Buffer Agents Do Not Reverse Intramyocardial Acidosis During Cardiac Resuscitation

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We investigated the effects of carbon dioxide–producing and carbon dioxide–consuming buffers on intramyocardial pH and on cardiac resuscitability. In 29 pigs, intramyocardial pH was continuously measured with a glass electrode advanced into the midmyocardium of the posterior left ventricle through a diaphragmatic window. Ventricular fibrillation (VF) was electrically induced by alternating current applied to the epicardium of the left ventricle. After 3 minutes of VF, precordial compression was begun and continued for an interval of 8 minutes. Sodium bicarbonate (a carbon dioxide–generating buffer), Carbicarb (a carbon dioxide–consuming buffer), and hypertonic sodium chloride (control solution) were infused into the right atrium during cardiac resuscitation. Defibrillation was attempted by transthoracic direct-current shock after 11 minutes of VF. Intramyocardial pH progressively decreased from an average value of 7.26 before VF to 6.87 before infusion of buffers. Systemic circulation and great cardiac vein pH significantly increased after administration of the two buffer agents. However, intramyocardial pH continued to decline to an average of 6.62 after 11 minutes of VF, and this decline was not altered by either buffer solution or by the saline control. As in previous studies, resuscitability was closely related to coronary perfusion pressure at the time of direct-current countershock but not to pH. Accordingly, the rationale of reversing acidosis by the administration of these buffer agents is not supported. Even more important, neither carbon dioxide–consuming nor carbon dioxide–producing buffers altered myocardial acidosis or improved myocardial resuscitability under controlled experimental conditions of cardiac arrest. (Circulation 1990;81:1660–1666)

The traditional concept that acidemia and especially myocardial acidosis impair contractility and preclude resuscitation prompted the aggressive use of buffer agents during the two decades that followed the introduction of closed-chest cardiac resuscitation.1,2 In a porcine model of cardiac arrest, we confirmed that intramyocardial pH rapidly decreased from 7.27 to 6.88 after 11 minutes of cardiac arrest.3 However, this decrease in myocardial pH was associated with concurrent increases in great cardiac vein PCO2 to average levels of 158 mm Hg.3 We therefore hypothesized that rapid accumulation of carbon dioxide contributed to early myocardial acidosis during cardiac arrest and cardiopulmonary resuscitation.

These observations had potentially important implications for buffer therapy. If myocardial acidosis is due to increases in myocardial PCO2, sodium bicarbonate may augment the carbon dioxide load and thereby exacerbate intracellular acidosis. This would be more likely to reduce contractility and thereby adversely affect resuscitability.4–9 Conversely, sodium carbonate, which is a constituent of Carbicarb, consumes carbon dioxide and may therefore ameliorate myocardial acidosis by reducing carbon dioxide.

These issues prompted our group to investigate the effects of buffer agents on myocardial pH during cardiac arrest. We specifically sought understanding of the different effects of carbon dioxide–generating and carbon dioxide–consuming buffers. Preliminary findings were previously reported in abstract form.10

Methods

Experimental Preparation

We adapted a porcine model of cardiac arrest and cardiopulmonary resuscitation for continuous mea-
measurements of myocardial pH. Experiments were performed on 29 domestic pigs, aged 3–4 months and weighing 20–35 kg. The animal care and procedure were in accord with the guidelines of the Institute of Laboratory Animal Resources of the National Research Council. The animals were sedated by injection of ketamine (20 mg/kg i.m.), and anesthesia was induced by administration of pentobarbital (25 mg/kg i.v.) and maintained by bolus injections of 5 mg/kg at intervals of approximately 30 minutes. After endotracheal intubation, neuromuscular blockade was induced by injection of pancuronium bromide 0.09 mg/kg i.v. and maintained with 0.05 mg/kg boluses at 1-hour intervals. Ventilation was maintained with a volume-controlled ventilator with an inspired gas mixture of 50% oxygen and 50% nitrogen. Ventilation was maintained at a frequency of 12–18 breaths/min and a tidal volume of 15 ml/kg. Frequency was adjusted to establish and maintain baseline arterial Pco2 at 35–45 mm Hg.

A 7F balloon-tipped thermodilution catheter (model 6523-8F, CR Bart, Billerica, Massachusetts) was advanced from the right femoral artery into the pulmonary artery. For arterial monitoring, an 8F angiographic catheter (USCI model 5470-7F, CR Bart) was advanced from the left cephalic vein into the thoracic aorta. A 7F angiographic catheter (USCI model 6523-8F, CR Bart) was advanced from the left cephalic vein into the coronary sinus and then an additional 4 cm into the great cardiac vein. All catheter positions were confirmed by fluoroscopy. Patency of the catheters was maintained with minimal pressure flushes of physiological saline containing 10 IU heparin/ml by the Intraflow system (Spectramed, Oxnard, California).

For measurement of intramyocardial pH, a midline laparotomy was performed. The tendinous portion of the diaphragm was excised exposing the pericardium, and a 1.5-cm horizontal incision was made in the pericardium overlying the diaphragmatic left ventricular myocardium. A 1-mm steel-jacketed glass-tipped pH electrode was advanced into a position midway between the epicardial and the endocardial surfaces of the diaphragmatic left ventricle. The myocardial temperature was measured with a sensor advanced into the myocardium within 1 cm of the pH electrode. It was secured with a suture that also served to close the pericardial incision. A potassium chloride reference electrode was placed in a subcutaneous pocket in the neck. Fluid losses were replaced with physiological saline infused in amounts of 10 ml/kg/hr. Blood temperature was maintained at 36–37°C with the aid of external infrared heat lamps.

Measurements

Myocardial pH was measured with an electrode system developed by Khuri et al. and supplied by Vascular Technology (Chelmsford, Massachusetts). The pH and myocardial temperature were digitally recorded at intervals of 20 seconds with a personal computer system (model 100, Tandy, Ft. Worth, Texas).

Arterial, pulmonary artery (mixed venous), and cardiac vein measurements of pH, Pco2, and lactic acid were obtained before and at 2, 5, and 9 minutes after onset of ventricular fibrillation. Additional samples were withdrawn from the great cardiac vein at 4, 7, and 10 minutes after onset of ventricular fibrillation. In successfully resuscitated animals, measurements were repeatedly obtained at 2, 30, and 60 minutes after resuscitation. Blood gases were measured with an automated pH blood gas analyzer (model IL-813, Instrumentation Laboratories, Lexington, Massachusetts) and corrected for blood temperature. Lactic acid levels were measured with an electrode technique (Lactate Analyzer, model 23 L, Yellow Springs Instruments, Yellow Springs, Ohio). Bicarbonate levels were computed from pH and Pco2.

Coronary perfusion pressure was computed as the difference between diastolic aortic pressure and time coincident diastolic right atrial pressure. Dynamic data, including electrocardiogram (lead II), and intravascular pressures were continuously recorded.

Procedure

The validity of measurements of myocardial pH were examined under physiological conditions in pigs by relating changes in FicO2 to concurrent changes in myocardial pH and their reversal. In the porcine model of cardiac arrest, animals were stabilized for 60 minutes before inducing ventricular fibrillation, which was induced by an alternating current shock of 10 mA delivered to the epicardium of the anterior left ventricle. External chest compression with a mechanical compressor (Thumper, model 1000, Michigan Instruments, Grand Rapids, Michigan) was begun after 3 minutes of untreated ventricular fibrillation. Compression was maintained at a rate of 60/min, an equal compression-relaxation interval (i.e., 50% duty cycle) and a compression depth of 25–30% of the animal’s anteroposterior chest width. After 11 minutes of ventricular fibrillation, a maximum of two 300-J countershocks were delivered in rapid sequence with a defibrillator (Lifepak, model 911, Physio-Control, Redmond, Washington). The shocks were applied by placing the paddles in the right infraclavicular area and the cardiac apex. If ventricular fibrillation persisted, the countershocks were repeated after a 30-second period of thumping. This resuscitation protocol was repeated for a maximum of three times in an effort to restore a viable ventricular rhythm.

Test drugs were supplied and coded by International Medication Systems (South El Monte, California). We were not aware of the contents, and the code was broken only after the study was completed. Hypertonic solutions of either sodium bicarbonate (2,000 mosm/kg solution), Carbicarb (1,667 mosm/kg), or NaCl (2,000 mosm/kg) were administered in a volume of 2.5 ml/kg body wt. This corresponded to doses of 5.0 mosm sodium bicarbonate/kg, 5.0 mosm...
NaCl/kg, and 4.2 mosm Carbicarb/kg body wt. The solutions were infused through the right atrial port of the pulmonary artery catheter during a 1-minute interval beginning 6 minutes after onset of ventricular fibrillation (3 minutes after start of precordial compression).

Autopsy was performed for confirmation of appropriate placement of catheters and to ensure that there were no adverse effects from the surgical procedures or from external chest compression.

Statistical Analysis

The changes over time were analyzed with single-factor repeated-measures analysis of variance. One-way analysis of variance with a least-significant difference test was used to compare the effects of the three drugs at corresponding time intervals. Differences in myocardial pH between resuscitated and nonresuscitated animals in each group were analyzed by the Mann-Whitney test. Categorical outcome was analyzed by the χ² test. The Wilcoxon test was used to compare the effect of drugs before and after infusion within groups. Relations of myocardial pH, coronary perfusion pressure, and resuscitability were examined by multiple regression analysis. The data are mean±SEM, and a p value less than 0.05 was regarded as significant.

Results

Myocardial pH

To address the reliability of measuring myocardial pH and, more specifically, to exclude the likelihood that the technique precluded valid measurements because of local tissue injury resulting from implantation of the electrode, we examined myocardial pH under variable conditions of Fico₂ in a subset of five pigs. When the Fico₂ was increased from 0 to 0.10, myocardial pH was correspondingly reduced from 7.09 to 6.94 during an interval of 11 minutes. With restoration of Fico₂ to 0.0, myocardial pH increased to 7.05 within 10 minutes and returned to 7.10 within 30 minutes.

The changes in myocardial pH before and after infusion of buffers or control saline solution are shown in Figure 1. Myocardial pH decreased from 7.26±0.02 to 7.14±0.02 (p<0.01) during the 3-minute interval of untreated ventricular fibrillation. During precordial compression, it declined to an average of 6.87±0.03 (p<0.001) before buffer administration. After infusion of buffers or control saline solutions, myocardial pH further declined to average levels of 6.62 (p<0.01) after 11 minutes of ventricular fibrillation. No statistically significant differences in myocardial pH were documented among the three drugs at the 11th minute of ventricular fibrillation. After administration of sodium bicarbonate, myocardial pH was 6.58±0.04; after Carbicarb, it was 6.59±0.08, and in the saline control group, it was 6.70±0.04.

Systemic and Coronary Blood pH, Pco₂, and Lactate Production

The effect of buffers on myocardial pH contrasted with the effects of buffers on blood sampled from the systemic and coronary circulations. Both buffers significantly increased pH and bicarbonate of arterial, mixed venous, and great cardiac vein blood (Table 1 and Figure 2). However, as expected, sodium bicarbonate significantly increased Pco₂, whereas Carbicarb significantly decreased Pco₂ of mixed venous blood (Table 2).

A large gradient in lactate concentration between aortic and great cardiac vein blood was observed during cardiac arrest, indicating continued myocardial lactate production. This was unaffected by buffer therapy (Figure 3).

Resuscitability

External countershocks successfully reversed ventricular fibrillation in each animal. However, sponta-
neous circulation was reestablished in only three of 13 in the sodium bicarbonate group, five of seven in the Carbicarb group, and six of nine in the saline control group (p < 0.05). There were no significant differences in myocardial pH immediately before defibrillation between the successfully resuscitated and nonresuscitated animals (Figure 4).

Successful resuscitation was followed by rapid reversal of myocardial acidosis. Intramyocardial pH averaged 6.90 at 2 minutes after stable, spontaneous circulation and reached 7.16 at 60 minutes after resuscitation (Figure 1). After resuscitation and restoration of spontaneous circulation, myocardial acidosis was reversed at approximately the same rate and to the same extent in the buffer and saline control solutions.

Coronary perfusion pressure measured before defibrillation was highly predictive of cardiac resuscitability. When coronary perfusion pressure exceeded 10 mm Hg, spontaneous circulation was restored in 14 of 15 animals after cardiac arrest. In 14 animals in which coronary perfusion pressure was lower than 10 mm Hg, a perfusing rhythm could not be restored (Figure 5). Multiple regression analysis confirmed that coronary perfusion pressure was highly predictive of resuscitability (p < 0.001), but myocardial pH failed to predict outcome.

**Myocardial Acid and Base Changes During Spontaneous Circulation**

Failing to find changes in myocardial pH, we made additional observations in normal pigs. In a subset of nine animals, the same doses of either buffer agent or saline were infused under physiological conditions and in the absence of cardiac arrest. After sodium bicar-
TABLE 2.  \( \text{PCO}_2 \) in Aortic, Mixed Venous, and Great Cardiac Vein Blood Before and After Infusion of Buffer Agents and Saline Control

<table>
<thead>
<tr>
<th>Site</th>
<th>Solution</th>
<th>Control Preinfusion</th>
<th>Precordial compression during ventricular fibrillation</th>
<th>Postresuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-2 Min</td>
<td>5 Min</td>
<td>9 Min</td>
</tr>
<tr>
<td>Aorta</td>
<td>NaHCO(_3)</td>
<td>41.1±1.0</td>
<td>40.4±2.6</td>
<td>53.0±3.0§</td>
</tr>
<tr>
<td></td>
<td>Carbicarb</td>
<td>41.2±1.7</td>
<td>37.6±3.3</td>
<td>31.2±6.0†</td>
</tr>
<tr>
<td></td>
<td>NaCl</td>
<td>45.5±1.8</td>
<td>37.5±2.8</td>
<td>38.5±3.7</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>NaHCO(_3)</td>
<td>51.2±2.3</td>
<td>66.3±5.0</td>
<td>77.1±4.6§</td>
</tr>
<tr>
<td></td>
<td>Carbicarb</td>
<td>49.2±2.9</td>
<td>64.3±7.2</td>
<td>54.5±5.9§</td>
</tr>
<tr>
<td></td>
<td>NaCl</td>
<td>53.5±2.2</td>
<td>66.5±3.7</td>
<td>60.5±4.4</td>
</tr>
<tr>
<td>Great cardiac vein</td>
<td>NaHCO(_3)</td>
<td>52.5±1.5</td>
<td>99.6±7.4</td>
<td>135.7±16.7§</td>
</tr>
<tr>
<td></td>
<td>Carbicarb</td>
<td>53.0±2.5</td>
<td>135.6±20.7</td>
<td>121.4±22.6</td>
</tr>
<tr>
<td></td>
<td>NaCl</td>
<td>55.0±2.1</td>
<td>120.4±19.5</td>
<td>101.1±13.4</td>
</tr>
</tbody>
</table>

\( \dagger p<0.05 \) vs. NaHCO\(_3\) and NaCl by one-way analysis of variance and a least-significant difference test; \( \ddagger p<0.01 \) vs. preinfusion by the Wilcoxon’s pair test; \( \ddagger p<0.05 \) vs. preinfusion.

bicarbonate administration, myocardial pH increased from 7.10±0.03 to 7.14±0.06, and great cardiac vein pH increased from 7.24±0.03 to 7.32±0.04 within 4 minutes and remained unchanged within 10 minutes. After Carbicarb administration, myocardial pH increased from 7.14±0.11 to 7.19±0.12, and great cardiac vein pH increased from 7.25±0.03 to 7.40±0.06. After saline administration, myocardial pH decreased insignificantly from 7.39±0.02 to 7.36±0.03.

**Autopsy**

No major injuries to internal organs were observed. As in previous experiments with this model, there were bilateral fractures in the anterior portions of the third and fourth ribs and mild hemorrhagic contusions of subjacent lung in each pig. The myocardial probes were in good position, and only minimal purpura of the myocardium was observed at the implantation sites.

**Discussion**

As demonstrated in earlier studies, cardiac arrest and cardiopulmonary resuscitation were associated with profound but reversible decreases in myocardial pH. In the present study, we documented failure of buffer agents, either carbon dioxide–producing or carbon dioxide–consuming, to neutralize such decreases in myocardial pH during cardiopulmonary resuscitation. Increases in pH and bicarbonate in systemic and coronary venous blood after infusion of either sodium bicarbonate or Carbicarb did not, of themselves, significantly alter myocardial pH during the relatively brief time interval of cardiac arrest. The conventional doses of buffers produced only minimal

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**FIGURE 3.** Plot of effects of hypertonic sodium bicarbonate, Carbicarb, and sodium chloride on myocardial lactate production. Marked myocardial lactate production was demonstrated after cardiac arrest, and this was not mitigated by the infusion of buffer solutions. Anaerobic generation of lactate was reversed only after spontaneous circulation was restored.
increases in myocardial pH under physiological conditions in the absence of cardiac arrest. This contrasts with buffer-induced increases in pH and bicarbonate in systemic and coronary venous blood. Therefore, we recognized that when buffer agents were delivered to the coronary circulation under conditions of either normal or reduced myocardial blood flow, they had no statistically significant effect on myocardial pH.

We addressed the possibility that local muscle injury stemming from the insertion of the electrode may invalidate measurements of myocardial pH. We were reassured by the observation that during spontaneous circulation and during cardiac arrest, the pH values measured by us corresponded to those measured with alternative techniques, and especially spectral nuclear magnetic resonance, fiberoptic sensors, and hydrogen-ion selective polymer pH electrode. Moreover, the time coincidence of decreases in myocardial pH after onset of cardiac arrest and its reversal after restoration of spontaneous circulation provided evidence that changes in myocardial pH corresponded to the changes in systemic and myocardial blood flow. In addition, we documented prompt and consistent decreases in myocardial pH when animals were ventilated with Fio2 0.10 and its equally prompt reversal. Accordingly, there is little likelihood that the technique of myocardial pH measurement precluded quantitative measurements of the effects of buffer agents on myocardial pH.

We also addressed the possibility that myocardial pH as measured by us may not be representative of intracellular pH. Although this constraint is acknowledged, Walters et al previously observed a high correlation between tissue electrode pH and intracellular pH by enzyme assay. Intracellular and tissue pH are closely related, and changes in intracellular pH are rapidly followed by corresponding changes in myocardial tissue pH.

The markedly reduced myocardial blood flow during cardiac arrest may explain, in part, the failure of intravascular buffer solutions to mitigate the profound myocardial acidosis. However, the significant increases in pH and bicarbonate in coronary venous blood suggest that the flow was indeed adequate to transport the buffers into the coronary circulation. Therefore, both the gradient and time required for buffer equilibration between the intravascular and the intracellular compartment across the cell membranes are probably not adequate to allow for significant myocardial buffer effect. More specifically, hydrogen ion exchange progresses throughout periods that substantially exceed the 5–30-minute interval of cardiac resuscitation.

Not fully clarified is the quantitative effect of carbon dioxide that is generated by buffering of bicarbonate. Because carbon dioxide, unlike sodium and hydrogen ions and bicarbonate, diffuses readily across cell membranes without the time constraint of ionic transfer, it could potentially produce a paradoxical decrease in myocardial pH. The present study provides evidence against such effect, because no differences were observed between myocardial pH after administration of bicarbonate (a carbon dioxide producer) and that after administration of Carbicarb (a carbon dioxide consumer) or the saline control solution. Moreover, the exogenous effect of buffers on myocardial PCO2 may be relatively small compared with the marked endogenous increases in myocardial PCO2 that may exceed 400 mm Hg during cardiac arrest.

The decreases in myocardial pH were associated with increases in great cardiac vein lactate production and are, therefore, characteristic of ischemia. The buffer agents had no effect on myocardial (or systemic) lactate production. These observations contrast with those of Arieff and coworkers in a canine model of hypoxic lactic acidosis. Return of spontaneous circulation was followed by spontaneous increases in myocardial pH and reversal of lactic acidosis. These data confirm our earlier observation that reversal of myocardial acidosis after cardiac arrest is coincident with successful cardiac resuscitation with restoration of spontaneous circulation.

Early studies by our group and other investigators have consistently demonstrated that success-
ful cardiac resuscitation is closely related to the threshold level of coronary perfusion pressure. The validity of the study is reinforced by the additional confirmation that coronary perfusion pressure, independently of myocardial pH, was predictive of resuscitability.

As yet, the precise mechanism of myocardial acidosis is unclear. In addition to lactic acidosis, hypercarbia has been implicated.23,32 The myocardial carbon dioxide tension is strikingly increased during myocardial ischemia and especially during the global myocardial ischemia of cardiac arrest.23,24,33 Nevertheless, the present study provides additional evidence that the administration of buffer agents is of little benefit. What does emerge is that buffer agents do not alter myocardial pH during the time frame of cardiopulmonary resuscitation. For that reason alone, the historical rationale for their use, that is, to counteract myocardial acidosis, may have to be revised.

References


Key Words • ventricular fibrillation buffer agents • coronary perfusion pressure • sodium bicarbonate • Carbicarb • cardiac arrest
Buffer agents do not reverse intramyocardial acidosis during cardiac resuscitation.
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