Brain Bioenergetics during Cardiopulmonary Resuscitation in Dogs

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Cardiac arrest causes a rapid loss of cerebral adenosine triphosphatase (ATP) and a decrease in cerebral intracellular pH (pHi). Depending on the efficacy of cardiopulmonary resuscitation (CPR), cerebral blood flow levels (CBF) ranging from near zero to near normal have been reported experimentally. Using 31P magnetic resonance spectroscopy, the authors tested whether experimental CPR with normal levels of cerebral blood flow can rapidly restore cerebral ATP and pHi, despite the progressive systemic acidemia associated with CPR. After 6 min of ventricular fibrillation in six dogs anesthetized with fentanyl and pentobarbital, ATP was reduced to undetectable concentrations and pHi decreased from 7.11 ± 0.02 to 6.28 ± 0.09 (± SE) as measured by 31P magnetic resonance spectroscopy. Application of cyclic chest compression by an inflatable vest placed around the thorax and infusion of epinephrine (40 μg/kg bolus plus 8 μg/kg/min, intravenously) maintained cerebral perfusion pressure greater than 70 mmHg for 50 min with the dog remaining in the magnet. Prearrest cerebral blood flows were generated. Cerebral pHi recovered to 7.03 ± 0.03 by 35 min of CPR, whereas arterial pH decreased from 7.41 ± 0.4 to 7.05 ± 0.04 and cerebral venous pHi decreased from 7.29 ± 0.03 to 7.01 ± 0.04. Cerebral ATP levels recovered to 86 ± 7% (±SE) of prearrest concentration by 6 min of CPR. There was no further recovery of ATP, which remained significantly less than control. Therefore, in contrast to hyperemic reperfusion with spontaneous circulation and full ATP recovery, experimental CPR may not be able to restore ATP completely after 6 min of global ischemia despite restoration of CBF and brain pHi to prearrest levels. (Key words: Brain; blood flow; metabolism. Cardiopulmonary resuscitation. Measurement techniques, magnetic resonance spectroscopy: adenosine triphosphatase; inorganic phosphate; pH; phosphocreatine.)

CARDIAC ARREST causes rapid deterioration in brain pH and chemical energy reserve, ultimately resulting in irreversible brain damage.1,2 The goal of cardiopulmonary resuscitation (CPR) is to reverse this process and maintain heart and brain viability during cardiac arrest by maintaining perfusion until unassisted circulation can be restored. However, the direct effect of CPR on brain metabolism is poorly understood. 31P magnetic resonance spectroscopy (MRS) is used routinely to measure brain high-energy phosphate and intracellular pH (pHi) in experimental models of global brain ischemia not involving CPR.3-6 In a previous non-CPR study,7 we found a rapid decrease in pHi during the first 6-8 min of near-complete global cerebral ischemia from 7.1 to 6.3, finally reaching a nadir of 6.2 in 12 min. Adenosine triphosphatase (ATP) was not detectable by 4 min. Reperfusion at normal perfusion pressures resulted in complete recovery of ATP and pHi. Moreover, others using cardiopulmonary bypass with normal blood gases after 8 min of cardiac arrest demonstrated good recovery of neurologic function as measured by physical examination and ATP and pHi as measured by 31P MRS.8 Unfortunately, application of external chest compression during CPR ordinarily does not generate prearrest levels of perfusion pressure.8-10 It is unclear whether subnormal cerebral perfusion pressure is adequate for restoration of brain ATP and pHi. Furthermore, acidemia during CPR may limit recovery of brain pHi.

Application of 31P MRS during CPR has been constrained by the high magnetic fields involved and inaccessibility of the animal. These constraints preclude the use of most common models of CPR that use a ferromagnetic programmable mechanical resuscitator or open chest massage.8-10 The technique of vest CPR11 in which an inflatable vest secured around the thorax is inflated cyclically allows normal levels of cerebral blood flow (CBF) to be generated during cardiac arrest. Moreover, this technique does not require the use of ferromagnetic components near the animal, thereby permitting CPR to be controlled remotely while the animal is in an MRS magnet.

In the current study on anesthetized dogs, we used a
6-min duration of cardiac arrest before starting CPR because brain ATP and pH were known to be fully recoverable with spontaneous circulation after complete cerebral ischemia of 6 min or longer durations. The objectives of the current study are threefold. First, we determined the feasibility of using 31P MRS to measure brain ATP and pH during the application of external CPR. Second, we determined whether CPR performed under conditions obtainable in the laboratory with normal levels of CBF, but without the profound hyperemia seen in other models of ischemia and reperfusion, is capable of rapidly restoring brain high-energy phosphates. Third, we determined whether rapid recovery of brain pH is possible during the progressive arterial and venous acidemia that ordinarily occurs during CPR.

Materials and Methods

All studies received approval of The Johns Hopkins University Animal Care and Use Committee. We studied nine male mongrel dogs weighing 16–18 kg. Six dogs underwent the full protocol, and three dogs served as controls. All dogs were fasted overnight but were given free access to water. Anesthesia consisted of sodium pentobarbital (10 mg/kg, intravenously) and fentanyl (50 μg/kg, intravenously). The trachea was intubated and the lungs were ventilated to maintain normal blood gases. Catheters were inserted by femoral cannulation into the descending thoracic aorta, left ventricle (for microsphere injections), and right atrium. An axillary artery was cannulated for microsphere reference sampling. Temporalis muscle and skin were retracted fully from the skull to prevent contamination of the MRS spectra. A midline burr hole was made in the skull, and a catheter was inserted into the sagittal sinus proximal to the confluence of the sinuses. The animal was placed onto a copper-lined cradle, with the head fixed in position by a stereotaxic frame. Dogs received an additional 6 mg·kg⁻¹·h⁻¹ sodium pentobarbital during the surgery. Pancuronium bromide (0.2 mg/kg, intravenously) was administered to prevent movement. Lactated Ringer’s solution containing no glucose (30 ml/kg) was infused during the surgery. A vest with an inflatable bladder that covered approximately two thirds of the thoracic circumference was secured snugly around the thorax with Velcro straps.

Measurements

31P MAGNETIC RESONANCE SPECTROSCOPY

Spectra were obtained with the use of a CSI MRS Spectrometer® (General Electric, Freemont, CA) with a 4.7-Tesla horizontal superconducting magnet (Oxford Instruments, Oxford, England). The magnet had a 40-cm bore with a sensitive volume of approximately 25 cm³, over which the magnetic field homogeneity is 0.1 parts per million. An inductively coupled, two-turn, 7-cm diameter copper surface coil double tuned to 81 MHz (31P) and 200 MHz (1H) was placed directly over the skull. The field was shimmed on the water proton signal to better than 0.2 parts per million. 31P MRS signals were collected every 3 s with the use of a 140-μs, 100-W excitation pulse and a 2.9-s, 1-W saturation pulse 10 parts per million upfield from phosphocreatine (PCr). Magnetic resonance spectroscopy data were averaged and stored as 1-min blocks.

Each 1-min spectrum was analyzed with the use of the CSI spectrometer’s least-squares best-fit routine (GEMCAP) to calculate percent of the total area (concentrations) of the resonance peaks corresponding to PCr, inorganic phosphate (Pi), and ATP. Intracellular pH was calculated from the shift of pH with the formula from Petroff et al.¹²: pH = 6.77 + log [(α − 3.29)/(5.68 − α)], where α = frequency difference from PCr to Pi per parts per million. The data then were reanalyzed, averaging five 1-min scans centered around the time of microsphere injection because, during CPR, that measurement of CBF is a time-weighted average over 5 min. Intracellular brain bicarbonate concentrations were calculated with the use of the Henderson-Hasselbach equation, a PB of 6.12, a carbon dioxide solubility coefficient of 0.0314 mM/mmHg, pH derived by MRS, and sagittal sinus PCO₂ as a close approximation of intracellular PCO₂.

BLOOD ANALYSIS

Arterial and sagittal sinus blood samples were analyzed for pH, PO₂, and PCO₂ with a Radiometer ABL3® electrode system. Oxygen content was measured by an Instrumentation Laboratories CO-oximeter® (model 282). Blood glucose concentrations were analyzed with a Yellow Springs glucose analyzer.

CEREBRAL FLOW

Fifteen-micron diameter spheres labeled with one of six isotopes (153Gd, 114mIn, 113Sn, 103Ru, 65Nb, 46Sc) (Du Pont–New England Nuclear Products, Boston, MA) allowed CBF to be measured six times per animal. A dose of approximately 1.5 million spheres (for control) or 0.5 million spheres (all other time points) was injected into the left ventricle, whereas an arterial reference sample was withdrawn with a Harvard syringe pump at a rate of 3.8 ml/min from the axillary artery for 2 min prearrrest and at a rate of 1.9 ml/min for 5 min during CPR to ensure full washout of spheres during the low cardiac output state with CPR. Use of microspheres during CPR has been validated previously in this laboratory. Cerebral blood flow and cerebral metabolic rate of oxygen consumption (CMRO₂) were calculated as previously described. Cerebral perfusion pressure was calculated as mean arterial pressure minus mean sagittal sinus venous
pressure. During CPR, sagittal sinus pressure is approximately equal to cerebrospinal fluid pressure.\textsuperscript{13}

**PROTOCOL**

Control arterial and sagittal sinus blood gases, arterial glucose concentration, radiolabeled microsphere blood flow measurement, and five 1-min MRS spectra were obtained. Ventricular fibrillation was induced and maintained throughout each animal study by passing a 60-Hz current through a bipolar electrode catheter inserted into the right heart. In a control group of three dogs, CPR started simultaneously with ventricular fibrillation. This group controlled for possible motion artifact on the MRS signal produced by the mechanics of CPR. In an experimental group of six dogs, CPR was started after 6 min of cardiac arrest. The thorax was compressed by cycling vest pressure with compressed nitrogen. A microprocessor controlled the opening and closing of solenoid valves between a reservoir of compressed nitrogen and tubing connected to the vest.\textsuperscript{11} The level of pressure in the vest was adjusted by varying the pressure in the reservoir. The rise time to achieve a stable level of vest pressure was 150 ms. Compressions occurred at a rate of 60–80/min with a 40% duty cycle. The microprocessor also controlled a pressure-limited ventilator to deliver 100% oxygen at a set airway pressure of 27 cmH\textsubscript{2}O interposed after every eighth chest compression to maintain prearrest concentrations of arterial P\textsubscript{CO\textsubscript{2}}.

All animals received a bolus of 40 \textmu g/kg epinephrine at the start of CPR, followed by an 8 \textmu g \textcdot kg\textsuperscript{-1} \textcdot min\textsuperscript{-1} continuous intravenous infusion.\textsuperscript{14} Additional MRS measurements, arterial and sagittal sinus blood samples, and microsphere blood flow measurements were obtained at 6 min in the control group and at 6, 12, 20, 35, and 50 min of CPR in the experimental group.

**STATISTICS**

One-way analysis of variance with the use of repeated measures and the Fisher protected least-significance difference test was used at a 0.05 significance level to analyze for changes in blood gases, blood flow, and MRS measurements from the prearrest baseline. Differences in the paired arterial and brain bicarbonate levels were compared with the use of two-tailed Student's \textit{t} test. Values are reported as mean ± SE.

**Results**

**CONTROL GROUP \((n = 3)\)**

The control group allows an estimation of MRS artifacts from the mechanisms of CPR itself without the effects of complete ischemia when there is no delay in onset of CPR. Figure 1 shows a normal \textsuperscript{31}P MRS spectrum before ventricular fibrillation (middle trace) and at minute 6 of CPR (upper trace). Subtraction of the two spectra (lower trace) indicates that differences between the two spectra were not detectable. There was little difference in critical measurements between the prearrest values and minute 6 of CPR: arterial \textit{pH}, 7.38 ± 0.01 to 7.34 ± 0.04; brain \textit{pH}\textsubscript{b}, 7.10 ± 0.06 to 7.08 ± 0.05; ATP, 100–103 ± 2 (percent control); CBF, 41 ± 9 to 31 ± 4 (ml \textcdot min\textsuperscript{-1} \textcdot 100 g\textsuperscript{-1}); and CMRO\textsubscript{2}, 1.07 ± 0.2 to 1.04 ± 0.2 (\textmu mol \textcdot min\textsuperscript{-1} \textcdot 100 g\textsuperscript{-1}).

**EXPERIMENTAL GROUP \((n = 6)\)**

Figure 2 shows a series of 1-min MRS spectra. There is a total absence of high-energy phosphates by minute 6 of ventricular fibrillation before CPR, with a reciprocal increase in Pi and sugar phosphate as is expected in a spectrum localized to the brain and devoid of muscle artifact. Beta-ATP had largely but not completely recovered after 6 min of CPR, at which time PCr and P\textsubscript{i} had recovered only partially. By 35 min of high-pressure vest CPR, P\textsubscript{i} decreased and PCr increased further, but \beta-ATP was still slightly less than that in the control spectrum. Figure 3 illustrates the speed at which changes in brain \textit{pH} occur. There was a rapid decrease with ventricular fibrillation and slower subsequent recovery with CPR. Brain \textit{pH} decreased from 7.11 to 6.28 within 6 min but did not recover to greater than 7.0 for 35 min.

Animals were well oxygenated and hyperventilated slightly throughout CPR (Table 1). The control glucose was 61 ± 3 mg/dl. Neither brain temperature nor serum glucose concentration was measured during CPR. Arterial
concentrations were depressed substantially at 6 min of CPR, continued to recover through 35 min, but still were different than control concentrations at 50 min. On average, brain bicarbonate concentrations began to exceed arterial bicarbonate concentrations within 35 min. Because there was a large difference in control brain and arterial bicarbonate concentrations (reflecting the known difference in brain and arterial pH), statistical analysis was performed on the change in bicarbonate concentration (Δbicarbonate) from the animal's control concentration. On a paired basis, the decrease in brain bicarbonate concentration exceeded the decrease in the arterial bicarbonate concentration at 6 min of CPR, whereas the decrease in arterial bicarbonate concentration exceeded the decrease in brain bicarbonate concentration at 35 and 50 min of CPR.

**Discussion**

The current study demonstrates the following: 1) the feasibility of measuring changes in cerebral high-energy phosphates and pH by $\text{^{31}P}$ MRS during CPR while the animal is in the magnet, 2) rapid but incomplete recovery of ATP and P$_{i}$/PCr ratio, and 3) increases in cerebral pH to near-normal levels even though arterial and cerebral venous pH progressively decrease during CPR.

All forms of CPR generate CBF by creating a pressure gradient between the feeding arteries and draining veins. Vest CPR generates this gradient by producing stable and reproducible increases in intrathoracic pres-
BRAIN BIOENERGETICS DURING CPR

Table 1. Blood Gas Results Analysis Prearrest and during CPR Starting 6 Min After Arrest

<table>
<thead>
<tr>
<th></th>
<th>Prearrest Control</th>
<th>6</th>
<th>12</th>
<th>20</th>
<th>35</th>
<th>50</th>
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</thead>
<tbody>
<tr>
<td>$P_{O_2}$ (mmHg)</td>
<td>469 ± 51</td>
<td>210 ± 47*</td>
<td>207 ± 32*</td>
<td>222 ± 59*</td>
<td>179 ± 35*</td>
<td>183 ± 51*</td>
</tr>
<tr>
<td>$P_{CO_2}$ (mmHg)</td>
<td>34 ± 3.5</td>
<td>30 ± 5.9</td>
<td>29 ± 2.6</td>
<td>27 ± 2.4</td>
<td>27 ± 3.9</td>
<td>29 ± 3.5</td>
</tr>
<tr>
<td>$p_{Ha}$</td>
<td>7.41 ± 0.04</td>
<td>7.29 ± 0.04*</td>
<td>7.21 ± 0.04*</td>
<td>7.24 ± 0.04*</td>
<td>7.08 ± 0.04*</td>
<td>7.02 ± 0.04*</td>
</tr>
<tr>
<td>$P_{S0_2}$ (mmHg)</td>
<td>42 ± 1.6</td>
<td>60 ± 2.6</td>
<td>64 ± 5.2*</td>
<td>58 ± 6.3*</td>
<td>55 ± 5.1*</td>
<td>52 ± 5.6</td>
</tr>
<tr>
<td>$P_{SSCo_2}$ (mmHg)</td>
<td>50 ± 4.6</td>
<td>44 ± 5.0</td>
<td>37 ± 2.5</td>
<td>44 ± 4.1</td>
<td>46 ± 5.7</td>
<td>52 ± 5.5</td>
</tr>
<tr>
<td>$p_{Hss}$</td>
<td>7.29 ± 0.03</td>
<td>7.21 ± 0.04*</td>
<td>7.17 ± 0.04*</td>
<td>7.11 ± 0.04*</td>
<td>7.01 ± 0.04*</td>
<td>6.94 ± 0.04*</td>
</tr>
</tbody>
</table>

Values are means ± SEM (n = 6).

$P_{O_2}$ = arterial oxygen tension; $P_{CO_2}$ = arterial carbon dioxide tension; $p_{Ha}$ = arterial $p_{H}$; $P_{S0_2}$ = sagittal sinus oxygen tension; $P_{SSCo_2}$ = sagittal sinus carbon dioxide tension; $p_{Hss}$ = sagittal sinus $p_{H}$.
* Different from control using ANOVA with $P < 0.05$.

sure. As long as peripheral vascular tone was maintained by epinephrine administration, cerebral perfusion pressure was well maintained over the 1-h period of this study. The radiolabeled microsphere technique for measurement of CBF has been validated previously during CPR with regard to adequate mixing, lack of sedimentation, lack of significant shunting, and adequate numbers of spheres in tissue and arterial blood samples. The maintenance of control levels of CBF, although not as significant as the hyperemia seen in some non-CPR models of cerebral ischemia, is indicative of the efficacy of vest CPR in these dogs. One major result of excellent CBF is rapid clearance of brain acid equivalents as reflected by the near-normal $P_{CO_2}$ levels in sagittal sinus blood after only 6 min of CPR. We did not see a significant subsequent decline in CBF (delayed hyperperfusion) typically observed in other models of global cerebral ischemia. However, we cannot exclude the possibility that incomplete recovery of the $P_{i}/P_{Cr}$ ratio is attributable to heterogeneous blood flow at the microcirculatory level.

Vest CPR with a dog model has been well studied, including survival studies with neurologic outcome scores. Vest CPR is pneumatically driven and, unlike conventional chest compression CPR, uses no ferromagnetic parts. The lack of ferromagnetic parts and motion artifact allows MRS to rapidly follow changes in brain $p_{H}$ and ATP during CPR. Application of an aluminum stereotactic holder with ear pins and a mouth gag prevents movement of the dog’s head during inflation of the vest and allows measurement of brain ATP with greater than 95% accuracy.

Adenosine triphosphatase levels recovered by 86% at 6 min of CPR, a rate similar to the rapid recovery seen in other ischemic models with high levels of perfusion pressure. However, no further recovery was reported. Although control values for $^{31}$P MRS high-energy phosphate values in the dog are unaltered by anesthetics, the CPR results may be model- and anesthetic-dependent. We chose the low-dose pentobarbital, high-dose fentanyl anesthetic combination because it does not depress cerebral metabolic rate of oxygen as much as that caused by pentobarbital alone and provided excellent stability in 4 h time controls. Using a different model, Steen et al. observed no effect of pentobarbital on the recovery rate of ATP. The lack of full recovery of ATP was an unexpected finding not previously reported in conventional ischemia–reperfusion studies with short ischemia times. However, quantitative measurements of ATP in small animals at high magnetic field strengths (gerbil, 8.5 Tesla) require 5–10 min, and those for large animals at low

Table 2. Cerebral Blood Flow and Oxygen Utilization during CPR $^{31}$P Magnetic Resonance Spectroscopy

<table>
<thead>
<tr>
<th></th>
<th>Prearrest Control</th>
<th>Min-6 V. Fib.</th>
<th>6</th>
<th>12</th>
<th>20</th>
<th>35</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>$DPP$ (mmHg)</td>
<td>88 ± 9</td>
<td>0</td>
<td>89 ± 4</td>
<td>78 ± 6</td>
<td>81 ± 4</td>
<td>82 ± 5</td>
<td>94 ± 6</td>
</tr>
<tr>
<td>$CBF$ (ml/min·100 g$^{-1}$)</td>
<td>35 ± 5</td>
<td>—</td>
<td>58 ± 12</td>
<td>57 ± 16</td>
<td>43 ± 12</td>
<td>35 ± 7</td>
<td>25 ± 6</td>
</tr>
<tr>
<td>$CMRO_2$ (µmol·g$^{-1}$·min$^{-1}$)</td>
<td>1.17 ± 0.11</td>
<td>—</td>
<td>0.87 ± 0.18</td>
<td>0.89 ± 0.47</td>
<td>0.79 ± 0.21</td>
<td>1.10 ± 0.25</td>
<td>0.89 ± 0.21</td>
</tr>
<tr>
<td>$ATP$ (%) of control</td>
<td>100</td>
<td>&lt;5*</td>
<td>86 ± 7</td>
<td>85 ± 7*</td>
<td>77 ± 7*</td>
<td>87 ± 7*</td>
<td>86 ± 9*</td>
</tr>
<tr>
<td>$P_{i}/P_{Cr}$</td>
<td>0.033 ± 0.07</td>
<td>10*</td>
<td>0.72 ± 0.09*</td>
<td>0.52 ± 0.11</td>
<td>0.65 ± 0.12</td>
<td>0.50 ± 0.06</td>
<td>1.0 ± 0.22*</td>
</tr>
<tr>
<td>$p_{H}$</td>
<td>7.11 ± 0.02</td>
<td>6.28 ± 0.09*</td>
<td>6.61 ± 0.07*</td>
<td>6.88 ± 0.05*</td>
<td>6.94 ± 0.05*</td>
<td>7.03 ± 0.03</td>
<td>6.99 ± 0.04*</td>
</tr>
</tbody>
</table>

Values are means ± SEM (n = 6).

$DPP$ = cerebral perfusion pressure; $V$. fib. = ventricular fibrillation; $CBF$ = cerebral blood flow; $CMRO_2$ = cerebral metabolic rate for oxygen; $ATP$ = brain adenosine triphosphate; $P_{i}$ = brain inorganic phosphate; $P_{Cr}$ = brain phosphocreatine; $p_{H}$ = intracellular brain $p_{H}$.
* Significantly different from control using ANOVA with $P < 0.05$.\n
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magnetic field strength (dog, 2.0 Tesla) require 4–8 min. The high signal-to-noise ratio obtainable in this study with a large animal and relatively high magnetic field (4.7 Tesla) allows 1-min measurements of the area under the ATP peaks. The most likely source of error would be the effect of the cephalic vessel pressure causing not only chest wall distortion, but also movement of the head and brain relative to the MRS coil. For this reason, three dogs had CPR started simultaneously with ventricular fibrillation. Adenosine triphosphatase concentrations after 6 min were unchanged from prearrest values, thereby excluding motion artifact as a source of error and demonstrating that CPR started immediately with cardiac arrest can prevent loss of brain ATP.

A second potential source of artifact occurs when the MRS repetition time (TR) is small compared with the T1 (spin-lattice) relaxation time. Variations in relaxation times between different brain components are responsible for the significant contrast between white and gray matter on a standard 1H magnetic resonance imaging scan. At 4.7 Tesla, T1 for β-ATP is 1.6 s, whereas T1 for PCr is 4.4 s. The MRS observed signal strength is $S_0(1 - e^{-TR/T1})$, where $S_0$ is the fully relaxed (maximal) signal. Using the technique of Gadian et al. with a TR of 0.6 s would result in an observed ATP value of 50%, whereas using the TR of 3 s employed in this study results in an observed ATP value of 85%. It is possible that the T1 of ATP changes after ischemia; however, the T1 needed to account for a 14% loss of observed ATP during recovery versus control with a TR of 3 s would be 2.4 s, corresponding to a 70% increase. Such an increase is extremely unlikely. However, the T1 of PCr would have to increase only 20% from 4.4 to 5.4 to create a 15% error in measurement.

The technique of least-squares best fit in the frequency domain is an interactive technique that allows subjective error on the part of the spectroscopist. Other techniques, including our own, are not as robust and are not used routinely for 31P MRS. To minimize the error, all experiments were analyzed by the same investigator (SME).

The MRS technique used in this study has the advantage of speed and signal localization to the brain. However, the current technique does not distinguish compartments within the brain. Thus, we cannot distinguish whether the 86% recovery of ATP represents a homogeneous 14% reduction among all cells or a heterogeneous response with greater ATP reduction in selectively vulnerable neurons, white matter, or glia. Although differences in pH recovery between neurons and glia have been reported differences in their in vivo ATP synthesis rates are less well understood and beyond the resolution of MRS. Finally, there is not a one-to-one correspondence between ATP recovery and neurologic outcome because a decreased evoked potential response and neurologic deficit persist after full recovery of ATP. The presence of ATP is certainly a necessary although perhaps not a sufficient prerequisite for neurologic recovery.

The chemical shift of P1 is pH-dependent, and the brain pH can be calculated from the position of P1 in the 31P MRS spectra. Careful comparison of the traces in figures 1 and 2 shows minimal degradation of the MRS signal during CPR. Five of these 1-min spectra were averaged together to better reflect brain pH during the 5-min averaging time required to measure CBF during CPR. This averaging further increases by a factor of 2.2 the signal to noise of the MRS data, allowing a digital pH accuracy of ±0.025. The rapid decrease in pH from 7.11 ± 0.02 to 6.28 ± 0.09 after 6 min of global ischemia results from organic acid production and the absence of blood flow needed for carbon dioxide clearance. Because pH is dependent in part on carbon dioxide accumulation, we chose to also compare arterial and brain bicarbonate,

### Table 3. Calculated Brain and Bicarbonate Concentrations

<table>
<thead>
<tr>
<th></th>
<th>Prearrest Control</th>
<th>6</th>
<th>12</th>
<th>20</th>
<th>55</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial bicarbonate (mEq/l)</td>
<td>20.0 ± 1↑‡</td>
<td>13.6 ± 1.1*‡</td>
<td>11.2 ± 0.8*‡</td>
<td>9.8 ± 0.4*‡</td>
<td>7.9 ± 0.4*‡</td>
<td>6.9 ± 0.5*‡</td>
</tr>
<tr>
<td>Brain bicarbonate (mEq/l)</td>
<td>17.0 ± 1.2*↑</td>
<td>4.4 ± 0.6*‡</td>
<td>6.6 ± 0.4*‡</td>
<td>8.4 ± 0.8*‡</td>
<td>12.7 ± 1.7*‡</td>
<td>12.9 ± 1.6*‡</td>
</tr>
<tr>
<td>ΔArterial bicarbonate (mEq/l)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ΔBrain bicarbonate (mEq/l)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>P value</td>
<td>0.001</td>
<td>0.155</td>
<td>0.281</td>
<td>0.001</td>
<td>0.0004</td>
<td></td>
</tr>
</tbody>
</table>

All values are mean ± SEM (n = 6).

ΔArterial bicarbonate = difference in the arterial bicarbonate from the control value; Δbrain bicarbonate = difference in the brain bicarbonate from the control value; P value refers to difference between arterial and brain bicarbonate by paired t test.

* Significantly different than 50-min value.
† Significantly different than 60-min value.
‡ Significantly different than control.
which are linear (not logarithmic) variables. Although part of the \( p_{H^1} \) recovery during early CPR is attributable to tissue carbon dioxide clearance, most of the \( p_{H^1} \) recovery after 6 min of CPR is mediated by regeneration of intracellular bicarbonate, which nearly tripled between 6 and 35 min. Because prearrest values of brain and arterial bicarbonate (as well as \( pH \)) are different, changes in bicarbonate from the animal’s control value were used.

We found that the decrease in brain bicarbonate concentration below prearrest concentrations exceeded that of arterial bicarbonate during early CPR but that, as CPR was prolonged, the opposite was true. The current study demonstrates that, given adequate cerebral perfusion generated during CPR, recovery of brain bicarbonate toward baseline occurs despite a continuing systemic acidosis as reflected by a decreasing arterial bicarbonate concentration. Thus, brain \( p_{H^1} \) is well protected from systemic acidosis when arterial \( pH \) does not decrease below control brain \( p_{H^1} \) levels.

Routine administration of sodium bicarbonate while giving chest compressions during CPR is no longer recommended by American Heart Association guidelines.\(^28\) Several studies did not show an improvement in outcome with bicarbonate administration,\(^29,30\) possibly because blood flow, rather than arterial \( pH \), is a dominant factor in recovery. In the current study, arterial \( pH \) decreased progressively throughout CPR, although it was never significantly less than prearrest brain \( p_{H^1} \) levels, reflecting the 0.3 \( pH \) unit difference between prearrest brain and arterial \( pH \) levels. It remains unclear whether situations with more extreme systemic acidosis would limit recovery of brain \( p_{H^1} \). It is also unclear how well brain \( p_{H^1} \) would recover with subnormal levels of brain reperfusion, as might occur with clinical CPR. Based on CBF arguments, the current results approach the upper limit for the rate of recovery of \( p_{H^1} \) after 6 min of complete ischemia during CPR. Indeed, full reperfusion at greater levels of perfusion pressure in other models of cerebral ischemia results in similar rates of \( p_{H^1} \) recovery.\(^4,6,7\)

In conclusion, MRS can be used to measure changes in brain energy state and \( pH \) during chest CPR in dogs with the use of a thoracic vest to generate cerebral perfusion. These studies show that CPR generating prearrest levels of blood flow alone can restore and maintain brain \( p_{H^1} \) without the use of alkalinizing agents, at least when arterial \( pH \) is a minimum of 7.1. Initial ATP concentrations are maintained at baseline concentrations when CPR is started immediately following initiation of ventricular fibrillation. Adenosine triphosphatase is hydrolyzed completely when CPR is delayed until after 6 min of ventricular fibrillation and rapidly restored to 86% within 6 min of CPR. However, recovery of ATP remained significantly below baseline concentrations for the full 50 min of CPR. The cause of incomplete ATP recovery, its cellular distribution, and correlation with integrative neurologic function is currently unknown.

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