Myocardial Acidosis Associated With CO₂ Production During Cardiac Arrest and Resuscitation

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Previous studies from our institution demonstrated significant hypercarbic acidosis in the mixed venous (pulmonary artery) blood in animals and human patients during cardiac arrest and cardiopulmonary resuscitation (CPR). In the present study, the acid-base state of the myocardium during cardiac arrest was investigated. Cardiac arrest was electrically induced in 11 pentobarbital-anesthetized and mechanically ventilated domestic pigs. Precordial compression was begun 3 minutes after onset of ventricular fibrillation and continued for 8 minutes. During CPR, there was rapid onset of profound myocardial acidosis with an increase in intramyocardial [H⁺] from 54±5 to 146±20 nmol/l (7.27±0.04 to 6.88±0.20 pH units). Great cardiac vein Pco₂ increased from 57±2 to 158±12 mm Hg. Profound hypercarbic acidosis in great cardiac vein blood was associated with myocardial lactate production to levels of 8.1±0.7 mmol/l. Only moderate decreases in cardiac vein bicarbonate concentrations from 31±1 to 23±1 mmol/l were observed. These acid-base changes were almost completely reversed over an interval of 60 minutes after the animals were successfully resuscitated by DC countershock. The Pco₂ in cardiac vein blood was significantly greater than that of mixed venous blood, demonstrating disproportionate myocardial production of CO₂ during CPR. Accordingly, it is CO₂ production during ischemia that is implicated as the predominant mechanism accounting for myocardial [H⁺] increases during cardiac arrest. Important clinical implications for buffer therapy during CPR and, in particular, treatment with bicarbonate emerge from these observations. (Circulation 1989;80:684–692)

In prospective investigations of the pH, Pco₂, and HCO₃⁻ in both arterial and mixed venous blood in pigs, rats, and human patients during CPR, we observed that acidemia is predominantly due to increases in Pco₂ in mixed venous (pulmonary artery) blood. This contrasted with decreases in Pco₂ in arterial blood. The venoarterial Pco₂ gradient exceeded 30 mm Hg, but there was no bicarbonate gradient.¹⁻³ Both excesses of CO₂ generated by HCO₃⁻ buffering of lactate and flow-limited pulmonary excretion of CO₂ were implicated as mechanisms accounting for increases in mixed venous Pco₂.¹⁴ Striking increases in cardiac venous Pco₂ to levels exceeding 150 mm Hg during experimental CPR were observed. The Pco₂ of cardiac vein blood consistently exceeded the Pco₂ of mixed venous blood.⁵ Similar observations were subsequently reported by Capparelli and his associates.⁶

Such profound acidemia has important clinical implications because the efficacy of adrenergic agents may be decreased,⁷ the administration of CO₂ generating buffer agents may be counterproductive,⁸,⁹ and intracellular respiratory acidosis may further reduce myocardial contractility.¹⁰,¹¹

It was, therefore, of interest to quantitate myocardial acidosis in relation to both myocardial CO₂ production and coronary perfusion during CPR. Accordingly, we measured myocardial [H⁺] and myocardial production and extraction of [H⁺], Pco₂, HCO₃⁻, SO₂, and lactate before, during, and after resuscitation from cardiac arrest. Because mean aortic and coronary perfusion pressures have been identified as major determinants of resuscitability, we also monitored these parameters in conjunction with continuous measurements of end-tidal Pco₂.
tension ($P_{ET}CO_2$) and intermittent measurement of cardiac output.4,12

Methods

Animal Preparation

Eleven domestic pigs weighing between 22 and 30 kg were investigated. The animal care and procedures were in accord with the guidelines stated in the Guide for the Care and Use of Laboratory Animals. The domestic pig was selected because the porcine coronary circulation,13 conduction system,14 and epicardial blood supply15 are more like those of the human than other nonprimate animal species.

Anesthesia was induced with 20 mg/kg ketamine and 25 mg/kg pentobarbital, which was subsequently supplemented with 5 mg/kg bolus injections of pentobarbital at intervals of 30 minutes. After endotracheal intubation, constant minute ventilation with a volume-controlled ventilator (Model MA-1, Puritan Bennett, Los Angeles, California) was initiated. FiO₂ was maintained at 0.5, the frequency between 12 and 15/min, the tidal volume at 15 ml/kg, and a maximal flow rate at 40 l/min. The tidal volume was subsequently adjusted such as to maintain baseline arterial $P_{CO_2}$ in the physiologic range of 40–45 mm Hg.

For hemodynamic monitoring, catheters were advanced from the right femoral artery into the thoracic aorta (USCI Model 6523-8F, CR Bart Inc, Billerica, Massachusetts), from the right femoral vein into the pulmonary artery (thermodilution catheter, Model SP5527, Gould Inc, Oxnard, California) and from the left cephalic vein through the coronary sinus into the great cardiac vein (USCI Model 5470-7F, CR Bart Inc, Billerica, Massachusetts). All catheter positions were confirmed by fluoroscopy and characteristic pressure pulse morphology, and appropriate oxygen saturation and lactate content of blood sampled from the catheters. Patency of the catheters was maintained with minimal pressure flushes with physiologic saline containing 10 IU heparin/ml saline using the Intraflow system (Gould Inc, Oxnard, California). Fluid losses were replaced with physiologic saline infused in amounts of 10 ml/kg/hr.

Measurements

Cardiac index was measured by bolus injection of thermal tracer using the thermodilution technique. The reproducibility and validity of this method in this experimental setting was previously reported.16 Coronary perfusion pressure was computed as the difference between diastolic aortic and time coincident diastolic right atrial pressure.

End-tidal $CO_2$ concentration was continuously measured with a side-stream infrared absorption $CO_2$ analyzer (Model 200, Instrumentation Laboratory Inc, Lexington, Massachusetts). The $CO_2$ analyzer was calibrated with room air and $CO_2$ gas standards (Air Products, Allentown, Pennsylvania). Linearity of the measurement was confirmed by stepwise 1% increases in the $CO_2$ concentration from 1% to 5%. The maximal error of the $CO_2$ measurement was less than 2% over the range of 0–40 mm Hg on 35 trials ($r=0.99; y=0.99x+0.01$). $P_{ET}CO_2$ was derived from the end-tidal $CO_2$ concentration corrected for barometric pressure and temperature. The sideline sample manifold of the $CO_2$ analyzer was adapted to the endotracheal tube, and the gas was sampled at a flow rate of 200 ml/min.

Dynamic data including electrocardiogram (lead II), intravascular pressures, tidal volume, and $P_{ET}CO_2$ were continuously recorded with the aid of an eight-channel physiologic amplifier-thermoprinter system (Model 7758A, Hewlett-Packard Inc, Waltham, Massachusetts). Blood temperature was maintained in the range of 36–37°C with the aid of external infrared heat lamps. Arterial, pulmonary artery (mixed venous) and cardiac vein [H⁺], $P_{CO_2}$, $P_O_2$, $P_SO_2$, and lactic acid were measured before and during cardiac arrest, during chest compression, and after resuscitation by techniques previously described.17,18 Bicarbonate was computed from [H⁺], $P_{CO_2}$, and hemoglobin with corrections for blood temperature, which was measured by the thermistor in the pulmonary artery. The acid-base nomograms for immature domestic pigs developed by Hannon10 were used.

For measurement of intramyocardial [H⁺], a midline laparotomy was performed. The tendinous portion of the diaphragm was excised, and a 1.5 cm vertical incision was made in the pericardium overlaying the diaphragmatic left ventricular myocardium. Earlier studies had demonstrated that neither the precardiac arrest hemodynamic status nor the effectiveness of precardial compression and resuscitation was compromised by these interventions in this porcine model.20 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 electrode was then anchored in the myocardium. A temperature sensor was placed in the myocardium within 1 cm of the pH electrode and secured with a suture; the pericardial incision was then closed with sutures. A potassium chloride reference electrode was placed in a subcutaneous pocket in the neck. [H⁺] was measured with a Khuri pH monitor at intervals of 20 seconds. The 95% in vitro response time to step changes in [H⁺] was less than 3 seconds with a linear response over the range of interest.21,22 It was calibrated in vitro before and after completion of the experiment with buffer solutions representing 4.0 and 7.0 pH units.

Experimental Protocol

After baseline hemodynamic, blood gas, and intramyocardial [H⁺] measurements were obtained, ventricular fibrillation was induced by 10 mA AC current delivered to the right ventricular epicar-
After 3 minutes of ventricular fibrillation, external chest compression with a mechanical compressor (Thumper®, Model 1000, Michigan Instruments, Grand Rapids, Michigan) was begun 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 and continued for another 8 minutes. After 11 minutes of ventricular fibrillation, DC defibrillation with 300 J (Model 911, Physio-Control, Redmond, Washington) was attempted. All animals were successfully resuscitated and observed for an additional interval of 60 minutes. The animals were then killed by injection of saturated potassium chloride. Autopsy was performed for confirmation of appropriate placement of catheters and to ensure that there were no adverse effects from the invasive procedures or major injuries stemming from external chest compression.

Statistical Analysis

The significance of changes over time were analyzed by single-factor repeated-measures ANOVA. Measurements are reported as mean±SEM. A p value of less than 0.01 was regarded as significant.

Results

The baseline intramyocardial [H+] after 30 minutes of equilibration was 54±5 nmol/l (7.27±0.04 pH units) with a myocardial temperature of 36.5±0.5°C. After 11 minutes of ventricular fibrillation, there was a significant increase in intramyocardial [H+] to 146±20 nmol/l (6.88±0.20 pH units) with an intramyocardial temperature of 36.8±0.2°C. Restoration of spontaneous circulation was followed by a prompt decline in intramyocardial [H+]. It declined to 58±6 nmol/l (7.24±0.04 pH units) during the 60-minute interval that followed successful defibrillation (Figure 1).

Highly significant increases in cardiac vein [H+], PCO2, and lactate were observed, which peaked during the fourth minute of ventricular fibrillation (i.e., 1 minute after start of external chest compression). This was associated with lesser increases in mixed venous PCO2 and small decreases in arterial PCO2 (Figures 1 and 2). Most impressive were the augmented [H+] and CO2 gradients between the aorta and the pulmonary artery (Figure 3) and between the aorta and the great cardiac vein (Figure 4). These were rapidly reversed after restoration of
normal sinus rhythm. Accordingly, there was marked myocardial production of CO$_2$ during CPR. However, cardiac venous HCO$_3^-$ was only modestly reduced from 31±1 to 23±1 mmol/l during precordial compression. Myocardial oxygen extraction increased from 69±4% to 82±1% at 2 minutes and to 84±1% after 6 minutes of precordial compression. Immediately after resuscitation, it decreased to 24±4% ($p<0.01$) (Figure 2).

Mean aortic pressure declined from 100±6 to 16±1 mm Hg after onset of ventricular fibrillation ($p<0.01$). During precordial compression, it increased to a plateau level of between 43±3 and 45±3 mm Hg ($p<0.01$). It increased to 93±5 mm Hg 60 minutes after resuscitation, which was not significantly different from the prearrest values. Cardiac index declined from 125±11 to 33±3 ml/kg/min after 2 minutes of precordial compression ($p<0.01$) and insignificantly increased to 38±3 ml/kg/min after 6 minutes of precordial compression (Figure 2 and Table 1). After successful defibrillation, it increased to 93±14 mm Hg within 2 minutes after restoration of spontaneous circulation. There was close correspondence between changes in coronary perfusion pressure and PETCO$_2$.

**Discussion**

Earlier studies from our laboratories in a similar porcine model of CPR demonstrated significant increases in the arteriovenous CO$_2$ and pH gradients during cardiac arrest.$^1$ These findings were later confirmed in patients during CPR by our group.$^3$ However, the HCO$_3^-$ before and during CPR in a subset of 13 patients was not altered. Accordingly, the gradients between arterial and mixed venous blood CO$_2$ were solely due to CO$_2$. We demonstrated that these were associated with decreases in pulmonary blood flow such that pulmonary CO$_2$ elimination was critically reduced. This accounted for corresponding decreases in the end-tidal CO$_2$ concentration.$^4,16,23$

Pilot studies subsequently demonstrated striking increases in cardiac venous CO$_2$ that exceeded the mixed venous CO$_2.$^5 We, therefore, anticipated and found profound intramyocardial acidosis during the course of the present studies and related such to the myocardial production of both carbon dioxide and
lactic acid. These acid-base alterations occurred under conditions of constant mechanical ventilation. The high ventilation-to-perfusion ratio accounted for arterial alkalemia in association with acidemia in blood sampled from the pulmonary artery and the great cardiac vein. Comparable or even higher Pco2 levels in mixed venous and cardiac vein blood have been reported in experimental and clinical CPR settings in which arterial Pco2 is reduced to average levels ranging from 16 to 35 mm Hg. 

Accordingly, increases in systemic and coronary venoarterial Pco2 gradients are more closely related to decreases in blood flow rather than changes in alveolar ventilation. Whether more vigorous ventilation would alter CO2 clearance by increasing intrathoracic pressure and, therefore, blood flow is as yet unresolved.

Parallel reductions in coronary perfusion pressure, cardiac index, and PetCO2 were observed. A close relation between coronary perfusion pressure and microsphere determined myocardial blood flow has been demonstrated by other workers. Accordingly, decreases in coronary perfusion pressure and, therefore, in myocardial blood flow accounted for failure to match the metabolic demand of the heart for oxygen with the blood supply to the myocardium. The buffering capacity of cardiac myocytes is greater than that of skeletal muscle, nervous tissue, or extracellular fluids, including blood. The present data, therefore, support the concept that it is bicarbonate buffering of the anaerobically generated lactate that accounts for the increases in intramyocardial CO2.

\[ [H^+] \text{, Pco}_2, \text{ and lactate peaked in cardiac vein blood after 4 minutes; the intramyocardial [H^+] peaked after 11 minutes. The early changes in blood sampled from the great cardiac vein are attributed to partial restoration of coronary blood flow during precordial compression with washout of metabolites accumulated during the no-flow interval of cardiac arrest. Nevertheless, coronary perfusion during precordial compression was not sufficient to reverse anaerobic metabolism. Consequently, the severity of intramyocardial acidosis was progressive during the 9-minute interval of ventricular fibrillation even though coronary venous Pco2 remained stable or decreased. The generation of additional protons by lipolysis and ATP hydrolysis in association with continuing lactate production would account for continued increase of intramyocardial [H^+].} \]

Indeed, intramyocardial lactate may be substantially increased during acute myocardial
ischemia without parallel increases of cardiac vein lactate. After successful resuscitation with restoration of near-normal cardiac index and coronary perfusion pressures, lactate production and intramyocardial acidosis were reversed. The observations of Lai et al would support this explanation.

Myocardial acidosis associated with CO₂ production is likely to be of clinical import. Experimentally, intracellular acidosis due to rapid CO₂ accumulation is associated with rapid loss of myocardial contractility. The myocardial depressant effect of CO₂ was recognized as early as 1910 by Ernest Starling and his coworker, E. Jerusalem. Poole-Wilson and Langer confirmed these findings on rat and rabbit myocardium. Both Steenbergen et al in studies on the perfused rat heart and MacGregor and his associates in dogs demonstrated marked depression of myocardial contractility when myocardial pH was decreased in association with increases in myocardial CO₂ tension. We confirmed in our laboratories in the isolated rat heart the earlier observations of Williamson et al that increases in PCO₂ rather than changes in pH of the perfusate adversely affect contractility over the pH range of 6.80–7.40.

The pH of myocardium and, therefore, its contractility are likely to be rapidly reduced in the setting of myocardial ischemia because of the ease with which CO₂ diffuses into myocardial cells and thereby increases in intracellular CO₂. In studies by Case et al in dogs, the intramyocardial CO₂ increased within 7–10 seconds after experimental coronary occlusion and progressively increased to 430 mm Hg when ventricular fibrillation was induced by coronary occlusion.

Changes in cardiac vein CO₂ at varying coronary flows and respiratory rates closely parallel those of intramyocardial CO₂. Unfortunately, we have not as yet been successful in our efforts to produce a reliable and rapid response electrode for measurement of myocardial PCO₂ during cardiac resuscitation. However, in studies that used slower response mass spectrometry methods, increases in myocardial CO₂ during ischemia correlated highly with increases in myocardial [H⁺], intramural ST segment changes, anaerobic generation of high energy phosphates, and histologic injury.

The interpretation of our findings may be challenged because our technique for measurement of intramyocardial [H⁺] includes extracellular or interstitial [H⁺] and is not selective for intracellular
TABLE 1. Acid-Base and Hemodynamic Parameters Before, During, and After CPR in 11 Domestic Pigs

<table>
<thead>
<tr>
<th>Minutes</th>
<th>Control</th>
<th>Ventricular fibrillation</th>
<th>Resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>H+ (nmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AO</td>
<td>38±2</td>
<td>40±2 (10)</td>
<td>38±1</td>
</tr>
<tr>
<td>MV</td>
<td>42±2</td>
<td>43±2 (10)</td>
<td>48±2</td>
</tr>
<tr>
<td>CV</td>
<td>43±2</td>
<td>60±6 (10)</td>
<td>162±14 (5)*</td>
</tr>
<tr>
<td>MYO</td>
<td>54±5</td>
<td>60±7</td>
<td>77±9</td>
</tr>
<tr>
<td>PCO2 (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AO</td>
<td>44±1</td>
<td>46±2 (10)</td>
<td>39±1</td>
</tr>
<tr>
<td>MV</td>
<td>52±2</td>
<td>53±2 (10)</td>
<td>59±3</td>
</tr>
<tr>
<td>CV</td>
<td>57±2</td>
<td>66±4 (10)</td>
<td>158±12 (5)*</td>
</tr>
<tr>
<td>HCO3− (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AO</td>
<td>27±1</td>
<td>28±1 (10)</td>
<td>25±1</td>
</tr>
<tr>
<td>MV</td>
<td>30±1</td>
<td>30±1 (10)</td>
<td>29±1</td>
</tr>
<tr>
<td>CV</td>
<td>31±1</td>
<td>27±1 (10)</td>
<td>23±1 (5)</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AO</td>
<td>1.2±0.1</td>
<td>1.1±0.1 (10)</td>
<td>2.0±0.1</td>
</tr>
<tr>
<td>MV</td>
<td>1.1±0.1</td>
<td>1.2±0.2 (10)</td>
<td>2.1±0.2</td>
</tr>
<tr>
<td>CV</td>
<td>0.8±0.2</td>
<td>2.6±0.5 (10)</td>
<td>8.1±0.7 (5)*</td>
</tr>
<tr>
<td>SO2 (%)</td>
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<td></td>
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<tr>
<td>AO</td>
<td>97±1</td>
<td>95±1 (10)</td>
<td>92±2</td>
</tr>
<tr>
<td>MV</td>
<td>62±3</td>
<td>62±4 (10)</td>
<td>35±4</td>
</tr>
<tr>
<td>CV</td>
<td>28±4</td>
<td>34±5 (10)</td>
<td>8±2 (5)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AO</td>
<td>100±6</td>
<td>16±1*</td>
<td>44±3*</td>
</tr>
<tr>
<td>MV</td>
<td>85±7</td>
<td>4±1*</td>
<td>23±2*</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AO</td>
<td>34±1</td>
<td>4±1*</td>
<td>15±3*</td>
</tr>
<tr>
<td>CI (ml/kg/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AO</td>
<td>125±11</td>
<td>33±3*</td>
<td>38±3*</td>
</tr>
</tbody>
</table>

MAP, mean aortic pressure; CPP, coronary perfusion pressure; PCO2, end-tidal CO2; CI, cardiac index; AO, aorta; MV, mixed venous (pulmonary artery); CV, great cardiac vein; MYO, intramyocardial.

Values are given as mean±SEM.

Single-factor repeated-measures ANOVA: *p<0.01 compared with baseline. Note: In instances in which less than 11 measurements were obtained, the numbers are shown in parenthesis. During chest compression (minute 4), the low-flow conditions allowed withdrawal of only five blood samples.

[H+]. However, Walters et al46 had previously observed a high correlation between tissue electrode pH and intracellular pH by enzyme assay. Intracellular and tissue pH are closely related such that changes in intracellular pH are rapidly followed by changes in myocardial tissue pH.47-49

We conclude that myocardial acidosis during cardiac arrest is associated with intramyocardial CO2 and lactate production with only minor effects on extracellular bicarbonate. Such increases in intramyocardial CO2 during reduced perfusion of the myocardium adversely affect myocardial contractility and, therefore, resuscitability.

This has potential implications for buffer therapy. If the administration of bicarbonate increases CO2 production, this buffer therapy might be counterproductive.50 This indeed may explain the recent documentation of adverse cardiac effects of sodium bicarbonate in the setting of lactic acidosis by Arieff and his coworkers (Arieff et al,51 Graf et al,52 and Bersin et al53). However, this is not securely established. We have investigated the effects of both CO2-generating and CO2-consuming buffer agents on myocardial H+ in our porcine model. Preliminary data demonstrated that intramyocardial [H+] was not altered by the buffers; and cardiac resuscitability was not changed.54 This would suggest that the sodium buffer fails to diffuse into the myocardium in the setting of cardiac arrest. Additional studies are in progress to define more precisely these pharmacodynamics of buffer therapy.

References


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**KEY WORDS** • acid-base imbalance • cardiac arrest
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