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Laboratory Investigations

Sodium bicarbonate may improve outcome in dogs with brief or prolonged cardiac arrest

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Objective: **Despite the absence of outcome evaluation, the use of sodium bicarbonate in cardiac arrest has declined based on advanced cardiac life-support guidelines. The effects of bicarbonate therapy on outcome in a canine model of ventricular fibrillation cardiac arrest of brief (5-min) and prolonged (15-min) duration were examined.**

Design: **Prospective, randomized, controlled trial.**

Setting: **Experimental animal laboratory in a university medical center.**

Subjects: **Thirty-two adult dogs, weighing 10 to 17 kg.**

Interventions: **The animals were prepared with ketamine, nitrous oxide/oxygen, halothane, and pancuronium. Ventricular fibrillation was then electrically induced and maintained in arrest for 5 mins (n = 12) or 15 mins (n = 20). Canine advanced cardiac life-support protocols were instituted, including defibrillation, cardiopulmonary resuscitation (CPR), and the administration of epinephrine (0.1 mg/kg), atropine, and lidocaine. The bicarbonate group received 1 mmol/kg of sodium bicarbonate initially, and base deficit was corrected to –5 mmol/L with additional bicarbonate, whereas acidemia was untreated in the control group. Cardiopulmonary values were recorded at intervals between 5 mins and 24 hrs, and the neurologic deficit score was determined at 24 hrs after CPR.**

Measurements and Main Results: **The treatment group received an additional 2 to 3 mmol/kg of bicarbonate in the early postresuscitation phase. Compared with controls, the bicarbonate group demonstrated equivalent (with brief arrest) or improved (with prolonged arrest) return of spontaneous circulation and survival to 24 hrs, with lessened neurologic deficit. The acidosis of arrest was decreased in the prolonged arrest group without hypercarbia. Improved coronary and systemic perfusion pressures were noted in the bicarbonate group with prolonged arrest, and the epinephrine requirement for return of spontaneous circulation was decreased.**

Conclusions: **The empirical administration of bicarbonate improves the survival rate and neurologic outcome in a canine model of cardiac arrest. (Crit Care Med 1995; 23:515–522)**

KEY WORDS: **sodium bicarbonate; acidosis; cardiac arrest; resuscitation; ventricular fibrillation; arrhythmia; critical illness; hypercapnia; cardiac emergencies; epinephrine; heart**

The outcome of out-of-hospital cardiac arrest may be especially dismal, with a 10% to 20% return of spontaneous circulation occurring outside the hospital setting, and only 6% of patients surviving to discharge (1, 2). Recently, interventions such as a modified cardiopulmonary resuscitation (CPR) technique, early defibrillation, and high-dose epinephrine have been purported to improve outcome in patients with cardiac arrest. Concurrently, the use of sodium bicarbonate has declined because of theoretic concerns that have not been tested.

Cardiac arrest and the resultant failure of perfusion and ventilation cause disruption of homeostasis by depleting cellular substrates. The development of systemic acidosis is inevitable using current

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resuscitation techniques, where closed- and open-chest CPR result in cardiac output values that are 17% and 30% of normal, respectively (3, 4). The mixed acidosis consists of a metabolic component caused by oxygenation failure, where anaerobic metabolism results in lactic acid accumulation, and hypercarbia caused by perfusion failure, where CO_2 accumulation overwhelms the normal buffering mechanisms. The primary buffering capacity rests with the carbonic acid-bicarbonate system, which produces CO_2 under both aerobic and anaerobic conditions.

Historically, the focus of cardiac arrest therapy has changed from metabolic to respiratory correction of acidosis. This transition is embodied in the Standards and Guidelines for Cardiopulmonary Resuscitation in Emergency Cardiac Care (1970, 1980, and 1986), which first recommended that empirical bicarbonate use be guided by blood gas analyses, and then later that it be completely eliminated except for certain circumstances (5–7). The 1992 Advanced Cardiac Life-Support guidelines offered a complex range of options, depending on clinical circumstances (8).

These recommendations are based, in large part, on theoretical considerations or uncontrolled studies, such as "paradoxical" cerebral spinal fluid acidosis or the coronary and systemic venous paradox, where intracellular pH is decreased when bicarbonate is administered during cardiac arrest because of the faster diffusion of CO_2 compared with bicarbonate (9, 10). Experimental models (11) have suggested adverse outcome in deliberately uncorrected hypoxic lactic acidosis when high-dose bicarbonate is administered. Human studies (12) have correlated alkalosis with increased mortality rates, but this association may be due to inappropriate administration of exogenous bicarbonate.

The acidosis of cardiac arrest is, in part, determined by the patient's antecedent medical condition. A second factor is the efficiency of CPR, where acidosis is progressively slowed by the institution of closed-chest CPR, open-chest CPR, or cardiopulmonary bypass and reversed by the return of spontaneous circulation (13). A third factor is the duration of cardiac arrest, with CPR times of 15 mins being associated with poor survival rates and neurologic outcome (14, 15).

Thus, acidosis is a function of the duration of cardiac arrest, not of bicarbonate administration. Sodium bicarbonate may be useful in reversing the acidosis of cardiac arrest if its buffer action is ensured by adequate ventilation, and if it is used within a reasonable therapeutic window. It is postulated that the administration of sodium bicarbonate as a single variable will improve outcome in a canine model of cardiac arrest.

MATERIALS AND METHODS

Protocol. This study was approved by the University of Pittsburgh Institutional Animal Care and Use Committee. The experimental subjects were 37 dogs of 10 to 17 kg in body weight with a thoracic anteroposterior to lateral diameter range ratio of ≤ 1.3. The animals had normal neurologic function before intervention and were cared for by standard methods. Exclusion criteria were met in five animals by specifically pulmonary or intraabdominal hemorrhage, respiratory apparatus disconnection, cecal volvulus, and blood gas analyzer malfunction. Thus, 32 dogs were randomly assigned to one of two groups: 12 animals were subjected to brief (5 mins), and 20 animals to prolonged (15 mins) ventricular fibrillation cardiac arrest. Resuscitation in all animals was with standard advanced cardiac life support. Half of the animals in each group received the experimental intervention, which was the administration of sodium bicarbonate in conjunction with standard advanced cardiac life support. Cardiopulmonary variables, neurologic outcome, and survival were assessed to 24 hrs, when the experiment was finished.

Preparation. Anesthesia included premedication with ketamine (10 mg/kg im), induction and maintenance with halothane (0.5% to 3.0%) and nitrous oxide/oxygen (50/50), and muscle relaxation with pancuronium (0.1 to 0.4 mg/kg iv). Endotracheal intubation was confirmed by capnography (LB-2 Medical Gas Analyzer, Beckman Instruments, Fullerton, CA). Mechanical ventilation was begun with an F_{IO_2} of 0.5 (OX-161, Riken Keiki, Japan) and positive end-expiratory pressure of 3 cm H_2O. Volume-controlled ventilation was begun with a tidal volume of 20 mL/kg, and the frequency was regulated to maintain an end-tidal CO_2 concentration ($EtCO_2$) of 3.5% to 4.5%.

Electrocardiographic (7D Polygraph, Grass Medical Instruments, Quincy, MA) and electroencephalographic monitoring were performed continuously. Hemodynamic monitoring included a right femoral artery and pulmonary artery catheter placed percutaneously. The right external jugular vein was cannulated, and a triple-lumen catheter was placed. These catheters allowed blood sampling; temperature regulation; arterial, venous, and intracardiac pressure monitoring; and drug or fluid administration. A bladder catheter and orogastric tube were also placed.

Analyses of arterial and venous blood gases (pH/blood gas analyzer 813, Co-Oximeter 482, Instrumentation Laboratory, Arlington, MA); serum sodium, potassium, and ionized calcium (electrolyte analyzer AVL 984, Scientific, Roswell, GA); blood glucose (Accu-check® II, Boehringerer-Mannheim, Indianapolis, IN);

and hematocrit (Clay Adams Readacrit, Becton and Dickinson, Franklin Lakes, NJ) were performed according to standard methods.

Temperature was maintained at 37.5 ± 0.5°C by a thermal blanket. The fluid requirements were calculated according to the formula: 4 mL/kg/hr for 0 to 10 kg, then 2 mL/kg/hr for 10 to 20 kg. Lactated Ringer's solution was administered at an accelerated rate (fivefold) in the initial resuscitation phase and reduced to a maintenance rate after 2 hrs. Base deficit was corrected to –5 mmol/L with sodium bicarbonate in all animals. After preparation, the dogs were randomized to either the bicarbonate or the control group.

Cardiac Arrest. The halothane and nitrous oxide anesthesia was discontinued 5 mins before cardiac arrest while 100% oxygen (1 min) and room air (4 mins) were administered. A 100-volt AC transthoracic shock was applied, resulting in ventricular fibrillation. This condition was maintained without ventilation for a brief (5-min) or prolonged (15-min) period.

Resuscitation. Resuscitation was initiated using standard advanced cardiac life-support interventions, as modified for dogs. The sequence began with defibrillation in empiric doses of 200-, then 300-, then 360-joules of energy as necessary. If no return of spontaneous circulation occurred, mechanical CPR (Thumper®, Michigan Instruments, Springfield, NJ) was begun with 60 compressions/min, 50% cycle, and a compression/ventilation ratio of 5:1.

Epinephrine (0.1 mg/kg) was administered to both groups initially and every 5 mins for the duration of the arrest. Once resuscitation was begun, the bicarbonate group received sodium bicarbonate in an empirical dose (1 mmol/kg) initially, followed by base deficit correction to –5 mmol/L subsequently requiring additional bicarbonate for the duration of the study, whereas the control group received no bicarbonate. Sampling for analysis of acid base state occurred every 10 mins for the first half hour, every 30 mins until 2 hrs, and then every 2 hrs until the 24-hr point. The subsequent bicarbonate dose was calculated by multiplying the base deficit by body weight (kg) and immediate volume of distribution (25%). In all dogs, arrhythmia was treated with a bolus of lidocaine (2 mg/kg) followed by an infusion (0.05 to 0.3 mg/kg/min), and asystole was treated with atropine (0.04 mg/kg). Recurrent bouts of ventricular tachycardia or fibrillation were treated with repeat defibrillation at 360 Joules of energy. The arrest interventions were continued for 30 mins, or until return of spontaneous circulation.

Intensive Care. Return of spontaneous circulation occurred with a systolic blood pressure of 60 mm Hg. Sustained hypotension (mean arterial pressure [MAP] <80 mm Hg) was treated with a continuous infusion of norepinephrine to a maximum of 10 µg/kg/min, and hypertension (MAP >120 mm Hg) was treated with trimethaphan. At the start of resuscitation, oxygen was provided at an F_{IO_2} of 1.0, and ventilation was adjusted to an $EtCO_2$ of 3.5 to 4.5 vol%. Sedation was reinstituted 2 hrs postresuscitation with nitrous oxide/oxygen (50/50) and supplemented with fentanyl (1 to 5 µg/kg iv), according to the presence of tachycardia. Ventilatory weaning was attempted at 20 hrs postarrest, accompanied by reversal of neuromuscular blockade with atropine (0.03 mg/kg) followed by neostigmine (0.07 mg/kg). The nitrous oxide was discontinued, and 100% oxygen was administered. Dogs were extubated if they were hemodynamically stable, required no vasopressors or antiarrhythmic agents, and were not hypoxic, hypercarbic, or acidemic. The pulmonary artery catheter was removed at 20 hrs postarrest if extubation was possible.

Assessment. Cardiopulmonary variables were determined at baseline every 5 mins for the first half hour postresuscitative effort and every 30 mins until 2 hrs postresuscitative effort, then every 2 hrs thereafter until 24 hrs. Oxygenation values were assessed every 10 mins for 30 mins by measurements of arterial and venous blood gases, then every 30 mins until 2 hrs postarrest, then every 2 hrs thereafter. A retrospective interpretation of hemodynamic variables was made for all cases at the immediate time before return of spontaneous circulation or at 5 mins after resuscitative efforts were begun, whichever came first, to examine the effects of bicarbonate alone, as well as arterial and venous gas sampling.

Outcome variables were survival and neurologic outcome to 24 hrs, as graded by a blinded observer. Neurologic outcome was assessed as the neurologic deficit score ranging from 0 to 500 expressed as a percentage (0% = normal; 100% = brain death) (16). This score summarizes assessments of level of consciousness, respiration, cranial nerve function, sensory motor function, and canine behavior (16). After either failed resuscitation or with successful return of spontaneous circulation and survival to 24 hrs, perfusion fixation was performed with an injection of 3% paraformaldehyde solution via a left anterolateral thoracotomy after halothane (4%) anesthesia was induced.

Necropsy was performed by a veterinary pathologist who was blinded to the experimental results. The histologic deficit score, specifically the ischemic neuronal change score (0 = necrosis, 300 = normal), was determined after necropsy (17). Brain sections stained with hematoxylin-eosin-phloxine were examined for ischemic neuronal change, as indicated by eosinophilic

shrunken neurons, and graded from 0 (none) to 4 (many). The ischemic neuronal score is more significant (two- to four-fold) than edema (0 to 4) and inflammation (0 to 4) in final analysis of the histologic deficit score (17). Thus, cerebral damage is reported as the ischemic neuronal change score in this model.

Data Analysis. Data from the proportion of dogs that had return of spontaneous circulation, tolerated extubation, and demonstrated 24-hr survival were analyzed by Fisher's exact test. The neurologic and histopathologic deficit scores were compared by analysis of variance and the Mann-Whitney U test. Arrest variables determined at baseline (0 min), before, and after return of spontaneous circulation (30 mins) were compared by Student's *t*-test and the unpaired two-tailed test (True Epistat®, Chicago, IL). Analyses of cardiopulmonary variables from 2 to 24 hrs were performed using repeated measures of analysis of variance (SPSS/PC+®, Chicago, IL). Variables that demonstrated a significant difference by repeated measures of analysis of variance were then evaluated by an unpaired two-tailed *t*-test.

RESULTS

There was no significant difference between baseline variables measured in either group. Bicarbonate was administered during the 30-min resuscitation phase in a total dose of 2.99 ± 1.32 mmol/kg for brief arrest and 4.31 ± 0.97 mmol/kg for prolonged arrest.

Arterial sampling found that the frequency of significant acidemia (pH <7.2) was substantial, affecting 17% and 67% with brief arrest and 22% and 80% ($p < .02$) with prolonged arrest for the bicarbonate and control groups, respectively. This sampling was performed before the onset of return of spontaneous circulation or 5 mins after the resuscitative effort was begun if recovery did not occur. Severity of acidosis also increased with the duration of arrest from brief (pH 7.25 ± 0.12) to prolonged (pH 7.19 ± 0.16) ($p < .01$). This acidosis was metabolic in origin, as indicated by a base deficit of –8.1 to –14.6 mmol/L with brief arrest and –7.3 to –16.3 mmol/L with prolonged arrest. In the dogs in the brief arrest group, which were not acidemic, bicarbonate failed to cause alkalemia. In the prolonged arrest group, acidemia was corrected ($p < .02$), also without producing alkalemia (Table 1).

The brief arrest bicarbonate group required less atropine ($p < .01$) during resuscitative attempts. However, there was no significant difference in the time to return of spontaneous circulation, the dose of epinephrine, lidocaine, and norepinephrine or fluid administered, or the minute ventilation delivered (Table 2).

The prolonged arrest bicarbonate group required less epinephrine ($p < .01$) to achieve return of spontaneous circulation. There was no difference in other interventions. However, there was an increase in mean minute ventilation in the bicarbonate group determined for the 30-min arrest phase, as determined by an increased ventilatory frequency rate. This discrepancy occurred when ventilation was adjusted for return of spontaneous circulation, compared with the fixed minute ventilation delivered during CPR (Table 3).

Survival and the return of spontaneous circulation were equal in the bicarbonate and control groups with brief arrest, but they were significantly improved in the bicarbonate group with prolonged arrest ($p < .01$) (Table 4). The neurologic deficit score was lower in the bicarbonate group compared with the control group after both brief and prolonged arrest ($p < .01$). However, there was no difference in the histologic deficit score (Table 4).

The acidosis of cardiac arrest was reduced in the bicarbonate group with prolonged arrest ($p < .05$). This effect was primarily on the metabolic acidosis component, and base deficit was reduced in the bicarbonate groups at both arrest times ($p < .01$). There was no alkalemia, hypoxia, or hypercarbia noted in either bicarbonate group, for both arterial pH and venous sampling (Table 5).

Venous sampling demonstrated acidemia in both brief (pH 7.21 vs. 7.09) and prolonged arrest (pH 7.06 vs. 6.93), which was more severe in the latter control

Table 1. Frequency of acidemia and alkalemia before return of spontaneous circulation (or 5-min postresuscitative effort)

	Brief (5 mins)		Prolonged (15 mins)	
	Bicarbonate	Control	Bicarbonate	Control
Arterial				
Number	6	6	10	10
Acidemia (pH <7.2)	1	4	2[a]	8
Physiologic (pH 7.2–7.5)	5	2	7[b]	2
Alkalemia (pH >7.5)	0	0	0	0
Venous				
Acidemia (pH <7.2)	2	5	2[a]	8
Physiologic (pH 7.2–7.5)	4	1	7[b]	2
Alkalemia (pH >7.5)	0	0	0	0

Number refers to subjects.

[a] $p < .02$ compared with controls; [b] $p < .01$ compared with controls.

Table 2. Therapeutic interventions used in dogs with brief (5-min) cardiac arrest during the initial resuscitation phase (30 mins) (mean ± SD)

	Bicarbonate	Control
Time to ROSC (min)	2.2 ± 0.6	4.4 ± 4.0
Defibrillation (n)	2.2 ± 0.7	3.8 ± 1.8
Energy (joule/kg)	43.2 ± 18.3	91.4 ± 52.0
Epinephrine (doses)	1.0 ± 0.0	1.3 ± 0.8
Atropine (mg)	0.3 ± 0.5[a]	1.2 ± 0.4
Lidocaine (mg)	37.5 ± 19.2	43.3 ± 23.1
Norepinephrine (μg)	332.0 ± 238.9	450.0 ± 268.6
Fluid (mL)	125.5 ± 4.5	124.2 ± 5.6
Bicarbonate (mmol/kg)	2.99 ± 1.32	—
Minute ventilation (L/min)	7.8 ± 0.3	7.7 ± 1.1
Tidal volume (mL/kg)	15.2 ± 0.9	14.9 ± 1.1
Ventilatory rate (f)	28.5 ± 1.0	27.8 ± 4.0

ROSC, return of spontaneous circulation.
[a]$p < .01$ compared with controls.

Table 3. Therapeutic interventions used in dogs with prolonged (15-min) cardiac arrest during the initial resuscitation phase (30 mins) (mean ± SD)

	Bicarbonate	Control
Time to ROSC (min)	5.1 ± 3.1	9.2 ± 2.6
Defibrillation (n)	7.1 ± 3.4	6.7 ± 1.6
Energy (joule/kg)	184.7 ± 97.6	173.1 ± 53.9
Epinephrine (doses)	3.3 ± 2.2[a]	5.6 ± 1.0
Atropine (mg)	1.4 ± 0.8	1.7 ± 0.7
Lidocaine (mg)	51.2 ± 19.9	58.5 ± 17.6
Norepinephrine (μg)	1571.2 ± 1227.1	2453.4 ± 1285.7
Fluid (mL)	120.9 ± 8.6	122.0 ± 3.6
Bicarbonate (mmol/kg)	4.31 ± 0.97	—
Minute ventilation (L/min)	6.5 ± 2.0[a]	4.0 ± 1.1
Tidal volume (mL/kg)	14.2 ± 1.7	14.3 ± 0.7
Ventilatory frequency (f)	25.9 ± 6.7[a]	16.0 ± 4.7

ROSC, return of spontaneous circulation.
[a]$p < .01$ compared with controls.

Table 4. Survival and neurologic outcome for brief (5-min) and prolonged (15-min) cardiac arrest evaluated at 24 hrs

	Brief (5 mins)		Prolonged (15 mins)	
	Bicarbonate	Control	Bicarbonate	Control
Number	6	6	10	10
ROSC	6	6	9[a]	3
Survival	6	6	7[a]	1
Neurologic				
NDS %	18 ± 8[b,c]	43 ± 27	72 ± 22[a]	99 ± 4
INC	28 ± 11	44 ± 24	98 ± 31	66 ± 4

Number refers to subjects; ROSC, return of spontaneous circulation; NDS, neurologic deficit score; INC, ischemic neuronal change score.
[a]$p < .01$ compared with controls; [b]$p < .05$ compared with controls; [c]mean ± SD.

Table 5. Cardiopulmonary variables (mean ± SD) with brief and prolonged cardiac arrest measures with return of spontaneous circulation on 5-min postresuscitative effort

	Brief (5 mins)		Prolonged (15 mins)	
Respiratory	Bicarbonate	Control	Bicarbonate	Control
Arterial				
pH	7.29 ± 0.08	7.22 ± 0.1	7.27 ± 0.14[a]	7.11 ± 0.15
P_{CO_2}				
(torr)	38.8 ± 5.3	31.7 ± 10.9	43.4 ± 13.7	37.9 ± 9.9
(kPa)	5.24 ± 0.72	4.28 ± 1.47	5.86 ± 1.85	5.12 ± 1.34
P_{O_2}				
(torr)	360.3 ± 139.7	288.2 ± 124.1	149.4 ± 45.5	132.9 ± 45.3
(kPa)	48.6 ± 18.9	39.0 ± 16.8	20.2 ± 6.1	18.0 ± 6.1
Bicarbonate (mmol/L)	17.8 ± 2.3[b]	11.8 ± 1.7	18.9 ± 5.5[c]	12.7 ± 3.9
Base deficit (mmol/L)	8.1 ± 3.5[c]	14.6 ± 3.7	7.3 ± 6.7[c]	16.3 ± 5.6
Saturation (%)	97.8 ± 0.5	95.2 ± 3.2	96.4 ± 1.9	96.2 ± 1.8
Venous				
pH	7.21 ± 0.04[a]	7.09 ± 0.12	7.06 ± 0.07[b]	6.93 ± 0.8
P_{CO_2}				
(torr)	48.5 ± 4.7	49.3 ± 12.3	62.3 ± 20.8	58.8 ± 13.6
(kPa)	6.6 ± 0.6	6.7 ± 1.7	8.4 ± 2.8	8.0 ± 2.0
P_{O_2}				
(torr)	62.6 ± 8.2	53.3 ± 15.5	40.8 ± 13.9	45.8 ± 19.4
(kPa)	8.5 ± 1.1	7.2 ± 2.1	5.5 ± 1.9	6.2 ± 2.6
Bicarbonate (mmol/L)	18.8 ± 3.0[c]	14.0 ± 1.8	16.5 ± 5.3	12.5 ± 4.2
Base deficit (mmol/L)	8.7 ± 3.5[c]	15.3 ± 3.0	14.1 ± 4.9	18.8 ± 5.4
Saturation (%)	78.8 ± 10.7	63.3 ± 21.3	52.5 ± 20.1	46.5 ± 20.3
Arterial Venous pH gradient	0.07 ± 0.04	0.13 ± 0.17	0.17 ± 0.14	0.18 ± 0.12

[a]$p < .05$ compared with controls; [b]$p < .001$ compared with controls; [c]$p < 0.01$ compared with controls.

group ($p < .01$), while there was no difference in the arterial venous pH gradient (Table 5).

Analysis of hemodynamic variables found a significant improvement in MAP and coronary perfusion pressure, measured as the difference between MAP and mean central venous pressure during CPR, in the bicarbonate group with prolonged arrest ($p < .05$). Mean central venous and pulmonary arterial pressures were unchanged. These cardiopulmonary variables were not significantly different in the group with brief arrest. The arteriovenous oxygen content difference as an indirect measure of tissue oxygen delivery was equivalent between groups, when

measured just before the return of spontaneous circulation (Table 6).

Metabolic variables in the bicarbonate group found an increase in serum sodium (142.6 to 152.2 mmol/L, $p < .05$) and a decrease in ionized calcium (1.15 to 0.95 mEq/L [0.58 to 0.48 mmol/L], $p < .01$) in prolonged arrest; while serum potassium decreased (3.1 to 2.5 mmol/L, $p < .001$) in the brief arrest group (Table 7). However, these differences were not found over 24-hr analysis.

DISCUSSION

The incidence of acidosis in cardiac arrest is variable, with up to 40% of those patients in cardiac arrest demonstrating a pH of <7.3 (16, 18). This study demonstrated metabolic acidemia with both brief and prolonged arrest. Previous studies (19) have suggested a delayed onset of acidosis, beginning at 8 mins, with a maximal delay of 18 mins seen in a canine model. This acidosis was corrected initially with an empirical dose of bicarbonate, and no cases were identified with "paradoxic acidemia" or rebound alkalemia at the time immediately before return of spontaneous circulation. This interval was chosen to delineate the effects of bicarbonate alone, before the effects of return of spontaneous circulation occurred.

The onset of ischemic acidosis with cardiac arrest has several likely physiologic effects. The systemic response to exogenously administered vasopressors such as epinephrine, norepinephrine, or metaraminol results in a 50% decrease in MAP if acidosis is present (20). The present study found a decreased requirement for atropine with brief arrest and for epinephrine with prolonged arrest to achieve return of spontaneous circulation. The effects may be due to desensitization and uncoupling of the cyclic AMP-adenylate cyclase enzyme system, resulting in decreased vasoconstriction in acidosis (21).

The administration of bicarbonate resulted in increased MAP during CPR, only with prolonged arrest, without adversely affecting central pressures (central venous pressure, pulmonary arterial pressure). However, critically ill patients with hypotension who receive bicarbonate often demonstrate no improvement in hemodynamics or pressor response (22).

Such observations raise the obvious question concerning a threshold level of acidosis that allows these effects to become manifest. Acidosis occurred even with brief arrest but was not significant between groups and worsened with prolonged arrest ($p < .02$). This effect was mitigated in the prolonged arrest group by the administration of bicarbonate. The metabolic acidosis was corrected by the administration of bicarbonate without resultant hypercarbia in this cardiac arrest model. The adverse effects of bicarbonate have been attributed to respiratory acidosis, usually found with ineffective ventilation or larger (2 to 3 mmol/kg) initial bicarbonate doses (23). Hypoxia has also been cited as an adverse side effect of bicarbonate administration (23). Oxygen delivery did not worsen, as indicated by equivalent arterial oxygen saturation and arteriovenous oxygen content difference.

Sampling of the venous circulation during cardiac arrest may be more representative of cellular metabolism. Analysis of venous oxygenation and saturation demonstrated no adverse effects in the bicarbonate group and confirmed acidosis in the venous tissue

Table 6. Cardiopulmonary variables (mean ± SD) with brief and prolonged cardiac arrest measured with return of spontaneous circulation on 5-min postresuscitative effort

	Brief (5 mins)		Prolonged (15 mins)	
	Bicarbonate	Control	Bicarbonate	Control
CVP (cm H_2O)	15.8 ± 3.4	16.7 ± 4.4	14.6 ± 3.4	13.8 ± 3.6
MPAP (cm H_2O)	19.3 ± 6.2	19.3 ± 10.3	16.7 ± 8.5	18.8 ± 7.7
MAP (mm Hg)	77.5 ± 34.3	58.3 ± 23.1	49.5 ± 25.3[a]	28.5 ± 17.1
CPP (mm Hg)	61.7 ± 37.1	45.5 ± 22.7	35.6 ± 25.2[a]	15.3 ± 16.0
$C(a\text{-}\bar{v})O_2$ (mL/dL)	4.5 ± 1.7	5.7 ± 5.9	7.1 ± 4.9	8.7 ± 3.5

CVP, central venous pressure; MPAP, mean pulmonary arterial pressure; MAP, mean arterial pressure; CPP, coronary perfusion pressure; $C(a\text{-}\bar{v})O_2$, arterial-venous oxygen content difference.

[a] $p < .05$ compared with controls.

Table 7. Metabolic variables (mean ± SD) with brief and prolonged cardiac arrest at 30-min postresuscitative effort

	Brief (5 mins)		Prolonged (15 mins)	
	Bicarbonate	Control	Bicarbonate	Control
Sodium (mmol/L)	145.9 ± 2.4	138.0 ± 8.6	152.2 ± 11.5[a]	142.6 ± 5.4
Potassium (mmol/L)	2.5 ± 1.3[b]	3.1 ± 0.3	5.0 ± 3.0	7.4 ± 3.4
Ionized calcium (mEq/L)	1.06 ± 0.10	1.06 ± 0.08	0.95 ± 0.16[c]	1.15 ± 0.13

[a] $p < .05$ compared with controls; [b] $p < .01$ compared with controls; [c] $p < .001$ compared with controls.

To convert calcium values from mEq/L to mmol/L, multiply the value by 0.500.

effluent. However, the venoarterial pH gradient did not correlate with duration of arrest.

The severity of acidosis has been correlated with cardiac effects. Significant metabolic acidosis with a pH <7.1 has resulted in decreased coronary perfusion pressures (24). However, the administration of bicarbonate resulted in improved coronary perfusion pressure that was accentuated with prolonged arrest. This finding suggests that the combination of bicarbonate and epinephrine is superior to buffer alone, which may worsen coronary perfusion pressure (25). The presence of acidosis may also impede cardiovascular recovery by decreasing the frequency of successful defibrillation (26). The success of defibrillation was equivalent in both bicarbonate and control groups with brief and prolonged arrest.

The adverse effect of acidosis on outcome becomes significant in the pH range of 6.9 to 7.2 (26–28). This effect is consistent for both respiratory and metabolic causes of acidosis if observation is continued for a sufficient period of time (24). Similarly, significant iatrogenic alkalosis (pH 7.45 to 7.60) due to excessive bicarbonate administration has proved to be an adverse prognostic indicator in cardiac arrest (12). Metabolic abnormalities associated with bicarbonate use include hypernatremia due to the sodium load (1 mmol/mL), hypokalemia due to intracellular shift with alkalosis, along with hypocalcemia. These findings were transient in this study, occurring immediately postarrest and dissipating quickly.

A clear survival benefit was associated with bicarbonate use in the group with prolonged arrest. This improvement in outcome was due predominantly to the higher rate of return of spontaneous circulation. Possible explanations of the beneficial effects demonstrated in this study include the reduction of metabolic acidosis enhancing the effect of epinephrine or increase in venous return due to the osmolar (2 mosm/mL) load of bicarbonate, as indicated by increased sodium in the treatment group. The use of bicarbonate with brief arrest may not be harmful, as acidemia was demonstrated even with a 5-min interval of no blood flow.

The presence of cerebral acidosis is an adverse prognostic indicator and may be even more severe than estimated because of the inability to ascertain tissue pH in cardiac arrest (29). However, most discussion has been centered on the adverse central nervous system effects of bicarbonate administration with increased acidosis or intracranial pressure (9, 30). The overall neurologic impairment after arrest was significantly lessened in both brief and prolonged arrest groups treated with bicarbonate, possibly as a result of improved regulation of intracellular pH, since bicarbonate dose and ventilation were carefully regulated. However, an equally likely explanation is a postulated increase in cerebral blood flow due to improved coronary perfusion pressure and return of spontaneous circulation. However, there was no significant difference noted on histopathologic grading of brain specimens. This effect may be due to the short maturation time (24 hrs) of ischemic lesions, as well as to a lack of sensitivity or specificity in the grading scale.

The empirical administration of sodium bicarbonate should be reevaluated in patients with cardiac arrest. When used within the appropriate time frame (5 to 15 mins after the onset of cardiac arrest), at a conservative dosage initially (1 mEq/kg), early in arrest immediately after the first epinephrine dose and with early postresuscitation base deficit correction, sodium bicarbonate reduces atropine (brief arrest) and epinephrine (prolonged arrest) requirements. Furthermore, it may not be harmful when used in dogs with brief arrest, may increase survival rates in those dogs with prolonged arrest, and may improve neurologic outcome overall. Postulated mechanisms for these results include an increase in coronary and systemic perfusion pressure possibly due to correction of acidemia or the hyperosmolar effect of bicarbonate increasing cardiac preload.

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