An Alternative Sodium Bicarbonate Regimen During Cardiac Arrest and Cardiopulmonary Resuscitation in a Canine Model

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We evaluated the effect of frequent, early bolus administration of low-dose sodium bicarbonate ($NaHCO_3$) on blood gas values during ventricular fibrillation and cardiopulmonary resuscitation (CPR) compared with normal saline and standard bolus doses of $NaHCO_3$. This was a randomized laboratory investigation involving 13 mongrel dogs and 18 experiments (5 dogs were used in a crossover manner). Each dog underwent 3 minutes of ventricular fibrillation, followed by 15 minutes of CPR. Animals were randomly assigned to one of three treatments administered early in the resuscitation effort: $NaHCO_3$ 0.5 mEq/kg at 5, 10, and 15 minutes of ventricular fibrillation (SB); $NaHCO_3$ 1 mEq/kg at 5 minutes and 0.5 mEq/kg at 15 minutes of fibrillation (B); or 0.9% NaCl 1 ml/kg at 5 minutes and 0.5 ml/kg at 15 minutes of fibrillation (P). A total of 15 experiments were included for analysis. Arterial and venous blood gases were sampled at 4, 8, 13, and 18 minutes of fibrillation. The SB group demonstrated the highest arterial partial pressures of carbon dioxide (pCO_2) at each sampling point after $NaHCO_3$, including the 18-minute sample: 42 ± 12, 29 ± 11, and 35 ± 10 torr for SB, P, and B, respectively. In addition, SB produced arterial alkalemia (pH > 7.45) after $NaHCO_3$ administration. The arterial pH at 18 minutes of fibrillation for SB, P, and B was 7.46 ± 0.14, 7.29 ± 0.07, and 7.41 ± 0.1, respectively. Similar trends for pCO_2 and pH were observed for venous samples. Early, frequent administration of low-dose $NaHCO_3$ during CPR is associated with elevated pCO_2 and pH (alkalotic) values that may be potentially detrimental in this setting. It appears that this mode of administration offers no advantage over B with regard to blood gas values during CPR in this canine model.
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During cardiac arrest and cardiopulmonary resuscitation (CPR), acidemia develops as a result of decreased oxygen delivery to the tissues, which leads to lactate production from anaerobic metabolism and tissue acidosis. The accumulation of lactate and the increased carbon dioxide concentrations contribute to the metabolic and respiratory acidemia.

Potential complications of profound acidemia during CPR are depressed myocardial contractility, a lowered ventricular fibrillation threshold, an increased ventricular defibrillation threshold, and attenuation of catecholamine effectiveness.[1-6] The current treatment of systemic acidemia that is not corrected by adequate ventilation is intravenous bolus injection of sodium bicarbonate ($NaHCO_3$) 1 mEq/kg followed every 10 minutes by 0.5 mEq/kg.[7] However, complications associated with standard bolus doses of $NaHCO_3$ include hypercarbia, intracellular acidosis, and alkalemia.

What is not known is whether or not these complications may be attenuated by altering both the timing and the method of drug delivery.

Standard administration of $NaHCO_3$ results in a high concentration of drug in an environment containing high concentrations of hydrogen ions, which results in alkalemia and increases partial pressure of carbon dioxide (pCO_2). This may potentially be avoided by administering small, frequent, bolus doses early in the resuscitation period. This may allow $NaHCO_3$ to counteract the increase in hydrogen ions when concentrations are lower without overwhelming the system, and may avoid the need for large doses later. In addition, early administration of small doses may attenuate the increase in pCO_2 and allow the excess to be eliminated by ventilation. Therefore, we attempted to determine if an alternative mode of $NaHCO_3$ administration (small frequent doses early during resuscitation) has beneficial effects on blood gas values.

Materials and Methods

Thirteen dogs that had previously undergone an episode of cardiac arrest with CPR were evaluated in a randomized fashion (random numbers in blocks of 3). Data analysis was performed in a blinded manner. The study was approved by the Unit for Laboratory Animal Medicine.

Before instrumentation, a forelimb vein was cannulated and surgical anesthesia was produced by intravenous injection of pentobarbital 25 mg/kg. The depth of anesthesia was routinely assessed, and supplemental pentobarbital 5 mg/kg was administered every 30 minutes as required. Each dog was secured in a supine position on a surgical table with a thermoblanket to maintain a body temperature of 37°C.

A cuffed endotracheal tube was placed, with respirations controlled by an Ohio Anesthesia Ventilator (Ohio Medical Products, Madison, WI) with a fraction of inspired oxygen (fiO_2) of 1.0. Respirations were initiated at a rate of 15 breaths/minute with a tidal volume of 15 ml/kg. The ventilatory rate and tidal volume were adjusted to achieve and maintain an arterial pH of 7.40 ± 0.05 and a pCO_2 of 40 ± 5 torr.

Blood samples were analyzed using a Radiometer ABL2 (Acid-Base Laboratory, Cleveland, OH) within 5 minutes of sampling. Samples not immediately analyzed were stored in ice and analyzed within 30 minutes. Arterial (aortic) samples were collected through a pigtail catheter inserted into the femoral artery and positioned with its tip in the aortic arch. Venous blood samples were collected through a 6F catheter inserted into the right jugular vein and positioned with its tip in the right atrium.

Aortic and right atrial pressures were measured through the pigtail catheters. All pressures were measured with a Gould P23 pressure transducer (after calibration), displayed on a monitor, and recorded by a Gould 8-channel RS 3800 graphic recorder (Gould Inc., Cleveland, OH). The position of each catheter was determined by evaluating the pressure waveform and confirmed.at the end of the experiment by autopsy. After catheter placement all dogs were anticoagulated with intravenous heparin 150 U/kg to ensure catheter patency. A three-lead surface electrocardiogram (ECG) was also continuously monitored and recorded.

After stabilization of arterial pH and pCO_2, ventricular fibrillation was induced using a pacing wire carrying a 24-mA, 60-Hz electrical current placed through a 6F catheter with its tip in the right ventricle. Ventricular fibrillation was confirmed by ECG pattern and loss of arterial pressures. After 3 minutes of unassisted cardiac arrest, CPR was begun using a pneumatic chest compression device (Thumper; Michigan Instruments, Grand Rapids, MI) set at a compression rate of 80/minute with a compression duration of 0.5 seconds. The compression force was adjusted to produce a coronary perfusion pressure gradient (aortic-right atrial middiastolic pressure) of approximately 20 mm Hg. After every fifth compression, diastole was prolonged by 0.5 seconds and the lungs were inflated with an inspiratory pressure setting of approximately 10 cm H_2O and fiO_2 of 1.0.

After 5 minutes of ventricular fibrillation (2 min CPR), the animals were randomly assigned to one of three treatment groups: $NaHCO_3$ 1 mEq/kg intravenous bolus over 20 seconds, followed by a second 0.5-mEq/kg bolus given at 15 minutes of ventricular fibrillation (B); $NaHCO_3$ 0.5 mEq/kg intravenous bolus over 20 seconds, followed by a 0.5-mEq/kg bolus at 10 and 15 minutes of ventricular fibrillation (SB); or 0.9% NaCl 1 ml/kg intravenous bolus over 20 seconds, followed by a second bolus of 0.5 ml/kg given at 15 minutes of ventricular fibrillation (P). All treatments were administered through an indwelling catheter in a forelimb vein. At 4, 8, 13, and 18 minutes of cardiac arrest, blood samples were simultaneously obtained from the aorta and right atrium to determine blood gas values.

Statistical analysis was performed using analysis

Table 1. Blood Gases Before and During CPR

Time (min)	B	SB	P	B	SB	P
			Treatment Group			
		pHa			pHv	
0	7.372 ± 0.019	7.400 ± 0.034	7.388 ± 0.027	7.334 ± 0.025	7.342 ± 0.026	7.350 ± 0.034
4	7.446 ± 0.058	7.476 ± 0.112	7.416 ± 0.040	7.262 ± 0.019	7.307 ± 0.058	7.300 ± 0.033
8	7.506 ± 0.205	7.498 ± 0.156	7.390 ± 0.077	7.278 ± 0.081	7.270 ± 0.037	7.242 ± 0.072
13	7.408 ± 0.143	7.466 ± 0.150	7.366 ± 0.067	7.246 ± 0.071	7.240 ± 0.042	7.224 ± 0.072
18	7.408 ± 0.104	7.466 ± 0.145	7.295 ± 0.071	7.227 ± 0.042	7.232 ± 0.056	7.200 ± 0.071
		$aPCO_2$ (torr)			$vPCO_2$ (torr)	
0	40.10 ± 3.904	37.62 ± 2.410	39.24 ± 3.008	43.58 ± 6.445	48.58 ± 4.342	46.42 ± 7.443
4	29.18 ± 5.206	28.02 ± 8.679	30.48 ± 5.528	55.68 ± 5.048	52.72 ± 9.077	52.82 ± 6.272
8	35.90 ± 12.723	36.50 ± 8.858	26.32 ± 10.495	64.84 ± 15.457	68.60 ± 5.680	54.14 ± 15.847
13	30.78 ± 12.479	37.02 ± 10.735	27.60 ± 8.660	64.06 ± 12.522	72.45 ± 7.233	55.28 ± 14.036
18	34.62 ± 10.084	42.10 ± 11.653	29.05 ± 11.181	65.85 ± 9.764	74.02 ± 5.874	59.94 ± 12.681
		$aHCO_3$ (mEq/L)			$vHCO_3$ (mEq/L)	
0	22.78 ± 1.678	22.98 ± 2.956	23.20 ± 2.027	22.54 ± 2.458	25.75 ± 3.472	24.92 ± 3.200
4	19.62 ± 2.273	20.04 ± 4.014	19.14 ± 1.674	23.62 ± 1.886	24.07 ± 4.881	25.22 ± 2.587
8	28.22 ± 9.318	27.82 ± 6.672	15.22 ± 4.200[a]	29.00 ± 3.833	30.82 ± 3.657	21.86 ± 3.684[a]
13	18.20 ± 3.947	25.88 ± 4.655[b]	15.20 ± 3.585	26.46 ± 1.923	29.88 ± 2.546	21.60 ± 3.004[a]
18	20.86 ± 2.456	27.20 ± 3.132	13.88 ± 5.432[a]	26.38 ± 1.348	30.08 ± 2.022	22.32 ± 2.298[a]

[a]p<0.05, P versus B and SB.
[b]p<0.05, SB versus B and P.

of variance (ANOVA) with a repeated measures design. Differences among means were evaluated using Tukey's Studentized range test with a p≤0.05 considered significant. Data are reported as means ± SD.

Results

Data suitable for analysis were obtained from 15 drug trials (experiments) in the 13 animals. Prior to breaking the randomization code, data from one trial in each of the treatment groups were excluded from analysis because of a decreased baseline aortic oxygen saturation greater than 2 SD from the population mean. Since all animals had a prior episode of cardiac arrest and CPR of similar duration (10 min), a decrease in aortic oxygen saturation could be an indication of underlying pathology, and therefore data from these animals were excluded. Five animals were evaluated in a crossover fashion, having been randomized to a different treatment arm after successful resuscitation. These were the only animals that were successfully resuscitated after $NaHCO_3$ administration.

In addition to baseline blood gas values, baseline and CPR hemodynamics were evaluated to ensure that the animals were comparable among groups. No significant differences were seen in baseline arterial systolic or diastolic pressures among the three groups: B 122 ± 30 mm Hg (range 80–160

mm Hg) and 89 ± 30 mm Hg (range 60–130 mm Hg); SB 116 ± 19 mm Hg (range 85–135 mm Hg) and 93 ± 17 mm Hg (range 65–110 mm Hg); and P 99 ± 38 mm Hg (range 50–135 mm Hg) and 80 ± 37 mm Hg (range 30–115 mm Hg; p>0.50). In addition, no significant difference was seen in coronary perfusion pressures after drug administration; at 5 minutes of ventricular fibrillation for B, SB, and P they were 19 ± 9, 23 ± 8, and 23 ± 12 mm Hg, respectively (p>0.78).

The mean arterial and right atrial pH, pCO_2, and HCO_3 measurements during CPR are shown in Table 1. There were no statistically significant differences in either pH or pCO_2 among groups at baseline or after 4, 8, 13, and 18 minutes of CPR. No significant difference in the arteriovenous pH gradient was detected; however, arterial alkalemia (pH > 7.45) occurred intermittently at times after drug administration in both $NaHCO_3$ groups compared with arterial acidemia (pH < 7.35) in the P group. In addition, the SB group had the greatest elevation in pCO_2 values at all times measured after drug administration.

Prior to inducing cardiac arrest and at 4 minutes of ventricular fibrillation, the arterial and venous bicarbonate concentrations in all groups were similar. After 8 minutes of ventricular fibrillation, both the arterial and venous concentrations were significantly higher in animals randomized to the B and SB groups compared with placebo (p<0.05).

After 13 minutes of ventricular fibrillation, the arterial bicarbonate level in the SB group remained significantly increased compared with the other two groups ($p < 0.05$). However, in both B and SB groups it was again significantly increased above P at 18 minutes ($p < 0.05$).

Discussion

Similar to results from other investigations, the current study demonstrated that systemic acidemia develops during CPR.[8, 9] To simulate CPR technique, aggressive ventilation was maintained, and the arterial pCO_2 decreased by approximately 10 torr at 4 minutes in all groups. This degree of arterial hypocarbia was maintained in the placebo group until the end of the CPR period. However, after $NaHCO_3$ administration, it increased in both treatment groups, being highest in the SB group at the end of CPR ($p > 0.05$).

Despite the failure to demonstrate a statistically significant difference in pCO_2 among the groups, there appeared to be a trend to an overall higher value in the $NaHCO_3$ groups, as discussed previously. This result is not unexpected, since other studies reported significant increases in pCO_2 after bicarbonate administration.[10, 11] Similarly, we found no statistically significant differences in pH values among the groups. However, arterial alkalemia did occur in both the B and SB groups after drug administration. A potential complication of this is enhanced glycolysis leading to increased lactic acid production and increased oxygen-hemoglobin binding. In addition, arterial alkalemia may result in lower coronary perfusion pressures after epinephrine therapy, compared with arterial acidemia.[12]

The guidelines for advanced cardiac life support promulgated by the American Heart Association do not support early, empiric administration of $NaHCO_3$ during cardiopulmonary resuscitation.[7] The rationale is that acidemia can be controlled by ventilation alone for a short period of time, and that $NaHCO_3$ may be detrimental and produce arterial alkalemia and paradoxic intracellular and intracerebral acidosis secondary to increased pCO_2. We observed no favorable effects for an alternative dosing method (SB group) on arterial or venous pH or pCO_2 when administered early during CPR. In fact, this method was associated with the greatest elevation in arterial pH and pCO_2 at the end of CPR.

With a larger sample these differences may have become significant (type II error). For example, to detect a difference in pCO_2, approximately seven more experiments would have to be done to detect a difference between placebo and SB ($\alpha = 0.05$, $\beta = 0.2$). Therefore, several low-dose boluses of $NaHCO_3$ administered every 5 minutes early during CPR may be less desirable than the currently recommended method, secondary to increased pCO_2 concentrations and the development of alkalemia.

In contrast to these results, another animal study suggested that alternative modes of $NaHCO_3$ administration may be beneficial. A continuous infusion of 0.1 mEq/kg/minute increased venous pH without significantly increasing pCO_2, compared with standard doses.[8] In addition, there was no indication of cerebrospinal fluid acidosis for the continuous-infusion group. Further work in this area is necessary to determine if alternative modes of $NaHCO_3$ administration may be beneficial during CPR.

The findings of the current study should be interpreted with caution since the duration of ventricular fibrillation and CPR was short, and intracellular pH and survival were not evaluated. The relatively small sample may have hindered our ability to detect significant differences among the treatment groups. In addition, the sampling scheme may not have allowed for the detection of peak increases in pH and pCO_2, which may have demonstrated significant differences from the placebo group. Finally, the applicability of these results to humans during cardiopulmonary arrest is unknown.

Our results demonstrate that early, frequent administration of low-dose $NaHCO_3$ during CPR is associated with elevated pCO_2 and pH (alkalotic) values that may be potentially detrimental in this setting. From these results it appears that this mode of administration offers no advantage over standard-dose $NaHCO_3$ as it relates to blood gas values during CPR in this canine model. Further studies will determine if alternate methods of $NaHCO_3$ administration for correcting acidemia during CPR are beneficial.

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