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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 *p*H (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 (± 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 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 pH_i recovered to 7.03 ± 0.03 by 35 min of CPR, whereas arterial *p*H decreased from 7.41 ± 0.4 to 7.08 ± 0.04 and cerebral venous *p*H 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 pH_i to prearrest levels. (Key words: Brain: blood flow; metabolism. Cardiopulmonary resuscitation. Measurement techniques, magnetic resonance spectroscopy: adenosine triphosphatase; inorganic phosphate; *p*H; phosphocreatine.)

CARDIAC ARREST causes rapid deterioration in brain *p*H 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 *p*H (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 CPR[11] 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 ^{31}P 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 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 $mg \cdot kg^{-1} \cdot h^{-1}$ 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

^{31}P 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 cm^3, 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 (^{31}P) 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. ^{31}P 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 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_{CO_2} as a close approximation of intracellular P_{CO_2}.[4]

Blood Analysis

Arterial and sagittal sinus blood samples were analyzed for pH, P_{CO_2}, and P_{O_2} 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 (^{153}Gd, ^{114m}In, ^{113}Sn, ^{103}Ru, ^{95}Nb, ^{46}Sc) (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_{O_2}) 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 cmH_2O interposed after every eighth chest compression to maintain prearrest concentrations of arterial P_{CO_2}.

All animals received a bolus of 40 $\mu g/kg$ epinephrine at the start of CPR, followed by an 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ 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 ^{31}P MRS spectrum before ventricular fibrillation (middle trace) and at minute 6 of CPR

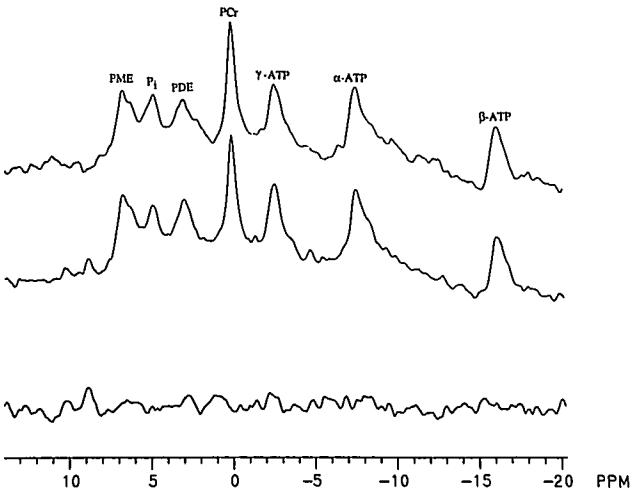

FIG. 1. ^{31}P magnetic resonance spectroscopy spectra from *in situ* dog brain before (middle trace) during cardiopulmonary resuscitation, which commenced immediately upon cardiac arrest (upper trace), and the difference between the two (lower trace) showing no change in high-energy phosphates. The three peaks on the right side of trace A are the β, α, and γ phosphorus species of ATP. PCr = phosphocreatine; PDE = phosphodiesters; 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 pH, 7.38 ± 0.01 to 7.34 ± 0.04; brain pH_i, 7.10 ± 0.06 to 7.08 ± 0.05; ATP, 100–103 ± 2 (percent control); CBF, 41 ± 9 to 31 ± 4 ($ml \cdot min^{-1} \cdot 100\ g^{-1}$); and CMR_{O_2}, 1.07 ± 0.2 to 1.04 ± 0.2 ($\mu mol \cdot min^{-1} \cdot g^{-1}$).

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 pH_i occur. There was a rapid decrease with ventricular fibrillation and slower subsequent recovery with CPR. Brain 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

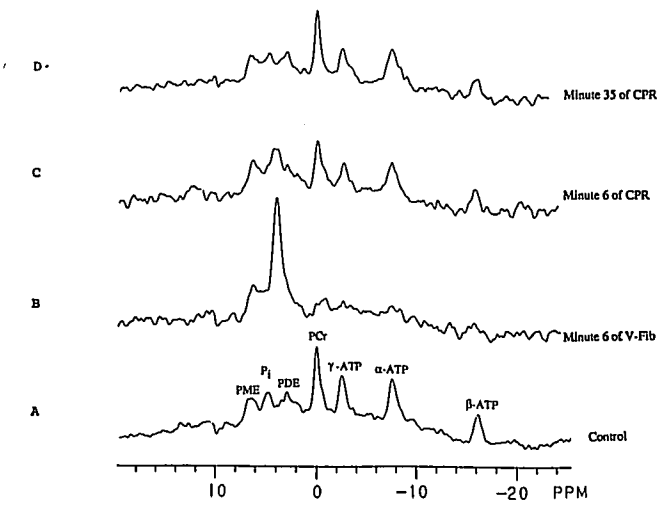

FIG. 2. ^{31}P magnetic resonance spectroscopy spectra from *in situ* dog brain during vest cardiopulmonary resuscitation (CPR) after a 6-min delay in the onset of CPR from time of arrest. Each spectrum was acquired in 1 min. The frequency of the inorganic phosphate (P_i) peak is *p*H-dependent. Notice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

*p*H decreased from 7.29 at 6 min of CPR to 7.02 by 50 min. Sagittal sinus *p*H decreased to 6.94 with normal venous P_{CO_2}. Sagittal sinus *p*H 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 ± 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 *p*H), 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_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 *p*H 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-

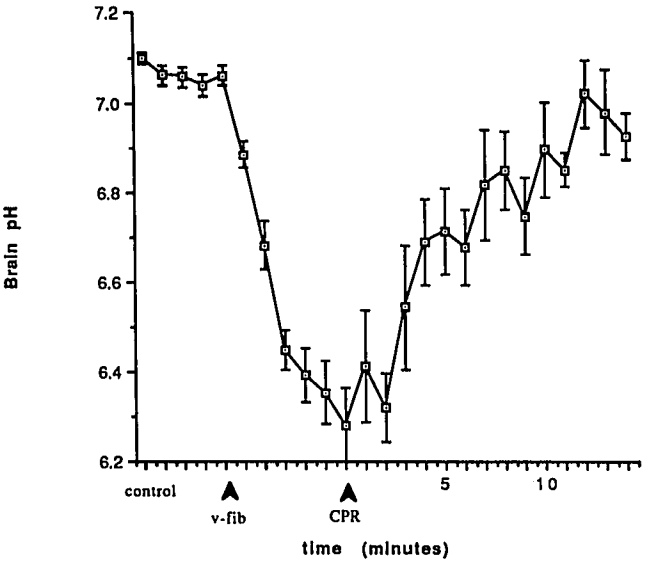

FIG. 3. ^{31}P magnetic resonance spectroscopy measurements of dog brain *p*H (pH_i) during vest cardiopulmonary resuscitation (CPR) after a 6-min delay in onset of CPR from time of cardiac arrest. Arrows indicate commencement of ventricular fibrillation (v-fib) and CPR. Note the rapid decrease in pH_i 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 ± 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
Pa_{O_2} (mmHg)	469 ± 31	210 ± 47*	207 ± 32*	222 ± 59*	179 ± 33*	183 ± 51*
Pa_{CO_2} (mmHg)	34 ± 3.5	30 ± 3.9	29 ± 2.6	27 ± 2.4	27 ± 3.9	29 ± 3.5
*p*Ha	7.41 ± 0.04	7.29 ± 0.04*	7.21 ± 0.04*	7.24 ± 0.04*	7.08 ± 0.04*	7.02 ± 0.04*
Pss_{O_2} (mmHg)	42 ± 1.6	60 ± 2*	64 ± 5.2*	56 ± 6.3*	53 ± 3.1*	52 ± 5.6
Pss_{CO_2} (mmHg)	50 ± 4.6	44 ± 5.0	37 ± 2.5	44 ± 4.1	46 ± 5.7	52 ± 5.5
*p*Hss	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).
Pa_{O_2} = arterial oxygen tension; Pa_{CO_2} = arterial carbon dioxide tension; *p*Ha = arterial *p*H; Pss_{O_2} = sagital sinus oxygen tension; Pss_{CO_2} = sagital sinus carbon dioxide tension; *p*Hss = sagital 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_{CO_2} 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 ^{31}P 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 ^{31}P 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 ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	35 ± 3	—	58 ± 12	57 ± 16	43 ± 12	33 ± 7	25 ± 6
$CMRO_2$ ($\mu mol \cdot g^{-1} \cdot min^{-1}$)	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; CMR_{O_2} = cerebral metabolic rate for oxygen; ATP = brain adenosine triphosphate; P_i = brain inorganic phosphate; PCr = brain phosphocreatine; pH_i = intracellular brain *p*H.
* 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 ^{1}H 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 $S_o(1 - e^{-TR/T1})$, 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 ^{31}P 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 *p*H recovery between neurons and glia have been reported,[25] differences in their *in vivo* ATP synthesis rates are less well understood[26] 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[4] and neurologic deficit[2] 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 *p*H-dependent, and the brain pH_i can be calculated from the position of P_i in the ^{31}P 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 *p*H 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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References

1. Steen PA, Milde JH, Michenfelder JD: Cerebral metabolic and vascular effects of barbiturate therapy following complete global ischemia. J Neurochem 31:1317–1324, 1978
2. Martin GB, Nowak RM, Paradis N, Rosenberg J, Walton D, Smith M, Eisiminger R, Welch KMA: Characterization of cerebral energetics and brain pH by ^{31}P spectroscopy after graded canine cardiac arrest and bypass reperfusion. J Cereb Blood Flow Metab 10:221–226, 1990
3. Gadian DG, Frackowiak RSJ, Crockard HA, Proctor E, Allen K, Williams SR, Russell RWR: Acute cerebral ischemia: Concurrent changes in cerebral blood flow, energy metabolites, pH, and lactate measured with hydrogen clearance and ^{31}P and ^{1}H nuclear magnetic resonance spectroscopy I. Methodology. J Cereb Blood Flow Metab 7:199–206, 1987
4. Nishijima MK, Koehler RC, Hurn PD, Eleff SM, Norris S, Jacobus WE, Traystman RJ: Postischemic recovery rate of cerebral ATP, phosphocreatine, pH, and evoked potentials. Am J Physiol 257: H1860–H1870, 1989
5. Nioka S, Chance B, Hilberman M, Subramanian VH, Leigh JS, Veech RL, Forster RE: Relationship between intracellular pH and energy metabolism in dog brain as measured by ^{31}P-NMR. J Appl Physiol 62:2094–2102, 1987
6. Chopp M, Welch KMA, Tidwell CD, Helpern JA: Global cerebral ischemia and intracellular pH during hyperglycemia and hypoglycemia in cats. Stroke 19:1383–1387, 1988
7. Eleff SM, Maruki Y, Monsein LH, Traystman RJ, Bryan RN, Koehler RC: Sodium, ATP and intracellular pH transients during reversible complete ischemia of dog cerebrum. Stroke 22: 233–241, 1991
8. Kern KB, Sanders AB, Badylak SF, Janas W, Carter AB, Tacker WA, Ewy GA: Long-term survival with open-chest cardiac massage after ineffective closed-chest compression in a canine preparation. Circulation 75:498–503, 1987
9. Koehler RC, Chandra N, Guerci AD, Tsitlik J, Traystman RJ, Rogers MC, Weisfeldt ML: Augmentation of cerebral perfusion by simultaneous chest compression and lung inflation with abdominal binding after cardiac arrest in dogs. Circulation 67: 266–275, 1983
10. Sanders AB, Kern KB, Atlas M, Bragg S, Ewy GA: Importance of the duration of inadequate coronary perfusion pressure on resuscitation from cardiac arrest. J Am Coll Cardiol 6:113–118, 1985
11. Halperin HR, Tsitlik JT: Programmable pneumatic generator for manipulation of intrathoracic pressure. IEEE Trans Biomed Eng BME-34:737–742, 1987
12. Petroff OAC, Prichard JW, Behar KL, Alger R, DenHollander JA, Shulman RG: Cerebral intracellular pH by ^{31}P nuclear magnetic resonance spectroscopy. Neurology 35:781–788, 1985
13. Schleien CL, Koehler RC, Gervais H, Berkowitz ID, Dean JM, Michael JR, Rogers MC, Traystman RJ: Organ blood flow and somatosensory-evoked potentials during and after cardiopulmonary resuscitation with epinephrine and phenylephrine. Circulation 79:1332–1342, 1989

14. Michael JR, Guerci AD, Koehler RC, Shi AY, Tsitlik J, Chandra N, Niedermeyer E, Rogers MC, Traystman JR, Weisfeldt ML: Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs. Circulation 69:822–835, 1984
15. Rudikoff M, Maugham W, Effron M, Freund P, Weisfeldt M: Mechanisms of blood flow during CPR. Circulation 61:345–356, 1980
16. Beattie C, Guerci AD, Hall T, Borkon AM, Baumgartner W, Stuart RS, Peters J, Halperin H, Robotham JL: Mechanisms of blood flow during pneumatic vests cardiopulmonary resuscitation. J Appl Physiol 70:454–465, 1991
17. Michenfelder JD, Milde JH: Postischemic canine cerebral blood flow appears to be determined by cerebral metabolic needs. J Cereb Blood Flow Metab 10:71–76, 1990
18. Snyder JV, Nemoto EM, Carroll RG, Safar P: Global ischemia in dogs: Intracranial pressures, brain blood flow and metabolism. Stroke 6:21–27, 1975
19. Todd MM, Tommasino C, Shapiro HM: Cerebrovascular effects of prolonged hypocarbia and hypercarbia after experimental global ischemia in cats. Crit Care Med 13:720–723, 1985
20. Halperin HR, Guerci AD, Chanddra N, Herskowitz A, Tsitlik JE, Niskanen RA, Wurmb E, Weisfeldt ML: Vest inflation without simultaneous ventilation during cardiac arrest in dogs: Improved survival from prolonged cardiopulmonary resuscitation. Circulation 74:1407–1415, 1986
21. Yaster M, Koehler RC, Traystman RJ: Interaction of fentanyl and pentobarbital on peripheral and cerebral hemodynamics in newborn lambs. ANESTHESIOLOGY 70:461–469, 1989
22. Evelhoch JL, Ewy CS, Siegfried BA, Ackerman JJH: ^{31}P spin-lattice relaxation times and resonance line widths of rat tissue in vivo: Dependence upon the static magnetic field strength. Magn Reson Med 2:410–417, 1985
23. Shinnar M, Eleff SM: A generalized Pisarenko technique for analyzing the NMR FID. J Mag Reson 76:200–208, 1988
24. Joliot M, Mazoyer BM, Huesman RH: In vivo NMR spectral parameter estimation: A comparison between time and frequency domain methods. Magn Reson Med 18:358–370, 1991
25. Kraig RP, Chesler M: Astrocytic acidosis in hyperglycemic and complete ischemia. J Cereb Blood Flow Metab 10:104–114, 1990
26. Erecinska M, Dagani F: Relationships between the neuronal sodium/potassium pump and energy metabolism. J Gen Physiol 95:591–616, 1990
27. Smith ML, von Hanwehr R, Siesjo BK: Changes in extra- and intracellular pH in the brain during and following ischemia in hyperglycemic and in moderately hypoglycemic rats. J Cereb Blood Flow Metab 6:574–583, 1986
28. Jaffe AS: Textbook of Advanced Cardiac Life Support. 2nd edition. Dallas, Dallas American Heart Association, 1990, pp 107–109
29. Guerci AD, Chandra N, Johnson E, Rayburn B, Wurmb E, Tsitlik J, Halperin HR, Siu C, Weisfeldt ML: Failure of sodium bicarbonate to improve resuscitation from ventricular fibrillation in dogs. Circulation 74(suppl IV):IV-75, 1986
30. Kette F, Weil MH, von-Planta M, Gazmuri RJ, Rackow EC: Buffer agents do not reverse intramyocardial acidosis during cardiac resuscitation. Circulation 81:1660–1666, 1990