death occurs at an incidence of 36%, estimated from 1986 national mortality data.<sup>1</sup> Cardiac arrest is the first manifestation of atherosclerotic heart disease in 66% of patients.<sup>2</sup> Arrests are witnessed in 60% of cases, occurring predominantly in the prehospital realm (74%).

Medical intervention, however, that results in significant improvement in outcome is limited to specific variables, such as a decreased interval of no blood flow and quick institution of bystander cardiopulmonary resuscitation (CPR), followed by intervention with Advanced Cardiac Life Support (ACLS)—specifically, early defibrillation for ventricular fibrillation. A recent, large survey of more than 3,000

out-of-hospital cardiac arrests reported dismal results, with a 91% prehospital mortality and only 2% of patients surviving to discharge.<sup>3</sup>

Recently, interventions such as modification of the CPR technique, early defibrillation, and administration of high-dose epinephrine have been purported to improve outcome in cardiac arrest patients. Concurrently, the use of sodium bicarbonate in cardiac arrest has been discouraged, mainly because of theoretical concerns.

### METABOLISM DURING CARDIAC ARREST

Cardiac arrest, and the resultant failure of perfusion and ventilation, causes disruption of homeostasis by depleting cellular energy-storing substances, resulting in systemic acidosis. This progression is inevitable using current resuscitation techniques, with which, at best, closed and open chest CPR results in cardiac outputs of 17% to 30% and 70% to 90% of normal flows, respectively.<sup>4,5</sup>

The resulting acidosis, due predominantly to perfusion failure, has two components. Simplistically, the major metabolic component is due to the failure of tissue oxygenation, resulting in anaerobic metabolism with less adenosine triphosphate (ATP) generation at the expense of lactic acid accumulation. The minor respiratory component is due to the failure of ventilation, resulting in carbon dioxide accumulation that overwhelms normal buffering mechanisms and their ability to eliminate metabolic acid by-products. Cellular effects of hypoxia and acidosis are associated with a decreased pH, resulting in reduced calcium ( $\text{Ca}^{2+}$ ) influx through N-methyl-D-aspartate (NMDA)-gated ion channels initially.<sup>6</sup> Later, as active transport mechanisms fail,  $\text{Ca}^{2+}$  influx and subsequent cell damage may increase.<sup>6</sup>

Classically described, the normal physiological buffering mechanism—the carbonic acid-bicarbonate system—is based on the equilibrium of the equation  $\text{H}^+ + \text{HCO}_3^- \leftrightarrow \text{H}_2\text{CO} \leftrightarrow \text{CO}_2 + \text{H}_2\text{O}$ . Buffering capacity is determined by the availability of base, expressed as the ratio of anion/acid ( $\text{HCO}_3^-/\text{H}_2\text{CO}_3$ ), as well as the ability to eliminate carbon dioxide ( $\text{CO}_2$ ). This relationship can be estimated by the Henderson-Hasselbach equation,  $\text{pH} = 6.1 + \log (\text{HCO}_3^-/0.03 \text{ PaCO}_2)$ .<sup>7</sup> This reaction will be driven to completion by the relative decrease in bicarbonate  $\text{HCO}_3^-$  (leftward) or  $\text{CO}_2$  (rightward).

From a pulmonary perspective the ideal situation is usually associated with aerobic conditions: readily available

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TABLE 1. Ion Transport Systems

	Site	Stoichiometry	Description
<b>Active Transport</b>			
1. Na <sup>+</sup> /K <sup>+</sup> ATPase	Membrane	3:2	Sodium Antiporter
2. Ca <sup>++</sup> /H <sup>+</sup> ATPase	Sarcoplasmic Reticulum Endoplasmic Reticulum	2:1	Calcium Antiporter Electrogenic
3. H <sup>+</sup> ATPase	Renal		Proton Antiporter
a.	Mitochondria		Electrogenic
b.	Vacuole		Electrogenic
c.	Vesicle		
4. H <sup>+</sup> /K <sup>+</sup> ATPase	Membrane Renal		Proton Antiporter Electroneutral
5. HCO <sub>3</sub> <sup>-</sup> ATPase	Membrane Renal		
<b>Countertransport—Carrier Mediated Exchange</b>			
6. Cl <sup>-</sup> /HCO <sub>3</sub> <sup>-</sup>			Anion antiporter
a. Na <sup>+</sup> dependent	Membrane	1:1	Electroneutral
b. Na <sup>+</sup> independent	Membrane	1:1	Electroneutral
7. Na <sup>+</sup> /H <sup>+</sup>	Membrane	1:1	Cation Antiporter
8. Na <sup>+</sup> /Ca <sup>++</sup>	Membrane	3:2	
<b>Cotransport</b>			
9. Na <sup>+</sup> /Lactate <sup>-</sup> , Acetate <sup>-</sup>	Membrane		Sodium Anion Symporter
10. Na <sup>+</sup> /Substrate <sup>-</sup>	Renal		Sodium (Amino Acid, Glucose) Symporter
11. Na <sup>+</sup> /HCO <sub>3</sub> <sup>-</sup>	Renal	1:1 3:2	Sodium Anion Symporter Electroneutral Electrogenic

Data from references 12 through 26.

exchanger has a less significant role in acid-base regulation. The Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> exchanger exists in both Na<sup>+</sup> dependent and independent configurations.<sup>14,15</sup>

Tonessen et al<sup>16</sup> postulated that the Na<sup>+</sup>/H<sup>+</sup> and the Na<sup>+</sup> dependent Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> antiporter responded to acidosis, while the Na<sup>+</sup> independent Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> antiporter responded to alkalosis. Thus, during significant acidosis (pH < 6.5) the Na<sup>+</sup>/H<sup>+</sup> antiporter with a greater than first-order dependence on the intracellular H<sup>+</sup> concentration assumes the major role in increasing pH by increasing H<sup>+</sup> efflux.<sup>17,18</sup> During less significant acidosis (pH < 7.1) the Na<sup>+</sup> dependent Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> antiporter increased pH by increasing HCO<sub>3</sub><sup>-</sup> influx.<sup>17</sup> The system is precisely controlled as slight acidosis is reached (pH > 7.1), when the Na<sup>+</sup> independent Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> antiporter increases HCO<sub>3</sub><sup>-</sup> efflux to decrease intracellular pH as a "fine tuning" mechanism.<sup>17</sup>

More recent work suggests that terminology should change from active carriers to transporters, exchange carriers to antiporters, and cotransporters to symporters. Later developments included observations that the Na<sup>+</sup>/H<sup>+</sup> antiporter and Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> antiporter may have more equivalent roles in acid-base homeostasis, with the latter responsible for 30% to 60% of regulation.<sup>19-21</sup> Thus, the Na<sup>+</sup>/H<sup>+</sup> antiporter responds in an "all or none" fashion below pH 7.0, whereas the Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> symporter is active over a pH range of 6.5 to 7.5, but most effective in a more physiological pH range of 6.9 to 7.1.<sup>20,21</sup>

Pathologic conditions such as hypoperfusion allow less energy (ATP) generation, decreasing the effectiveness of the Na<sup>+</sup>/K<sup>+</sup> ATPase and Na<sup>+</sup>/Ca<sup>++</sup> ATPase pump systems, resulting in decreased flow gradients. The extracellular sodium gradient is affected driving the H<sup>+</sup> outflow and Ca<sup>++</sup> sequestration less effectively. Lastly, when energy stores are

depleted, membranes become freely permeable and passive diffusion overcomes active transport mechanisms. Further research has suggested that in addition to the Na<sup>+</sup>/H<sup>+</sup> and Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> antiporters, the Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup> symporter plays an active role in acid-base homeostasis, found in connective tissue, eg, glial cell lines but not neurons.<sup>22</sup> Electrogenic Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup> cotransport has been described in more primitive species, but there appears to be a role for electroneutral Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup> transport in mammals.<sup>12</sup> The significance of the Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup> symport in several experimental models have suggested an equivalent or greater role in intracellular buffering compound to the Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> or Na<sup>+</sup>/H<sup>+</sup> antiporter.<sup>19-22</sup>

Studies of isolated myocytes or culture lines suggest that recovery from acidosis proceeds more rapidly and effectively in the presence of bicarbonate than in bicarbonate-free media, perhaps related to the Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> antiporter and Na<sup>+</sup> symporter.<sup>21-25</sup> Vandenberg et al<sup>26</sup> used an isolated ferret heart preparation to analyze mechanisms of recovery after global ischemia in a perfused heart. The pH recovery predominately resulted from metabolic (CO<sub>2</sub> and lactate) washout, followed by the Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup> symporter, the Na<sup>+</sup> dependent Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> antiporter, and lastly, the Na<sup>+</sup>/H<sup>+</sup> antiporter contributions.<sup>26</sup> Thus, in the "low flow" or "no flow" state followed by reperfusion, both ventilatory (CO<sub>2</sub> elimination) and metabolic (HCO<sub>3</sub> buffering) correction may be necessary to optimize recovery. However, there may be adverse effects related to the additional influx of calcium.<sup>23,26</sup>

Clinically relevant issues include the suggestion that even with adequate ventilation, progressive acidosis ensues as a result of decreased cardiac output and failure of perfusion

that is refractory to hyperventilation.<sup>27,28</sup> Acidosis depends on the patient's medical status before arrest, along with the duration and efficacy of CPR.

The onset of acidosis is inevitable but is delayed progressively by the institution of closed chest CPR, open chest CPR, cardiopulmonary bypass (CPB), or, most reliably, when the return of spontaneous circulation (ROSC) occurs.<sup>29</sup> The second factor affecting the generation of acidosis is the duration of cardiopulmonary arrest. Analysis of Abramson et al's Brain Resuscitation Research Trial I<sup>30</sup> suggests that complete neurological recovery was unlikely (0%) if associated with cardiopulmonary arrest durations of 6 minutes or greater, as well as CPR times of 15 minutes or greater for prehospital events in this specific sample. Gilston<sup>31</sup> also found that 85% of arrest survivors had CPR times of 15 minutes or less. Thus, acidosis is a function of the duration of arrest, not of sodium bicarbonate administration, as has been suggested. Perhaps, the hypothesis that sodium bicarbonate is effective in reversing the acidosis of cardiac arrest if the buffer action is ensured by adequate ventilation, and if it is used in a reasonable time frame (ie, 15 minutes), should be evaluated.

## RECENT TRENDS

Historically, the focus of cardiac arrest therapy has changed. Since 1960, the emphasis of therapy in arrest has been directed toward metabolic acidosis using sodium bicarbonate to combat the ongoing metabolic derangement. Development of resuscitation techniques over the next three decades suggested that respiratory concerns were paramount and that the acidosis of arrest could be reversed by aggressive hyperventilation.

This philosophy is embodied in the Standards and Guidelines for CPR and Emergency Cardiac Care,<sup>32-34</sup> which in 1980 first suggested the empirical administration of bicarbonate, with dosing based on systemic arterial acidosis, and, finally, in 1986, curtailed empirical administration of bicarbonate, except in certain circumstances.<sup>32,33</sup> The most recent 1992 guidelines suggest a complex decision tree for the use of bicarbonate based on presumed efficacy or lack thereof in specific circumstances.<sup>34</sup> Here the use of sodium bicarbonate is categorized as follows: (1) definitely helpful for hyperkalemia; (2A) acceptable, probably helpful in known acidotic conditions and in tricyclic antidepressant or drug overdoses; (2B) acceptable, possibly helpful in prolonged arrest states; and (3) not indicated, may be harmful in hypoxic lactic acidosis.<sup>34</sup>

Evidence supporting these changes has been suggested by predominately theoretical considerations or recommendations from uncontrolled studies. These include the description of "paradoxical cerebral spinal fluid acidosis" or the coronary and systemic venous paradox.<sup>35,36</sup> These theoretical constructs suggest that because of the preferential diffusion of CO<sub>2</sub> compared with HCO<sub>3</sub> in arrest, the cellular pH may be rendered more acidotic if bicarbonate is administered as a result of excess CO<sub>2</sub> accumulation.

Animal studies have suggested adverse outcome in lactic acidosis when bicarbonate was administered, but only for high-dose models.<sup>37</sup> Human studies have described alkalosis and its negative effect on mortality retrospectively, but the

quantitative relation to the amount of exogenous bicarbonate administered is unclear.<sup>38</sup> Another large trial of cardiac arrest found that patients who received a "nonstandard" resuscitation protocol, in which bicarbonate administration was included, had decreased survival compared with patients who were resuscitated according to the current ACLS recommendations (3.6% vs 12.3%).<sup>39</sup> However, bicarbonate administration was only a single factor in a host of protocol alterations.

The debate over the use of bicarbonate in lactic acidosis is best summarized by the discussion of Stacpoole,<sup>40</sup> who suggested significant adverse metabolic and cellular effects, whereas the rebuttal by Narins and Cohen<sup>41</sup> offered a more moderate approach. The most significant issue is the fact that no controlled evaluation of bicarbonate in human cardiac arrest has demonstrated an adverse effect on survival. However, a large study (n = 72) using a canine model of cardiac arrest found significant benefits in survival and neurological outcome after 5, 10, and 15 minutes of arrest.<sup>42,43</sup>

Thus, the use of bicarbonate in arrest is controversial. Current recommendations suggest that bicarbonate should not be used without effective ventilation in those patients with compromised pulmonary function, for arrests of brief duration, or in repetitive doses without confirmation of acidosis.<sup>44</sup> If it is used, then aggressive hyperventilation and frequent pH monitoring, as well as a reduction of total dose should be instituted.<sup>45</sup> The recommendation for ACLS instruction was succinct: "Use if at all, only after application of more definitive and better substantiated interventions, even in unwitnessed arrest."<sup>46</sup> This constitutes the standard of cardiac arrest therapy to this day, with little modification.

## HISTORY OF USE

The use of sodium bicarbonate in human disease has a defined historical progression. Gaskill<sup>47</sup> in 1880 suggested that the *in vitro* administration of acid causes relaxation of vascular tone and diminished myocardial contraction, which was then reversed by the administration of a basic solution.

World War I battlefield casualties allowed Wright<sup>48</sup> in 1917 to define "acidemia" as a septic condition manifested as gas gangrene due to the "bacillus of Welch." Cannon<sup>49,50</sup> in 1918 then correlated the reduction of blood alkali with hypotension and poor myocardial contraction *in vivo*. The administration of sodium bicarbonate improved the acidotic clinical state, reducing "air hunger" or compensatory hyperventilation.<sup>49,50</sup>

Courmand et al<sup>51</sup> in 1943 suggested lactate accumulation as a marker for acidosis, designating an oxygen supply and demand imbalance. This work culminated in the recommendations of Redding and Pearson<sup>52</sup> who in 1962 suggested the use of sodium bicarbonate to improve outcome in experimental models of canine cardiac arrest. Ledingham and Norman<sup>53</sup> concurrently reported similar findings in a model of canine ventricular fibrillation.

## GENERAL INFORMATION

The onset of either extreme in the acid-base status can be associated with both cellular and systemic dysfunction (Table 2).<sup>54-67</sup> Several isolated observations regarding the

**TABLE 2.** Physiological Effects of Acid-Base Imbalance in Normal or Low Flow States

Acidosis	Alkalosis
<b>Cardiac</b>	
Myocardial depression	Myocardial depression
Decreased contractility <sup>54,55</sup>	Decreased contractility <sup>62</sup>
Decreased cardiac output <sup>56</sup>	
Arrhythmogenic	Arrhythmogenic <sup>28,57,63</sup>
Decreased fibrillation threshold <sup>57</sup>	Ventricular fibrillation
Increased defibrillation threshold <sup>57</sup>	
<b>Vascular</b>	
Decreased pressor response <sup>55,58</sup>	Catecholamine inactivation <sup>64,65</sup>
Peripheral vasoconstriction <sup>41</sup>	Peripheral venodilation
Centralization of plasma volume	
<b>Pulmonary</b>	
Increased pulmonary vascular resistance <sup>56</sup>	
Increased tissue O <sub>2</sub> Delivery <sup>59,60</sup>	Decreased tissue O <sub>2</sub> delivery <sup>59,60</sup>
<b>Central Nervous System</b>	
Increased anaerobic metabolism <sup>45</sup>	Increased cerebral vascular resistance
Cerebral depression	Cerebral depression <sup>35,63</sup>
	Paradoxical acidosis in cerebral spinal fluid <sup>35,38,66</sup>
<b>Metabolic</b>	
Decreased hepatic perfusion	
Increased lactate <sup>56</sup>	
Hypernatremia <sup>61</sup>	Hypernatremia <sup>61</sup>
Hyperkalemia <sup>61</sup>	Hypokalemia <sup>63</sup>
Hyperosmolarity	Hyperosmolarity <sup>67</sup>

NOTE: Reference numbers provided for data reference.

disruption of acid-base homeostasis have been reported. However, the issue is more complex, requiring delineation of cellular (acidosis, alkalosis) versus systemic (acidemia, alkalemia) conditions and clarification of the perfusion state—arrest or normal cardiovascular integrity. The extent of acidosis has been correlated with the length of arrest, as much as any other factor. Harrison et al<sup>68</sup> demonstrated that 40% of cardiac arrest cases had a pH < 7.3, even when sodium bicarbonate was administered. However, with brief arrest (less than 3 minutes) in a canine model the onset of acidosis may be delayed, from 8 to 18 minutes.<sup>69</sup> Efficient ventilation is required to realize this delay in acidosis onset, which may be difficult with suboptimal pulmonary function.

## PHYSIOLOGICAL EFFECTS

The analysis of acid-base physiological effects should precisely define the state of cardiopulmonary integrity—arrest, shock, or adequate perfusion—as well as the population or model examined. Extrapolation of results beyond group boundaries should be analyzed on an individual basis for validity.

The onset of acidosis with cardiac arrest has clear physiological effects, which may be different from those found in patients with adequate perfusion. The systemic response or improvement in mean arterial pressure to

exogenously administered pressors such as epinephrine, norepinephrine, and metaraminol may be decreased by 50% when respiratory acidosis is present.<sup>70</sup>

Such observations raise an obvious question concerning the level of acidosis that allows these adverse effects to become manifest. Zwanger et al<sup>71</sup> found that acidosis with pH 7.1 resulted in a significant decrease in mean arterial pressure and, more importantly, coronary perfusion pressure, which may be related to tissue ischemia. Morimoto et al<sup>72</sup> found that a pH level of 6.5 or less precluded resuscitation in 0% (0/10) of cases, whereas pH of 6.8 allowed a 60% (3/5) recovery, with (100%) (10/10) survival in the pH range of 7.1 to 7.4, in a 5-minute rat VF model. Interestingly, this recovery from VF arrest correlated inversely with acidosis in the absence of hypercarbia. This acidosis, indicated by a peak pH range of 6.9 to 7.2, has been suggested to be associated with adverse outcome.<sup>61,73</sup> However, one study found that with the administration of epinephrine alone in acidosis, there was an equivalent increase in mean arterial and coronary perfusion pressures, a factor that has been correlated with subsequent ROSC and survival with or without bicarbonate administration.<sup>71,74</sup> Thus, experimentally induced acidemia (pH 7.1) has been shown not to adversely affect perfusion in a “low flow” state.

Correlation of the isolated adverse effects of acidosis has been studied by Kerber and Sarnat,<sup>75</sup> who found decreased success of defibrillation and survival in acidotic (pH 7.23 ± 0.12) versus nonacidotic (pH 7.36 ± 0.22) patients, potentially explained by a prolonged arrest time as much as by a causal relationship. Furthermore, Clowes et al<sup>75</sup> suggested that both metabolic (pH < 7.25) and respiratory (PCO<sub>2</sub> > 65 mm Hg) acidosis were associated with decreased survival in postoperative patients.

Similarly, the onset of significant alkalosis has been associated with adverse systemic effects (Table 2). Weil<sup>38</sup> retrospectively analyzed cardiac arrest patients and suggested that increased ventricular ectopy and mortality were noted in the idiopathic alkalotic state (pH > 7.45). In fact, there were no survivors in the extreme condition (pH > 7.60).<sup>38</sup> However, this effect has been observed as secondary to the “no flow” state with central blood-base pooling and sampling rather than to a cause-and-effect relation. Also, the administration of a smaller dose (1 mEq/kg vs 2 mEq/kg) of bicarbonate may decrease the adverse effects.<sup>76</sup>

### Cardiac Effects

The cardiac effects of acid-base imbalance are numerous, and should be assessed based on the effect on coronary perfusion pressure. Cellular or local metabolic changes in the myocardium accompany cardiac arrest. Monitoring of intramyocardial parameters values demonstrates a sixfold increase in CO<sub>2</sub> (54 to 346 torr) and a sevenfold increase in H<sup>+</sup> (65 nmol/L = pH 7.20, to 441 nmol/L = pH 6.38) from baseline, which results in a significant decrease in pH inversely correlated with coronary perfusion pressure.<sup>77</sup> This intracellular acidosis is most sensitive to changes in CO<sub>2</sub>, is not prevented by closed chest compressions, and is reversed approximately 10 minutes after ROSC.<sup>77</sup> This pH change can affect both high- and low-affinity calcium receptor

binding, resulting in a rapid decline in "left ventricular function," if ROSC occurs.<sup>78</sup> This depression in myocardial contractility may be reversed by the intracoronary infusion of sodium bicarbonate affecting intracellular pH, but the loss of buffering ability is noted with excessive infusion ( $\text{HCO}_3^- > 43 \text{ mEq/L}$ ).<sup>79</sup>

Acidosis is associated with myocardial depression, which is multifactorial in nature. The dromotropic effect of acidosis ( $\text{pH} = 6.77$  to  $7.27$ ) causes a decreased heart rate, whereas appropriate correction with sodium bicarbonate causes an increased heart rate of up to 150%.<sup>54,80</sup> "Contractility" is significantly decreased because of decreased potassium efflux, which occurs under both in vitro and in vivo conditions if ROSC occurs.<sup>54,81,82</sup> However, in an acidemic condition ( $\text{pH} < 6.8$ ) the effect of respiratory acidosis is greater than that of metabolic acidosis, suggesting the rapid diffusibility of  $\text{CO}_2$ .<sup>83,84</sup> Although sodium bicarbonate correction may increase the ability of muscle fibers to contract or shorten, measured as the slope ( $\text{dP/dT}$ ) of the ratio of change of ventricular pressure to change in time when administered before ROSC, it results in brief (1 min) decreases in  $\text{dP/dT}$  (25% to 60%) with increased left ventricular end-diastolic pressure when administered rapidly in large doses after ROSC.<sup>73,80,85,86</sup> An isolated perfused guinea pig heart model has demonstrated slight myocardial depression in the setting of increased exogenous bicarbonate (50 mmol/L),<sup>54</sup> whereas the porcine lactic acidosis model of Cooper et al<sup>87</sup> showed no improvement in contractility measured as the slope of the end systolic pressure-volume relationship.

Acidosis ( $\text{pH} 7.1$ ) has been noted to result in a decrease in cardiac output in postoperative patients.<sup>88</sup> However, a paradoxical response has been noted with acidosis ( $\text{pH} 6.8$ ), resulting in increased cardiac output (182% vs 144%) compared with control groups in isolated preparations, whereas alkalosis results in a decrease in left ventricular stroke volume, myocardial oxygen consumption, and cardiac output.<sup>74,89-91</sup>

Acidosis in the pH range of 6.9 may be protective in cardiac muscle as measured by increased rest and developed muscle tension.<sup>92</sup> The presumed mechanism in the setting of tissue acidosis is local vasodilation resulting in increased coronary blood flow due to a pH decrease reflecting  $\text{PCO}_2$  or  $\text{HCO}_3^-$  levels.<sup>54</sup> However, progressive acidosis or hypocalcemia may result in decreased rest tension, myocardial fiber length, and subsequent ROSC in the setting of hypoxia.<sup>93</sup> This finding has also been noted with the correction of acidosis with sodium bicarbonate where coronary blood flow increases fivefold.<sup>80</sup> Paradis et al<sup>94</sup> examined both extremes of pH in humans with cardiac arrest ( $n = 87$ ) who were treated with high-dose epinephrine and reported higher coronary perfusion pressures in acidotic ( $\text{pH} 7.26$ ) than in alkalotic ( $\text{pH} 7.42$ ) patients.

Sodium bicarbonate administration has been noted to cause angina or ST elevation, presumably as a result of the increased myocardial oxygen consumption.<sup>91,95</sup> Severe metabolic acidosis, quantified as base deficit, predisposes a canine model to spontaneous ventricular fibrillation.<sup>57,96</sup> The ventricular fibrillation threshold is increased by significant alkalosis and is independent of hyperventilation and the subsequent decrease in carbon dioxide.<sup>57,96</sup> The defibrillation threshold may be unchanged in acid-base extremes; how-

ever, a slower rate of ROSC has been demonstrated in acidotic canine models.<sup>97,98</sup>

### *Hemodynamic Effects*

The hemodynamic effect of acidosis in the nonarrest condition includes a decrease in the adrenergic response, manifested as decreased vasoconstriction (alpha 1) and increased vasodilation (beta 2) resulting in lower systemic perfusion pressures. This effect may result from desensitization and uncoupling of the cyclic adenosine monophosphate CAMP-adenylate cyclase system.<sup>58</sup> The administration of sodium bicarbonate in arrest models results in an increased mean arterial pressure.<sup>80,82</sup> However, a double-blinded study of the administration of sodium bicarbonate to 14 acidotic ( $\text{pH} 6.90$  to  $7.20$ ) critically ill patients found no change in hemodynamics, lactate levels, or pressor response.<sup>99</sup> Mathieu et al<sup>100</sup> demonstrated a similar result with no improvement of hemodynamics or tissue oxygenation, in patients with lactic acidosis.

Sodium bicarbonate has several limitations when used rapidly in large doses. First, the effect of exogenously administered pressors such as epinephrine may be reduced.<sup>64</sup> However, in vitro analysis suggested that experimental solutions of low-dose (1 mg/250 mL) and high-dose (10 mg/250 mL) epinephrine were 70% and 100% effective, respectively, at 30 minutes.<sup>65</sup> The solution is rendered inactive only after 2 weeks of exposure.<sup>65</sup> Second, the rapid administration of bicarbonate causes a biphasic response based on the reflex-mediated and direct effect of hyperosmolarity, causing blood pressure to increase maximally at  $22 \pm 1.5$  seconds and then return to baseline by 120 seconds.<sup>101</sup>

### *Respiratory Effects*

The respiratory effects of bicarbonate are modified by the integrity of the pulmonary system, the amount and rate of bicarbonate administered, and the multifactorial  $\text{CO}_2$  response. First, the efficacy of  $\text{CO}_2$  elimination can be modified by pulmonary integrity. The "fixed system" is limited by pulmonary parenchymal disease with an abnormal respiratory mechanism or perfusion.<sup>102,103</sup> This state may occur with the pediatric or adult respiratory distress syndrome, and the administration of bicarbonate results in an unmanageable  $\text{CO}_2$  load. However, the "open system" is capable of avoiding hypercarbia by effectively eliminating  $\text{CO}_2$ , thereby maintaining the buffering action of bicarbonate.<sup>102,103</sup>

Steichen and Kleinman<sup>104</sup> demonstrated the adverse effects of bicarbonate (2 mEq/kg) administered over 3 minutes with increased  $\text{Paco}_2$  and decreased  $\text{Pao}_2$ . However, a report of a canine model of ischemic arrest in left ventricular dysfunction suggested that hyperventilation and metabolic correction is the superior mode to maintain a stable cardiac output and coronary blood flow<sup>105</sup>; hypercapnia worsened left ventricular dysfunction, but this change was mitigated by pH correction. Griffel et al<sup>106</sup> also concluded that hyperventilation alone was incapable of halting the progression of acidosis and bradycardia.

Second, the prototype use of bicarbonate in cardiac arrest suggests smaller doses, 1 mEq/kg versus 2 to 5 mEq/kg, administered slowly as optimal therapy. The  $\text{CO}_2$  load of 2

studies showing adverse outcome with bicarbonate may have used models that were of moderate cardiac arrest duration, overcorrection of acidosis, or presence of respiratory arrest. However, the studies are mixed, showing both worsening and improvement in outcome in models of ventricular fibrillation arrest, and warrant further evaluation.

The utility of bicarbonate in arrest of noncardiac etiology is also debatable. Models of respiratory arrest suggest that the administration of bicarbonate during hypoxic lactic acidosis results in a paradoxical increase in lactate and a decrease in cardiac output and blood pressure.<sup>148</sup> However, Carroll<sup>149</sup> found improved systemic blood pressure and no worsening of survival in an asphyxial model. Thompson et al<sup>150</sup> found improved survival (100% vs 50%) with bicarbonate (10 mEq/kg) administered in a porcine model of 10-minute respiratory arrest. Thus, even with asphyxial arrest, if pH is not overcorrected, survival is improved with epinephrine and bicarbonate compared with either drug alone.<sup>80</sup>

Models of hemorrhagic shock have suggested that bicarbonate administration is of limited usefulness, with unchanged hemodynamic values and outcome.<sup>151</sup> However, the progression of acidosis during arrest is inevitable and correlated more with duration of arrest than with any other factor.<sup>152</sup> A recent canine postresuscitation low flow (VF 6 minute, open chest CPR 8 minute) model found that acidosis persisted for 120 minutes in the control group, 15 to 45 minutes in the bicarbonate treatment (0.1 mEq/kg/min) group, while neither the arterial and venous pH or PCO<sub>2</sub> were normalized in the hyperventilation group.<sup>116</sup> It has been suggested that the benefits of bicarbonate may occur with effective fluid loading. Comparison of colloid and bicarbonate administration in a hemorrhagic model indicates a more rapid improvement in mean arterial pressure and cardiac output with correction of acidosis.<sup>66</sup> Analysis of the effects of sodium bicarbonate administration on outcome in a group of seventeen experimental cardiac arrest models found no significance in 53% (9), improvement in 35% (6), and worsening in 12% (2) of studies (Table 3).<sup>44,52,53,116,137-139,143,145,153-156</sup>

## DOSAGE

Early recommendations concerning the use of bicarbonate in arrest are best summarized by Stewart<sup>157</sup> in 1965. He stated, "If you were to ask him why he would correct acidosis, his answer would be, 'I would correct it because it was there.' The acidosis that results from cardiac arrest may be sufficiently severe to cause asystole, thus perpetuating arrest, and cardiac function can be restored by correcting the acidosis."<sup>157</sup> Stewart suggested a dose of 50 mEq for suspected acidosis and 150 mEq empirically for profound cases as indicated by pupillary dilatation.<sup>157</sup>

Recommendations from the Standards and Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC) suggest ensuring adequate alveolar ventilation and using therapy with proven benefit such as defibrillation or epinephrine before bicarbonate is administered.<sup>32-34</sup> This recommendation is tempered by consideration of special circumstances such as (1) hyperkalemia; (2A) confirmed acidosis, tricyclic antidepressant, or drug overdose;

**TABLE 3.** Effects of Sodium Bicarbonate on Outcome in Experimental Cardiac Arrest Models

Animal Model	Outcome		
	Improved	No Effect	Worsened
Canine	Redding, 1962 <sup>52</sup>		
Canine	Ledingham, 1962 <sup>53</sup>		
Canine	Kirimli, 1966 <sup>137</sup>		
Canine	Redding, 1967 <sup>135</sup>		
Canine	Redding, 1968 <sup>138</sup>		
Canine		Bishop, 1976 <sup>44</sup>	
Canine		Minuck, 1977 <sup>153</sup>	
Canine		Guerci, 1986 <sup>139</sup>	
Porcine		von Planta, 1988 <sup>154</sup>	
Canine	Sanders, 1990 <sup>142</sup>		
Porcine		Gazmuri, 1990 <sup>155</sup>	
Porcine			Kette, 1990 <sup>145</sup>
Porcine			Wiklund, 1990 <sup>146</sup>
Canine		Blecic, 1991 <sup>143</sup>	
Porcine		Federiuk, 1991 <sup>147</sup>	
Canine		Nitta, 1992 <sup>116</sup>	
Canine		Bleske, 1992 <sup>156</sup>	
Summary	6 (35%)	9 (53%)	2 (12%)

and (2B) prolonged arrest states. The administration of bicarbonate in a dose of 1 mEq/kg followed by 0.5 mEq/kg every 10 minutes may be considered, guided by arterial blood gas analysis and the clinical scenario.<sup>32-34</sup>

Summarizing, the current empiric data may suggest that use of sodium bicarbonate in ventricular tachycardia or fibrillation, pulseless electrical activity, or asystolic arrests would warrant evaluation of a mode of bicarbonate administration between these two extremes—the historical excessive role for bicarbonate in cardiac arrest therapy, and its restricted use in resuscitation today. The dose of 1 mEq/kg in arrests of significant duration (5 to 15 minutes) guided by measurement and correction of venous pH or base deficit, as well as by the clinical scenario, seem warranted.<sup>32-34</sup> The indications for the use of bicarbonate in the arrest setting have been described as "nonrespiratory acidosis due to organic acid excess resulting from the hypoperfusion of cardiac arrest and shock."<sup>28</sup>

Bicarbonate is available in unit dose ampules of 50 mL of 7.5% solution providing 45 mEq/kg or 90 mOsm of Na<sup>+</sup> and HCO<sub>3</sub>.<sup>67</sup> The adverse hemodynamic effects are attributed to hyperosmolarity (1,800 mOsm/L), hypercarbia (PCO<sub>2</sub> = 260 to 280 mm Hg), and alkalemia (pH = 8.0).<sup>158</sup> These effects may be minimized by slower rates of administration to decrease myocardial depression.

A wide range of dosage recommendations exists for bicarbonate administration, resulting in difficulty with study comparison. An empirical dose of 0.5 to 0.9 mEq/kg is appropriate, but an extensive range of bicarbonate dosing from 1 mEq to 10 mEq/kg is described.<sup>32,44,150</sup> The maximum dosage has been associated with adverse survival and less effect on pH.<sup>159</sup> Specific dosing is determined by the base deficit or the amount (mEq) of base added per liter of blood volume to create neutrality (range 0 ± 2.3 mEq/L) or

the difference between the estimated (24 mEq/L) or measured  $\text{HCO}_3^-$ .

Astrup et al<sup>160</sup> suggested that the dose of bicarbonate (mEq/L) is equal to base deficit (mEq/L)  $\times$  body weight (kg)  $\times$  0.3 extracellular fluid (L). This dosage is increased in the systemically ill patient with an increased volume of distribution and extracellular fluid fraction of 0.3 to 0.6, as well as in the canine model (0.43).<sup>53</sup> Gilston<sup>31</sup> suggested that the base deficit calculated as body weight (kg)  $\times$  duration of CPR (minute)  $\times$  0.1 should be used for correction. This observation used clinically determined doses of  $69 \pm 15$  mEq for CPR durations of 15 to 165 minutes with a final pH range of 7.27 to 7.44.<sup>161</sup>

Newer strategies explore both dosing reduction and continuous infusion strategies for bicarbonate administration. Bleske et al<sup>156</sup> reported a 12-minute canine VF model ( $n = 36$ ) using bolus (0.5 to 1.0 mEq/kg) and/or continuous-infusion (0.1 mEq/kg/min) bicarbonate therapy. The decline in arterial and venous pH was predictable and greatest in control (pH  $7.15 \pm 0.05$ ) compared with a low dose bolus/continuous-infusion (pH  $7.27 \pm 0.05$ ) strategy.<sup>156</sup> Hypercarbia (pCO<sub>2</sub>  $81 \pm 14$  mm Hg) was noted in the bolus group, but was not significant ( $P .07$ ) compared with control.

Another study evaluated earlier administration of smaller (0.5 mEq/kg), incremental (5, 10, 15 minute) bicarbonate doses were explored in a 3-minute VF, 15-minute CPR canine model.<sup>162</sup> The increase in pCO<sub>2</sub> ( $42 \pm 12$  vs  $35 \pm 10$  torr) and pH ( $7.46 \pm 0.14$  vs  $7.41 \pm 0.01$ ) were greatest, using an incremental 0.5 mEq/kg (5, 10, 15 minutes) instead of a bolus 1.0 mEq/kg (5 minute) and 0.5 mEq/kg (15 minute) dosing strategy.

Thus, a 0.5 to 1.0 mEq/kg dose at the initiation of CPR is appropriate empirically, and later correction calculated from base deficit is probably prudent. Alternative treatment strategies aimed at reduced dosing, early administration, or continuous infusion may warrant further evaluation.

### ALTERNATIVE THERAPY

The use of non-CO<sub>2</sub>-generating buffers including dichloroacetate, tromethamine, or Carbicarb (sodium carbonate and bicarbonate; International Medical Systems, Los Angeles, CA) has been evaluated. Dichloroacetate has been used in human trials at doses of 50 to 100 mg/kg.<sup>163,165</sup> The main effects include more rapid normalization of serum lactate and slight improvement in hemodynamics and pH, but only if ROSC occurs.<sup>163,165</sup>

Tromethamine, distributed as Tham (Abbott, Abbott Park, IL) or Tris, is administered as a 0.86-mmol/kg/h dose. This compound supports both the bicarbonate and carbonic acid buffers, avoids sodium load, and affects intracellular acidosis in its unionized form.<sup>165</sup> A canine model of 12-minute ventricular fibrillation and bypass demonstrates comparable efficacy to 4 mEq/kg bicarbonate, but correction is delayed.<sup>119</sup> Von Planta et al<sup>154</sup> used a porcine model to demonstrate worsened survival and decreased perfusion pressure compared with bicarbonate or control groups. Nitta<sup>116</sup> in a low flow arrest model demonstrated equivalent improvement in arterial and CSF pH, pCO<sub>2</sub>, and HCO<sub>3</sub> in bicarbonate and Tham (0.1 mEq/kg/min) groups, both manifesting hyperosmolarity (320 to 324 mOsm), whereas only the bicarbonate group had increased serum lactate.

Carbicarb, composed of disodium carbonate (1/3 M Na<sub>2</sub>CO<sub>3</sub>) and sodium bicarbonate (1/3 M NaHCO<sub>3</sub>), may be the most efficacious of these alternate agents. Rather than exogenous bicarbonate, this compound generates endogenous carbonate ion (CO<sub>3</sub><sup>2-</sup>) scavenging the available H<sup>+</sup> ions from endogenous buffer H<sup>+</sup> compounds and CO<sub>2</sub>. The resultant HCO<sub>3</sub> ion provides additional buffering capability, further decreasing CO<sub>2</sub> levels, theoretically decreasing cellular pH. Kucera et al<sup>115</sup> used a rat of model asphyxia to demonstrate a better buffer effect (change of pH 0.08 vs 0.03) without an increase in pCO<sub>2</sub> (2 vs 9 mm Hg) using Carbicarb versus bicarbonate, respectively. Bersin and Arieff<sup>60</sup> used a canine of model hypoxic acidosis to demonstrate improved pH lactate and hemodynamics compared with bicarbonate. Rhee et al<sup>166</sup> compared Carbicarb, sodium bicarbonate, and saline in a lactic acid normoperfusion dog model, and suggested that Carbicarb was the most effective agent in improving stroke volume index and contractility.

### OUTCOME

Trends concerning survival and neurological outcome of cardiac arrest should be considered. The outcome of prehospital arrest ( $n = 1,283$ ) is poor, with 2% achieving ROSC and only 0.2% surviving to discharge in a single sample.<sup>167</sup> Resuscitation efforts are more successful in hospitalized patients ( $n = 226$ ), with ROSC in 40% overall and 49% with the first arrest.<sup>168</sup> However, poor outcome was noted in patients with an initial pH of 7.2 or less, whether responsive to therapy or not. The best results are noted in pediatric arrest cases ( $n = 121$ ), with a 69% ROSC rate and 39% surviving to discharge. Incidentally, 28% of pediatric patients received 6 mEq/kg sodium bicarbonate or more during arrest.<sup>169</sup>

One significant correlate in arrest outcome is respiratory efficiency. Respiratory acidosis occurs in as many as 50% ( $n = 132$ ) of arrests, with 25% manifesting metabolic acidosis. Survival rates were 1.3% and 0%, respectively, in patients without versus those with metabolic acidosis.<sup>170</sup> However, CO<sub>2</sub> elimination correlates with cardiac output and survival.<sup>81</sup> Although acid-base extremes are suggested as causative for resuscitation failure, other covariables are often present.

Survival is related to the duration of cardiac arrest before resuscitative attempts are begun. Ornato et al<sup>171</sup> suggested that response time correlated with neurological outcome and survival in prehospital arrest ( $n = 119$ ). Hallstrom et al<sup>172</sup> suggested that a delay in CPR is an adverse prognostic factor in prehospital arrest. Murphy et al<sup>173</sup> in a study of 503 elderly patients with cardiac arrest found a 3.8% survival rate, with unwitnessed asystolic events responsible for the worst prognosis. A longer duration of arrest with a CPR time greater than 15 minutes also had adverse effects on outcome.<sup>173</sup>

The duration of arrest may be quantified by the degree of acidosis. Progressive acidosis occurred with closed chest CPR in both survivors and nonsurvivors experimentally.<sup>174</sup> Human studies demonstrated a pH decrease of  $0.09 \pm 0.03$  units for closed chest and  $0.05 \pm 0.03$  units for open chest CPR, with values continuing to decrease as the length of arrest increased.<sup>175</sup>

Acid-base imbalance at either extreme ( $\text{pH} < 7.2$  or  $> 7.5$ ) results in decreased tissue oxygen delivery, worsening the outcome.<sup>27,60</sup> After duration of arrest, the major determinant of acidosis is whether ROSC occurs ( $\text{pH} 7.40 \pm 1.3$ ) or is absent ( $7.18 \pm 0.20$ ).<sup>171</sup> The presence of acidosis ( $\text{pH} < 7.1$ ) is universal, occurring in most patients with cardiac arrest.<sup>176</sup> The severity of acidosis is significant, with mild to moderate ( $7.10$  to  $7.30$ ) pH associated with shorter arrest times, resulting in measurable survival rates of 24% to 27%, respectively.<sup>177</sup> Severe acidosis ( $\text{pH} < 7.1$ ) was associated with a 0% survival rate in prehospital arrest.<sup>177</sup> Thus, acidotic patients generally have poor outcomes, independent of bicarbonate administration.

Studies citing adverse outcome in the alkalotic state ( $\text{pH} > 7.5$ ) failed to establish a cause and effect relation as is the case with acidosis. Deloos et al<sup>178</sup> found equivalent ROSC with bicarbonate administration but improved neurological outcome. Prior outcome studies used bicarbonate only in refractory arrest, a group predisposed to poor survival.<sup>179</sup> It is plausible that secondary bicarbonate pooling and sampling from central circulation occurs because of a lack of ROSC, not alkalosis, as its primary cause.

Prospective evaluation of bicarbonate administration in cardiac arrest is limited. Kirby and McNicol<sup>180</sup> found a 22% survival rate in patients ( $n = 100$ ) administered 200 mEq of bicarbonate and undergoing 20 minutes of CPR (3 to 110 minutes). Of these patients, 74% had a  $\text{pH} < 7.3$ .<sup>180</sup> Aurderheide et al<sup>181</sup> demonstrated 43% ROSC ( $n = 625$ ) in a retrospective analysis of brief (control) and prolonged (bicarbonate) arrests, with no difference in pH or alkalemia. However, the bicarbonate group had a mean arrest time lasting 10 minutes longer than controls. Lastly, Ishida et al,<sup>182</sup> in a controlled study ( $n = 60$ ), found equivalent pH but improved systemic perfusion pressure, as noted by a palpable pulse in the bicarbonate group. Analysis of the effects of bicarbonate on outcome in a group of nine human cardiac arrest studies finds 67% (6) demonstrating improved outcome, 33% (3) showing no effect, and no studies showing worsened outcome (Table 4).<sup>157,176,178-184</sup>

Thus, summary of experimental animal models and retrospective human trials performed to date document no benefit or slight improvement in survival. However, there is an apparent temporal relationship, with early studies suggesting benefit and later trials concluding that bicarbonate has a detrimental effect on outcome.

**TABLE 4.** Effects of Sodium Bicarbonate on Outcome in Human Cardiac Arrest Studies

Improved	No Effect
Stewart, 1968 <sup>157</sup>	
Smith, 1965 <sup>176</sup>	
Kirby, 1967 <sup>180</sup>	
Martinez, 1979 <sup>183</sup>	
Skovron, 1985 <sup>179</sup>	Ishida, 1987 <sup>182</sup>
	Deloos, 1989 <sup>178</sup>
Gueugniaud, 1989 <sup>184</sup>	Aurderheide, 1992 <sup>181</sup>

NOTE: Six studies (67%) showed improved outcome and 3 (33%) showed no effect; no studies showed worsened outcome.

## CONCLUSION

The analysis of acid-base disturbances in the setting of cardiac arrest suggests that either extreme is associated with adverse outcome. Acceptable use of sodium bicarbonate requires the presence of several factors. Bicarbonate should be used for cardiac rather than respiratory arrest, as well as for specific conditions known to benefit from administration. An empirical dose (0.5 to 1.0 mEq/kg) may be administered for arrests of moderate duration (5 to 15 minutes) titrated by venous or arterial pH measurement. Arrest times falling outside this therapeutic window will most likely not benefit from bicarbonate administration. Maximal ventilation should be insured, and subsequent dosing may be necessary, guided by the base deficit or venous pH.

The mechanism of action is debated, but the effect is due perhaps to altered coronary perfusion pressure, making return of spontaneous circulation more likely in the setting of current resuscitation effects. Perhaps the current decision for bicarbonate or alternative buffer agent administration in cardiac arrest requires clinical validation.

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