

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 (pH_i). 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 ^{31}P magnetic resonance spectroscopy, the authors tested whether experimental CPR with normal levels of cerebral blood flow can rapidly restore cerebral ATP and pH_i 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 pH_i decreased from 7.11 ± 0.02 to 6.28 ± 0.09 (\pm SE) as measured by ^{31}P magnetic resonance spectroscopy. Application of cyclic chest compression by an inflatable vest placed around the thorax and infusion of epinephrine (40 $\mu\text{g}/\text{kg}$ bolus plus 8 $\mu\text{g}/\text{kg}/\text{min}$, 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 pH_i recovered to 7.03 ± 0.03 by 35 min of CPR, whereas arterial pH decreased from 7.41 ± 0.4 to 7.08 ± 0.04 and cerebral venous pH decreased from 7.29 ± 0.03 to 7.01 ± 0.04 . Cerebral ATP levels recovered to $86 \pm 7\%$ (\pm 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 pH_i to prearrest levels. (Key words: Brain: blood flow; metabolism. Cardiopulmonary resuscitation. Measurement tech-

niques, 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. ^{31}P magnetic resonance spectroscopy (MRS) is used routinely to measure brain high-energy phosphate and intracellular pH (pH_i) 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 pH_i 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 pH_i . 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 pH_i as measured by ^{31}P MRS.² 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 pH_i . Furthermore, acidemia during CPR may limit recovery of brain pH_i .

Application of ^{31}P 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

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6-min duration of cardiac arrest before starting CPR because brain ATP and pH_i are known to be fully recoverable with spontaneous circulation after complete cerebral ischemia of 6 min or longer durations.^{4,6,7} The objectives of the current study are threefold. First, we determined the feasibility of using ³¹P MRS to measure brain ATP and pH_i 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_i 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 μ g/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 \cdot kg⁻¹ \cdot 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, Fremont, 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- μ s, 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 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 (P_i), and ATP.⁵ Intracellular pH was calculated from the shift of pH_i with the formula from Petroff *et al.*¹²: $pH_i = 6.77 + \log[(\alpha - 3.29)/(5.68 - \alpha)]$, where α = frequency difference from PCr to P_i in 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.⁹ Intracellular brain bicarbonate concentrations were calculated with the use of the Henderson-Hasselbach equation, a pK_a of 6.12, a carbon dioxide solubility coefficient of 0.0314 mM/mmHg, pH_i derived by MRS, and sagittal sinus P_{CO₂} as a close approximation of intracellular P_{CO₂}.⁴

BLOOD ANALYSIS

Arterial and sagittal sinus blood samples were analyzed for pH , P_{CO₂}, and P_{O₂} 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 BLOOD FLOW

Fifteen-micron diameter spheres labeled with one of six isotopes (¹⁵³Gd, ^{114m}In, ¹¹³Sn, ¹⁰³Ru, ⁹⁵Nb, ⁴⁶Sc) (Dupont–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 prearrest 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.⁹ Cerebral blood flow and cerebral metabolic rate of oxygen consumption (CMR_{O₂}) were calculated as previously described.¹³ 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.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.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 cmH₂O interposed after every eighth chest compression to maintain prearrest concentrations of arterial P_{CO₂}.

All animals received a bolus of 40 µg/kg epinephrine at the start of CPR, followed by an 8 µg·kg⁻¹·min⁻¹ continuous intravenous infusion.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 *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 ³¹P MRS spectrum before ventricular fibrillation (middle trace) and at minute 6 of CPR

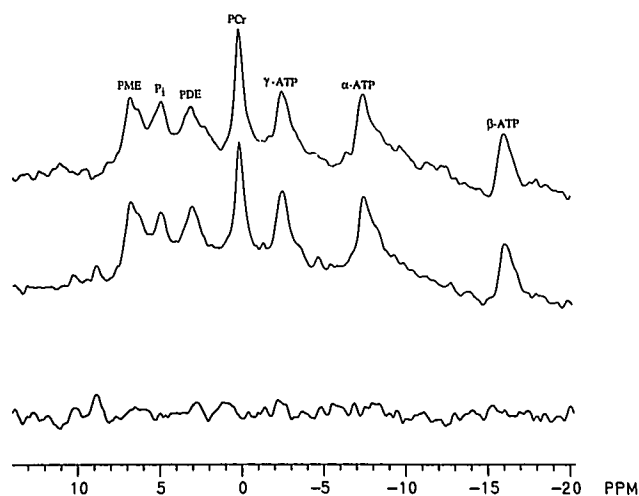


FIG. 1. ³¹P magnetic resonance spectroscopy spectra from *in situ* dog brain before (middle trace) during cardiopulmonary resuscitation, which commenced immediately upon cardiac arrest (upper trace), and the difference between the two (lower trace) showing no change in high-energy phosphates. The three peaks on the right side of trace A are the β, α, and γ phosphorus species of ATP. PCr = phosphocreatine; PDE = phosphodiester; P_i = inorganic phosphate; PME = phosphomonoesters (comprised mainly of sugar phosphates).

(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 *p*H, 7.38 ± 0.01 to 7.34 ± 0.04; brain *p*H_i, 7.10 ± 0.06 to 7.08 ± 0.05; ATP, 100–103 ± 2 (percent control); CBF, 41 ± 9 to 31 ± 4 (ml·min⁻¹·100 g⁻¹); and CMR_{O₂}, 1.07 ± 0.2 to 1.04 ± 0.2 (µmol·min⁻¹·g⁻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 P_i 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_i had recovered only partially. By 35 min of high-pressure vest CPR, P_i decreased and PCr increased further, but β-ATP was still slightly less than that in the control spectrum. Figure 3 illustrates the speed at which changes in brain *p*H_i occur. There was a rapid decrease with ventricular fibrillation and slower subsequent recovery with CPR. Brain *p*H 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

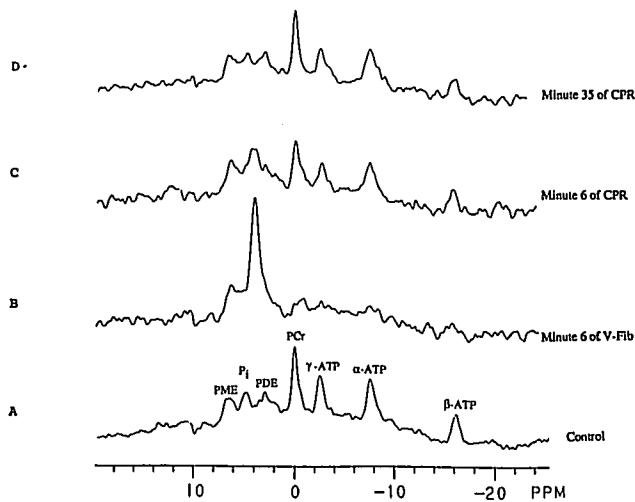


FIG. 2. ^{31}P magnetic resonance spectroscopy spectra from *in situ* dog brain during vest cardiopulmonary resuscitation (CPR) after a 6-min delay in the onset of CPR from time of arrest. Each spectrum was acquired in 1 min. The frequency of the inorganic phosphate (P_i) peak is pH -dependent. Notice complete absence of ATP and phosphocreatine (PCr), and $\text{pH}_i = 6.28$ in trace B after 6 min of ventricular fibrillation (v-fib) without CPR. After 6 min of CPR (trace C), ATP is more than 85% recovered, but pH is only 6.61. After 35 min of CPR (trace D), pH_i has returned to 7.0.

pH decreased from 7.29 at 6 min of CPR to 7.02 by 50 min. Sagittal sinus pH decreased to 6.94 with normal venous P_{CO_2} . Sagittal sinus pH was less than brain pH_i in four of six dogs at 50 min of CPR.

Cerebral perfusion pressure was maintained at near-normal levels throughout CPR, and CBF was restored to normal levels during CPR (table 2). However, CBF at 35 and 50 min were significantly less than that at 6 and 12 min despite constant cerebral perfusion pressure. CMR_{O_2} was not different from prearrest levels. Brain ATP was depleted after 6 min of ventricular fibrillation and before the start of CPR. ATP recovered to 86% of control at 6 min of CPR. However, no additional recovery of ATP was observed. The average ATP recovery from spectra obtained between 6 and 50 min for all dogs was $84 \pm 5\%$, which was significantly less than control. However, two dogs had full recovery (102 ± 5 and 96 ± 5), whereas four dogs did not (80 ± 6 ; 77 ± 2 ; 74 ± 4 ; and 74 ± 5). The P_i/PCr ratio was not significantly different from baseline within 12 min of CPR. However, at 50 min, the P_i/PCr ratio was elevated despite stable brain ATP and pH_i levels.

Table 3 compares arterial and brain bicarbonate concentrations. Arterial bicarbonate concentrations continued to decrease throughout CPR. Statistical analysis (analysis of variance) was applied to the difference (Δ) between the concentrations before arrest and those during CPR to follow trends during CPR. Brain bicarbonate

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 (Δ bicarbonate) 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_i by ^{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_i 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.¹⁵ Vest CPR generates this gradient by producing stable and reproducible increases in intrathoracic pres-

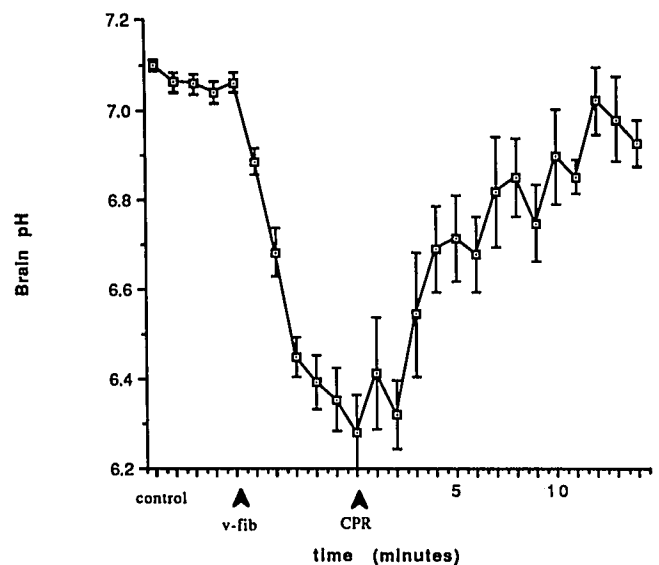


FIG. 3. ^{31}P magnetic resonance spectroscopy measurements of dog brain pH_i during vest cardiopulmonary resuscitation (CPR) after a 6-min delay in onset of CPR from time of cardiac arrest. Arrows indicate commencement of ventricular fibrillation (v-fib) and CPR. Note the rapid decrease in pH_i during the first minutes of v-fib and the slow recovery to baseline with CPR. Prearrest levels of cerebral blood flow were maintained throughout CPR. Data are mean \pm standard error ($n = 6$).

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

	Prearrest Control	CPR Time (min)				
		6	12	20	35	50
PaO ₂ (mmHg)	469 ± 31	210 ± 47*	207 ± 32*	222 ± 59*	179 ± 33*	183 ± 51*
PaCO ₂ (mmHg)	34 ± 3.5	30 ± 3.9	29 ± 2.6	27 ± 2.4	27 ± 3.9	29 ± 3.5
pHa	7.41 ± 0.04	7.29 ± 0.04*	7.21 ± 0.04*	7.24 ± 0.04*	7.08 ± 0.04*	7.02 ± 0.04*
PSSO ₂ (mmHg)	42 ± 1.6	60 ± 2*	64 ± 5.2*	56 ± 6.3*	53 ± 3.1*	52 ± 5.6
PSSCO ₂ (mmHg)	50 ± 4.6	44 ± 5.0	37 ± 2.5	44 ± 4.1	46 ± 5.7	52 ± 5.5
pHss	7.29 ± 0.03	7.21 ± 0.04*	7.17 ± 0.04*	7.11 ± 0.04*	7.01 ± 0.04*	6.94 ± 0.04*

Values are means ± SEM (n = 6).

PaO₂ = arterial oxygen tension; PaCO₂ = arterial carbon dioxide tension; pHa = arterial pH; PSSO₂ = sagittal sinus oxygen tension; PSSCO₂

= sagittal sinus carbon dioxide tension; pHss = sagittal sinus pH.

* Different from control using ANOVA with P < 0.05.

sure.¹⁶ 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.⁹ The maintenance of control levels of CBF, although not as significant as the hyperemia seen in some non-CPR models of cerebral ischemia,⁴ 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_{CO₂} levels in sagittal sinus blood after only 6 min of CPR. We did not see a significant subsequent decline in CBF (delayed hypoperfusion) typically observed in other models of global cerebral ischemia.^{4,17-19} However, we cannot exclude the possibility that incomplete recovery of the P_i/PCr 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.²⁰ 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 pH_i 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.^{1,4,6} However, no further recovery was reported. Although control values for ³¹P MRS high-energy phosphate values in the dog are unaltered by anesthetics,⁵ 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^{4,21} and provided excellent stability in 4 h time controls.⁴ Using a different model, Steen *et al.*¹ 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,³ and those for large animals at low

TABLE 2. Cerebral Blood Flow and Oxygen Utilization during CPR ³¹P Magnetic Resonance Spectroscopy

	Prearrest Control	Min-6 V. Fib.	CPR Time (min)				
			6	12	20	35	50
DPP (mmHg)	88 ± 9	0	89 ± 4	78 ± 6	81 ± 4	82 ± 5	94 ± 6
CBF (ml · min ⁻¹ · 100 g ⁻¹)	35 ± 3	—	58 ± 12	57 ± 16	43 ± 12	33 ± 7	25 ± 6
CMRO ₂ (μmol · g ⁻¹ · min ⁻¹)	1.17 ± 0.11	—	0.87 ± 0.18	0.89 ± 0.47	0.79 ± 0.21	1.10 ± 0.23	0.89 ± 0.21
ATP (% of control)	100	<5*	86 ± 7	85 ± 7*	77 ± 7*	87 ± 2	86 ± 9*
P _i /PCr	0.033 ± 0.07	>10*	0.72 ± 0.09*	0.52 ± 0.11	0.65 ± 0.12	50 ± 0.06	1.0 ± 0.22*
pH _i	7.11 ± 0.02	6.28 ± 0.09*	6.61 ± 0.07*	6.88 ± 0.05*	6.94 ± 0.05*	7.03 ± 0.03	6.99 ± 0.04*

Values are means ± SEM (n = 6).

CPR = cardiopulmonary resuscitation; V. fib. = ventricular fibrillation; CPP = cerebral perfusion pressure; CBF = cerebral blood flow; CMRO₂ = cerebral metabolic rate for oxygen; ATP = brain adenosine

triphosphate; P_i = brain inorganic phosphate; PCr = brain phosphocreatine; pH_i = intracellular brain pH.

* Significantly different than control using ANOVA with P < 0.05.

TABLE 3. Calculated Brain and Bicarbonate Concentrations

	Prearrest Control	CPR Time (min)				
		6	12	20	35	50
Arterial bicarbonate (mEq/l)	20.0 ± 1*†	13.6 ± 1.1*‡	11.2 ± 0.8*†‡	9.8 ± 0.4*†‡	7.9 ± 0.4†‡	6.9 ± 0.5†‡
Brain bicarbonate (mEq/l)	17.0 ± 1.2*†	4.4 ± 0.6*‡	6.6 ± 0.4*‡	8.4 ± 0.8*†‡	12.7 ± 1.7†‡	12.9 ± 1.6†‡
ΔArterial bicarbonate (mEq/l)	—	-6.5 ± 1.4*	-9.1 ± 1.5*†	-9.5 ± 1.1*†	-12.0 ± 1.1†	-12.1 ± 0.7†
ΔBrain bicarbonate (mEq/l)	—	-12.5 ± 1.3*	-10.6 ± 1.6*	-8.6 ± 1.4*†	-4.3 ± 1.9†	-3.2 ± 1.1†
P value		0.001	0.135	0.281	0.001	0.0004

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

Δarterial and Δbrain bicarbonate by paired t test.

* Significantly different than 50-min value.

† Significantly different than 6-min value.

‡ Significantly different than control.

magnetic field strength (dog, 2.0 Tesla) require 4–8 min.⁴ 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 cyclical vest 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.²² 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.*³ with a TR of 0.6 s would result in an observed ATP value of 30%, 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,²³ are not as robust and are not used routinely for ³¹P MRS.²⁴ 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,²⁵ differences in their *in vivo* ATP synthesis rates are less well understood²⁶ 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 response⁴ and neurologic deficit² 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 P_i is pH-dependent, and the brain pH_i can be calculated from the position of P_i in the ³¹P MRS spectra.¹² 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_i during the 5-min averaging time required to measure CBF during CPR.⁹ 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_i 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.²⁷ Because pH_i is dependent in part on carbon dioxide accumulation, we chose to also compare arterial and brain bicarbonate,

which are linear (not logarithmic) variables. Although part of the pH_i recovery during early CPR is attributable to tissue carbon dioxide clearance, most of the pH_i 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 pH_i is well protected from systemic acidosis when arterial pH does not decrease below control brain pH_i 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 pH_i 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 pH_i . It is also unclear how well brain pH_i 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 pH_i 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 pH_i recovery.^{4,6,7}

In conclusion, MRS can be used to measure changes in brain energy state and pH_i during vest 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 pH_i 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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