Nuclear Magnetic Resonance Spectroscopy Study of Human Brain After Cardiac Resuscitation

Gerard B. Martin, MD; Norman A. Paradis, MD; J.A. Helpern, PhD; Richard M. Nowak, MD; and K.M.A. Welch, MD

We used $^{31}$P nuclear magnetic resonance spectroscopy to study the cerebral metabolic function of eight patients with severe postsischemic anoxic encephalopathy secondary to cardiac arrest. Spectroscopy was performed at 18±13 and 64±20 hours after resuscitation. Glasgow Coma Scale scores at the time of initial and repeat spectroscopy were 3.6±1.2 and 3.5±1.2, respectively. In those patients whose spectra were of adequate quality to monitor pH, all demonstrated tissue alkalosis in at least one brain region. The mean brain pH at initial spectroscopy was 7.14±0.09 and was significantly alkalotic when compared with age- and sex-matched normal controls (pH=6.98±0.04, p<0.0001). Five of the eight patients showed at least one region of persistent alkalosis at repeat spectroscopy, whereas one patient demonstrated severe acidosis with a pH of 6.42. Spectra demonstrated marked metabolic heterogeneity, ranging from normal in appearance to complete obliteration of all high-energy phosphates with only inorganic phosphate remaining. (Stroke 1991;22:462-468)

Postischemic anoxic encephalopathy occurs predominantly in the setting of successful cardiac resuscitation after cardiac arrest. Numerous animal models have addressed various aspects of this disease entity1-3; however, the invasive nature of the techniques used have precluded their application to human subjects. Although there have been some studies of cerebral blood flow and metabolism in humans after resuscitation from cardiac arrest,4,5 the majority of clinical studies to date have focused on describing the clinical course of this encephalopathy and identifying prognostic markers of outcome.6

Phosphorus-31 nuclear magnetic resonance (NMR) spectroscopy is a noninvasive technique that permits serial monitoring of phosphate metabolic function and tissue pH. It has been used in humans to study the pathophysiology of stroke,7-9 dementia,10,11 and hypoxic-ischemic injury in newborns.12,13 The purpose of this study was to use $^{31}$P NMR spectroscopy to study cerebral pH and phosphate metabolism in adult patients with postsischemic anoxic encephalopathy secondary to cardiac arrest.

Subjects and Methods

This study was approved by the Internal Review Board of Henry Ford Hospital. Patients were eligible if they were 18 years or older and were unresponsive with a Glasgow Coma Scale score of 9 or less after successful resuscitation from cardiac arrest. Any patient with a history of stroke was excluded. After informed consent was obtained from the patient's next of kin, the patient was entered into the study. A standardized neurological examination was performed within 2 hours of transport to the NMR facility for spectroscopy. The high-field magnet (1.9 T) used in this study has a specially designed shielding system14 that allows it to be located in the basement of the main hospital. During patient transport and throughout NMR spectroscopy, electrocardiogram and arterial blood pressure were continuously monitored. Pulmonary artery pressure and central venous pressure also were continuously monitored in patients, with the appropriate catheters in place. While the patient was in the magnet, the portable monitors were positioned outside the facility Faraday cage at a distance of approximately 20 feet and were connected to the patient through filtered lines. The tracings achieved were of high quality and acceptable for monitoring purposes. While the patient was in the magnet, mechanical ventilation was
accomplished with a nonferromagnetic ventilator (225 SIMV volume ventilator, Monaghan Medical Corp., Plattsburgh, N.Y.). Any medication infusions (i.e., vasopressors) were continued during spectroscopy with controlled infusion pumps (521 Intelligent Pump, Quest Medical Inc., Carrollton, Tex.). Arterial blood gases and serum glucose were obtained immediately before spectroscopy. Spectroscopy was repeated 24–72 hours after the initial examination.

Nuclear magnetic resonance spectroscopy was performed with a Biospec I spectrometer (Bruker/Oxford Research Systems, Billerica, Mass.) and a 1.9-T whole-body magnet. Topical magnetic resonance was used for spectroscopic localization. Spectra were obtained from both hemispheres, usually in the parietal and occipital regions, with a signal source volume of 65 cm³. The pH was measured using the chemical shift difference between inorganic phosphate (P$i$) and phosphocreatine (PCr). In spectra in which only P$i$ was apparent, the resonant frequency of protons on water was used as an internal reference frequency reference point. This method of pH assessment was validated using normal controls. The term alkalosis is used in this paper to describe any brain pH greater than two standard deviations above our normal of 6.98±0.04 for age- and sex-matched controls.

Not all spectra were of adequate quality to allow quantitative assessment. These spectra will be descriptively presented. When spectra were of adequate quality, resonance signal areas were estimated using a Lorentzian curve-fitting algorithm (New Methods Research, Inc., Syracuse, N.Y.). A signal-to-noise ratio of 2 was used as the minimum ratio necessary for peak assignment and subsequent analysis. Data comparisons without the appropriate $p$ values represent descriptive analysis only.

Statistical analysis was performed using $t$ tests, Pearson’s correlation, and Spearman’s rank correlation. A value of $p<0.05$ was considered statistically significant.

**Results**

We studied eight patients whose mean age was 66±12 years. Table 1 shows their clinical profiles and Table 2 the metabolic and NMR spectroscopic data. Cases 1 and 2 are presented below for illustration.

**Case 1.** A 67-year-old black woman awoke on the morning of admission complaining of severe shortness of breath and diaphoresis. The patient suffered a cardiopulmonary arrest during ambulance transport. Basic cardiac life support was immediately instituted, and on arrival in the emergency department approximately 5 minutes later, advanced cardiac life support was instituted. The initial rhythm was asystole. The patient was successfully converted to sinus rhythm 19 minutes after arrival with a blood pressure of 100/50 mm Hg. Nuclear magnetic resonance spectra were obtained from the parietal and occipital areas bilaterally at 15 and 63 hours after resuscitation and demonstrated severe and persistent impairment of phosphate metabolite levels in the right hemisphere when compared to the left. Other than an increase in P$i$, in the parietal and occipital regions, spectra obtained from the left hemisphere appeared normal at both 15 and 63 hours postresuscitation. Brain pH was measurable from the left hemisphere only and was normal initially, with alkalosis present on repeat spectroscopy (7.03 and 7.19, respectively). Life support was withdrawn, and the patient died approximately 84 hours after initial resuscitation.

**Case 2.** A 62-year-old black woman collapsed while walking down the stairs at home. Emergency Medical Service was called and found the patient in cardiopulmonary arrest. Basic cardiac life support was instituted, and the patient was transported to the emergency department where her initial rhythm was ventricular fibrillation. She was defibrillated to supraventricular rhythm with a blood pressure of 140/80 mm Hg within 6 minutes of her arrival. Nuclear magnetic resonance spectroscopy was performed at 20 and 62 hours after resuscitation. There was no change in the neurological status of the patient between NMR examinations. Spectroscopy revealed severe impairment of high-energy phosphate metabolite levels in both hemispheres acutely, which progressed to complete obliteration of all metabolites except for a large P$i$, resonance 48 hours later (Figure 1). At the time of the repeat study, both hemispheres were acidic (pH, 6.40–6.44). The patient died 128 hours after initial resuscitation. Postmortem examination revealed a subdural occipital hematoma with bilateral occipital lobe contusions that apparently had been sustained when the patient fell after suffering the cardiopulmonary arrest.

Mean values for Glasgow Coma Scale score, Pittsburgh brain stem score, arterial pH, and glucose are presented in Tables 1 and 2. We modified slightly the Pittsburgh brain stem score using these five tests: 1) presence of corneal reflex, 2) response to ice-water calories, 3) reactivity of right pupil to light, 4) reactivity of left pupil to light, and 5) presence of a gag or cough reflex. A positive or normal response is scored 1 point, and a negative or abnormal response is scored 2 points. Metabolite ratios and pH values were not obtainable from all spectra because of low signal-to-noise ratios in some instances and because of an inability to identify specific peaks precisely in others.

Only two of the mean brain pH values obtained lie within the age- and sex-matched normal range of brain pH determined in our NMR facility (Figure 2). The mean brain pH at initial spectroscopy was 7.14±0.09, which is significantly higher than normal controls ($p<0.0001$). The mean brain pH at repeat spectroscopy was 6.97±0.32 ($p=0.75$, compared with controls). If case 2, the only case with brain acidosis, is excluded, the mean brain pH was also alkalotic at repeat examination, with a value of 7.14±0.12 ($p=0.0038$, compared with controls). Interhemispheric differences existed in pH in all cases in which simultaneous bilateral readings were obtained.

There was no significant correlation between brain pH and the serum glucose at either initial or repeat spectroscopy ($r=0.04$, $p=0.94$ and $r=0.58$, $p=0.22$, respectively).
### TABLE 1. Cardiac Arrest Patient Clinical Profiles

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age/sex</th>
<th>Medical history</th>
<th>Duration of Arrest (min)</th>
<th>Duration of Survival (hrs)</th>
<th>Neurologic scoring (GCS/PBSS) (at time of spectroscopy)</th>
<th>CT scan</th>
<th>EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67/F</td>
<td>CHF, HPTN, IDDM, mild renal insufficiency</td>
<td>24</td>
<td>84</td>
<td>Initial: 6/5 (13 hrs) Repeat: 6/5 (61 hrs)</td>
<td>58 hrs: Decreased density bilaterally involving basal ganglia and periventricular white matter. Obscuration of cortical sulci compatible with edema.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>62/F</td>
<td>Alcohol abuse</td>
<td>24</td>
<td>128</td>
<td>Initial: 3/10 (18 hrs) Repeat: 3/10 (60 hrs)</td>
<td>NP</td>
<td>70 hrs: Electrocerebral silence.</td>
</tr>
<tr>
<td>3</td>
<td>78/M</td>
<td>HPTN, IDDM, prostatic cancer</td>
<td>10</td>
<td>216</td>
<td>Initial: 3/10 (46 hrs) Repeat: 3/10 (70 hrs)</td>
<td>7 hrs: Focal ischemic areas, edema. 74 hrs: Massive infarction involving the temporal and occipital lobes, cerebellum, and entire brain stem. Obstructive hydrocephalus of third and lateral ventricles.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>74/M</td>
<td>NS</td>
<td>33</td>
<td>360</td>
<td>Initial: 3/5 (16 hrs) Repeat: 3/5 (96 hrs)</td>
<td>10 hrs: Moderate diffuse cerebral atrophy.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>75/F</td>
<td>HPTN, CHF</td>
<td>50</td>
<td>54</td>
<td>Initial: 3/7 (13 hrs) Repeat: 3/10 (44 hrs)</td>
<td>8 hrs: No abnormality identified</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>73/M</td>
<td>HPTN, IDDM</td>
<td>23</td>
<td>124</td>
<td>Initial: 3/5 (3 hrs) Repeat: 3/6 (39 hrs)</td>
<td>25 hrs: No abnormality identified.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>42/F</td>
<td>Asthma, heroin, cocaine abuser</td>
<td>45</td>
<td>44</td>
<td>Initial: 3/9 (10 hrs) Repeat: NP</td>
<td>NP</td>
<td>NP</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Mean±SD</th>
<th></th>
<th></th>
<th>GCS:3.6±1.2</th>
<th>GCS:3.5±1.2</th>
<th>PBSS: 7.0±2.3</th>
<th>PBSS: 7.7±2.6</th>
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<tbody>
<tr>
<td>66±12</td>
<td>30±13</td>
<td>130±110</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

All times except duration of arrest represent the interval between resuscitation and performance of indicated study. 

GCS, Glasgow coma score; PBSS, Pittsburgh brain stem score; CT, computed tomography; EEG, electroencephalogram; CHF, congestive heart failure; HPTN, hypertension; IDDM, insulin-dependent diabetes mellitus; NS, not significant; FIRDA, frontal intermittent rhythmic delta activity; NP, not performed.

respectively), nor was there any correlation between arterial pH and brain pH initially ($r = -0.61, p = 0.14$). However, there was a significant positive correlation between arterial pH and brain pH at repeat spectroscopy ($r = 0.85, p = 0.024$). If case 2 is excluded, the significance of this correlation is lost, with $r = -0.11$ and $p = 0.86$. The dependence of this correlation on case 2 and the fact that the relationship is positive rather than negative, as it is between the initial arterial and brain pH, casts doubt on the validity of this correlation between the arterial and brain pH at repeat spectroscopy.

There was heterogeneity of changes in energy status both between patients as well as within indi-
individuals from hemisphere to hemisphere. Some patients had normal appearing spectra in one hemisphere, while the contralateral hemisphere was grossly abnormal. Most patients had at least one area of abnormal-appearing spectra at both initial and repeat examination. The mean PCr/Pi ratio was 1.51±0.31 and 1.61±0.10 at initial and repeat spectroscopy, respectively. This value does not differ significantly from the normal range of 1.51±0.31 determined for age-matched controls in the NMR facility (p=0.72 and p=1.00, respectively). There was no consistent relationship found with the PCr/Pi ratio; this ratio was normal in some patients and depressed in others. There was no significant correlation between neurological scoring and either PCr/Pi or brain pH (all p>0.05).

Discussion

The NMR techniques used in this study obtained signals from primarily cortical tissue. We studied the parietal and occipital areas in most cases because the greatest histopathologic changes have occurred in these regions in previous studies of global ischemia.18,19 The increase in brain pH demonstrated in these patients is consistent with data obtained from stroke patients in which brain alkalosis was also demonstrated.8,20,21 We have proposed that this pH shift to alkalosis signals the end of a therapeutic window and possibly irreversible injury.8 Given the complex mechanisms that have evolved to maintain cerebral acid–base homeostasis, the persistent loss of this control may well be indicative of severe, irreversible injury. Several mechanisms have been proposed to account for postischemic alkalosis. These have been described in detail elsewhere and include edema, gl Ioss with buffering by the glial cells and measurement of a signal that is predominantly glial in origin, and cell death with equilibration of intracellular and extracellular pH.2,3,21-24 No specific conclusion can be made regarding the mechanism of the alkalosis observed in this study.

We reviewed the relationship between the serum glucose and brain pH because some evidence suggests that glucose levels are inversely related to brain pH after ischemia25 and that hyperglycemia may adversely affect outcome. Although all patients were hyperglycemic at initial spectroscopy, there was no correlation between the extent of hyperglycemia and the pH of the brain. This is consistent with our previous finding that hyperglycemia does not corre-

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Time post-resuscitation (hrs)</th>
<th>Serum arterial pH</th>
<th>Glucose (mg/dl)</th>
<th>Brain region</th>
<th>Brain pH</th>
<th>PCr/Pi</th>
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<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Repeat</td>
<td>Initial</td>
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<tr>
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<td>62</td>
<td>7.39</td>
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<td>1.52</td>
<td>132</td>
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<tr>
<td>3</td>
<td>48</td>
<td>72</td>
<td>7.50</td>
<td>7.40</td>
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<td>271</td>
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<td>4</td>
<td>18</td>
<td>98</td>
<td>7.55</td>
<td>7.47</td>
<td>237</td>
<td>226</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>46</td>
<td>7.40</td>
<td>7.47</td>
<td>315</td>
<td>160</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>NP§</td>
<td>7.46</td>
<td>NP</td>
<td>430</td>
<td>NP</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>42</td>
<td>7.27</td>
<td>7.45</td>
<td>401</td>
<td>303</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>NP§</td>
<td>7.39</td>
<td>NP</td>
<td>355</td>
<td>NP</td>
</tr>
</tbody>
</table>

Mean±SD: 18±13 64±20 7.43±0.09 7.43±0.60 322±103 203±74 7.14±0.09 6.97±0.32 1.51±0.31 1.61±1.01

PCr, phosphocreatine; P, inorganic phosphate; LO, left occipital; NP, not performed; LP, left parietal; NI, spectra not quantitatively interpretable; RO, right occipital; RP, right parietal; LF, left frontal; RF, right frontal; LPO, left parieto-occipital; RPO, right parieto-occipital.

*Large P, peak; otherwise normal; †normal high-energy phosphates; #severely depressed high-energy phosphates; §only a single large P, peak detected; || no identifiable high-energy phosphates; ¶patient died before study; #depressed high-energy phosphates; **no detectable high-energy phosphates.
late with brain pH during alkalosis but may only correlate during acidosis.25

The heterogeneity of cerebral metabolic response to the global ischemic insult of cardiac arrest may be secondary to inhomogeneous blood flow both during and after resuscitation from cardiac arrest. Heterogeneity of cerebral blood flow has been noted in animal models of cerebral ischemia26,27 and in patients both during and after resuscitation from cardiac arrest.5,28 Such heterogeneity in blood flow may be due to the no-reflow phenomenon29 combined with the cerebrovascular disease that probably existed in our patients.

There was no consistent finding with respect to the energy status and the PCr/Pi ratio. In some patients it was relatively normal, whereas in others it was depressed. This is in contrast to NMR data obtained by Hope et al13 in birth-asphyxiated infants. In this study a PCr/Pi ratio <0.80 was associated with a poor prognosis, whereas a ratio >0.80 was associated with a good neurological recovery. These findings were substantiated in a larger follow-up study by the same group12 in which a PCr/Pi ratio below the 95% confidence limits for normal was associated with a poor outcome. Although the number of patients in our study is small and there were no survivors, the PCr/Pi ratio does not appear to have the same prognostic ability in adults as it does in infants. This may be related to differences between the neonatal and adult brain.

Although recovery of energy status and pH must occur in the brain if there is to be a return of preischemic neurological function, animal studies have shown that after an acute event, the presence of normal pH and energy state do not necessarily imply intact neurological function.30 The normal signal obtained in these cases may be from a population of
neurons that are irreversibly injured but have not died. The injury may have been significant enough to disrupt certain neuronal functions, for example, neurotransmission, while the basic energy metabolism remains intact. An alternative explanation is that neurons in the region from which normal metabolism is measured are indeed dead and that the signal is generated from glia that are more resistant to ischemia.31 Neutrophils infiltrating an area may be a further source of signal.21

The spectroscopic findings in case 2 are of interest because they represent the most severe case in the spectrum of postischemic injury. The markedly abnormal spectra initially obtained progressed to complete obliteration of all metabolites except P. This indicates severe ongoing ischemia that has infarcted all tissue in the area including the relatively ischemia-resistant glial cells. Only the second set of spectra from this patient was interpretable for pH. The pH in all three spectral locations was markedly acidotic (i.e., 6.40–6.42). The patient at this point was clinically brain dead, with a flat electroencephalogram. The acidosis is a result of the absence of cerebral blood flow, a finding characteristic of brain death.32–34 The diffuse and bilateral extent of this acidosis in conjunction with the similar extent of energy failure is supportive evidence of brain death. The potential utility of diffuse acidosis and energy failure as an NMR marker for brain death requires further investigation.

The initial spectra from the right parieto-occipital area in case 7 showed complete absence of all 31P metabolites (Figure 3). Unlike case 2, in which the absence of cerebral blood flow may have prevented the washout of any residual P, in case 7 all metabolic

Figure 2. Mean brain pH values at individual study times of all patients. Solid line at 6.98 is mean pH from age-matched controls. Dotted lines represent two standard deviations from this mean. Each symbol represents an individual case study, and each data point represents the mean pH value from all brain regions studied at that time. □, case 1; ×, case 2; ∆, case 3; ○, case 4; ●, case 5; +, case 6; ○, case 7; *, case 8.

Figure 3. Case 7, spectra from right parieto-occipital region 6 hours postresuscitation (top panel) with no evidence of any 31P metabolites and 42 hours postresuscitation (bottom panel) with the same area showing marked improvement from previous spectra with 31P metabolites present.
by-products may have been washed out, resulting in no signal. By the time of repeat spectroscopy 36 hours later, a signal, albeit abnormal, was obtained from this area. The presence of identifiable phosphorus metabolites at the time of the second study may indicate reperfusion of dead tissue.

To our knowledge, this is the first report of the use of $^{31}$P NMR spectroscopy in the assessment of patients with postischemic anoxic encephalopathy. The data presented suggest heterogenous cerebral metabolic and pH disturbances that occur soon after resuscitation from the global ischemia of cardiac arrest. In one case, the data suggest the existence of additional markers of brain death. Further investigation with this technique should improve our understanding and treatment of the cerebral metabolic events related to postischemic anoxic encephalopathy.

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References


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