Effect of Mild Hyperthermia on Recovery of Metabolic Function After Global Cerebral Ischemia in Cats

M. Chopp, PhD, K.M.A. Welch, MD, C.D. Tidwell, BS, R. Knight, BS, and J.A. Helpern, PhD

We investigated the effect of mild whole-body hyperthermia before and after 16 minutes of global cerebral ischemia on metabolic recovery during recirculation in cats using in vivo phosphorus-31 nuclear magnetic resonance spectroscopy. Hyperthermia (temperature 40.6±0.2°C) was induced ≥1 hour before ischemia and was maintained during 1.5–2 hours of recirculation in nine cats; four cats were subjected to hyperthermia without cerebral ischemia, six to hyperthermia during recirculation (after return of intracellular pH to preischemic values), and 14 to normothermic ischemia and recirculation. Our data indicate that preischemic hyperthermia results in an intracellular cerebral pH during recirculation significantly lower than that in normothermic cats. In hyperthermic cats β-ATP and phosphocreatine (PCr) concentrations and the ratio of PCr to inorganic phosphate failed to return to preischemic levels during recirculation in contrast to normothermic cats. Hyperthermia without ischemia and hyperthermia during recirculation had no significant effect on intracellular pH. Thus, preischemic hyperthermia has a detrimental effect on metabolic recovery after transient global cerebral ischemia. (Stroke 1988;19:1521-1525)

Fever or subfebrility in stroke patients causes deterioration of neurologic function by mechanisms as yet unknown.1 In normal brain, body temperature increases of 1–2° C over a period of hours in response to infection or even ambient thermal conditions have no significant detrimental effects on cerebral metabolism.2 The effects of similar hyperthermia (temperature of ≤41°C) on cerebral high-energy phosphate metabolism and intracellular pH has not been addressed under conditions of cerebral ischemia. Accordingly, we used in vivo phosphorus-31 nuclear magnetic resonance (31P-NMR) spectroscopy to measure relative concentrations of high-energy phosphate metabolites and intracellular pH before, during, and after transient global cerebral ischemia in cats subsequent to mild whole-body hyperthermia. Our data suggest that preischemic mild hyperthermia prolongs ischemic brain acidosis and has a detrimental effect on metabolic recovery from transient global cerebral ischemia.

Materials and Methods

We used 38 conditioned cats weighing 2.2–3.6 kg. Surgical preparation and induction of transient (16 minutes) global cerebral ischemia using a combination of systemic arterial hypotension and inflation of a cervical cuff were identical to those previously reported.3 Each cat was placed on a water blanket. A water bath recirculator-heater (Model E-12, Haake, Berlin, FRG) connected to a feedback-regulated temperature controller (YSI model 73-A, Yellow Springs Instrument Company, Yellow Springs, Ohio) was used to regulate the cat’s temperature. Temperature probes were placed rectally and in the abdominal wall. Over 1–1.5 hours the rectal temperature of cats made hyperthermic rose to between 40° and 41°C. Temperature gradients between rectal and subcutaneous temperatures were kept to <0.2°C.

The time course and relations between cerebral, rectal, esophageal, and subcutaneous temperatures were measured in five cats: two cats made hyperthermic before ischemia, two cats subjected to normothermic ischemia, and one cat made hyperthermic without being subjected to ischemia. We used two copper constantan thermocouples (100

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We studied four groups of cats. Nine cats were made hyperthermic and the hyperthermia was maintained (±0.1°C) for ≥1 hour before ischemia, during ischemia, and during recirculation. In six cats, hyperthermia was initiated after 1–1.5 hours of recirculation, when intracellular pH returned to control values; hyperthermia was maintained and these six cats were monitored for 2–4 hours after reaching steady-state temperature. Technical difficulties associated with our method of heating the cats precluded the induction of steady-state hyperthermia during recirculation before the return of pH to control values. Fourteen normothermic (temperature between 38.5°C and 39.2°C) cats were subjected to ischemia and recirculation; data from seven of these normothermic cats have been reported. The effect of hyperthermia on cerebral energy metabolism without cerebral ischemia was measured in four cats made hyperthermic over 1–1.5 hours and maintained at a constant temperature (40.8±0.1°C) for 3–5 more hours.

Profile analysis was performed on all 31P-NMR and physiologic measures. Only six recirculation spectra (4, 16, 32, 48, 64, and 96 minutes) were analyzed; for each, a mean value of the 31P-NMR parameter was calculated from the time of interest and the times immediately before and immediately after (except for the 4-minute time, which was averaged only with the 16-minute time). Physiologic data were obtained before ischemia, before and after hyperthermia, and four times during recirculation (16, 32, 64, and 96 minutes). If the group effect or the group × time interaction were found to be significant in the profile analysis, subanalyses (t tests) were performed with Bonferroni’s multiple comparison adjustment made for each subanalysis. 31P-NMR and physiologic values at all points of interest within each group were compared with control values using paired t tests.

Results

Table 1 shows the physiologic data for the normothermic and hyperthermic groups. No significant differences between groups were found in pH, PCO2, Po2, and serum glucose concentration except for pH

<table>
<thead>
<tr>
<th>Time</th>
<th>pH</th>
<th>PCO2 (mm Hg)</th>
<th>Po2 (mm Hg)</th>
<th>MABP (mm Hg)</th>
<th>SAG (mg/dl)</th>
<th>pH</th>
<th>PCO2 (mm Hg)</th>
<th>Po2 (mm Hg)</th>
<th>MABP (mm Hg)</th>
<th>SAG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.34±0.06</td>
<td>31.7±2.4</td>
<td>142±22</td>
<td>114±10</td>
<td>145±34</td>
<td>7.33±0.04</td>
<td>32.9±4.0</td>
<td>131±28</td>
<td>111±11</td>
<td>176±24</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>7.32±0.04</td>
<td>30.0±2.6</td>
<td>110±9.5</td>
<td>110±17</td>
<td>200±66</td>
</tr>
<tr>
<td>(Re)circulation</td>
<td>16 min</td>
<td>7.17±0.08*</td>
<td>40.7±12.9</td>
<td>122±32*</td>
<td>111±17</td>
<td>126±31</td>
<td>7.07±0.14*</td>
<td>41.0±13.7</td>
<td>95±23</td>
<td>113±11</td>
</tr>
<tr>
<td></td>
<td>32 min</td>
<td>7.16±0.06*</td>
<td>37.1±6.5</td>
<td>150±53</td>
<td>113±7</td>
<td>204±77</td>
<td>7.07±0.16*</td>
<td>36.1±13.2</td>
<td>115±38</td>
<td>102±18</td>
</tr>
<tr>
<td></td>
<td>64 min</td>
<td>7.18±0.08*</td>
<td>36.3±8.1</td>
<td>127±11</td>
<td>105±15</td>
<td>190±77</td>
<td>7.08±0.13*</td>
<td>31.8±4.4</td>
<td>105±11†</td>
<td>105±33</td>
</tr>
<tr>
<td></td>
<td>96 min</td>
<td>7.24±0.15</td>
<td>33.4±10.4</td>
<td>129±30</td>
<td>105±20</td>
<td>142±67</td>
<td>7.02±0.14†</td>
<td>33.0±7.2</td>
<td>109±13</td>
<td>91±33</td>
</tr>
</tbody>
</table>

Data are mean±SD. MABP, mean arterial blood pressure; SAG, serum arterial glucose concentration.

*p<0.01 different from control.
†p<0.006, ‡p<0.009 different from normothermia.
at 96 minutes of recirculation \((p<0.009)\) and \(P_0_2\) at 64 minutes of recirculation \((p<0.006)\). Comparison of recirculation values with control values within each group showed that arterial pH remained acidic throughout recirculation for the hyperthermic group. Except for a 16-minute \(P_0_2\) in the normothermic group, there were no significant differences within the groups for any other physiologic measure during recirculation compared with control values. There were also no significant differences in the hyperthermic group for physiologic parameters after heating compared with control values.

Figure 1 shows \(3^1\)P-NMR spectra from representative normothermic and preischemia hyperthermic cats before ischemia (control), during ischemia, and during recirculation. In the preischemia hyperthermic group, \(\beta\)-ATP concentration declined approximately 4.7\% from control values \((p<0.02)\) after heating, before ischemia; there were no changes observed in other peak heights with heating. Both normothermic and preischemia hyperthermic cats exhibited a rapid decline in adenylate peaks to noise levels during ischemia. During recirculation, spectra from the normothermic group returned to control values; in contrast, the preischemia hyperthermic cats failed to regain control values. Table 2 presents \(\beta\)-ATP, \(P_Cr\), \(P_i\), \(P_Cr/P_i\), and \(P_Cr/\beta\)-ATP contents during six recirculation time points as fractions of control values. The data suggest a failure in the preischemia hyperthermic group of the adenylate peaks to return to control values.

Figure 2 shows the time course of intracellular pH for the normothermic and preischemia hyperthermic groups. The normothermic group exhibited a transient 4–8-minute prolongation of intracellular acidosis during recirculation, with a return to >95\% of the control pH value within 40 minutes. In the preischemia hyperthermic group, intracellular pH remained acidic during recirculation. Profile analysis revealed a marginally nonsignificant group \(\times\) time interaction for pH \((p<0.07)\). t tests revealed significantly lower pH for the hyperthermic than for the normothermic group after 32 and 48 minutes of recirculation \((p<0.0005\) and \(p<0.0006\), respectively); immediately upon recirculation, pH values were not significantly different. At the other recirculation times analyzed, pH values for the preischemia hyperthermic group were lower than for the normothermic group \((0.02<p<0.05)\).

The four no-ischemia hyperthermic cats failed to exhibit intracellular tissue acidosis or declines in high-energy phosphate peak heights or ratios. Intracellular pH and adenylate peak heights were also unaltered by recirculation hyperthermia.

Figure 3 shows the time course of cerebral and rectal temperatures for a representative preischemia hyperthermic cat. Brain and rectal temperatures in the two preischemia hyperthermic cats rose in unison. Esophageal, subcutaneous (not shown), and rectal temperatures remained within 0.2\°C of each other throughout the experiment. Cerebral temperature dropped precipitously during ischemia (3.8±0.1\°C). During recirculation, brain temperature increased rapidly and achieved a steady state approximately 0.3\°C below rectal temperature.

**Discussion**

Our data indicate that mild hyperthermia induced before transient global cerebral ischemia causes severe tissue acidosis that is prolonged during recirculation and that concentrations of high-energy phosphate metabolites fail to return to control levels. Measurements of brain temperature versus core temperature revealed that the average brain temperature was likely no more than 1–2\°C above normal body temperature for cats (38.5–39.2\°C) during...
hyperthermia. Although we did not measure the distribution of brain temperatures, particularly cortical temperature, it is unlikely that cortical temperatures were higher than those measured. Patterns of metabolic recovery during recirculation and ischemic neuronal damage have not been correlated. However, there is recent evidence relating biologic outcome, as measured by changes in electroencephalographic amplitudes, to the degree of metabolic dysfunction in middle cerebral artery occlusion in cats. Likewise, increased cerebral acidosis associated with hyperglycemia has been implicated to adversely affect the viability of cerebral tissue. Thus, hyperthermia and the associated failure to reestablish preischemic spectral values may lead to a worsened biologic outcome. The detrimental effects of hyperthermia on cerebral ischemia is also supported by a recent study by Busto et al in which small increments of intraschemic striatal brain temperature in rats were shown to accentuate cerebral histopathologic changes 3 days after ischemia. The implications of these findings for clinical stroke patients are profound since an increase in body and brain temperature of 1-2°C is not uncommon. The data also have important implications for the management of cardiac arrest patients, in whom

<table>
<thead>
<tr>
<th>Time after recirculation (min)</th>
<th>β-ATP</th>
<th>PCR</th>
<th>Pi</th>
<th>PCR/Pi</th>
<th>Pcr/β-ATP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normothermia (n=14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.73±0.12*</td>
<td>0.68±0.07*</td>
<td>2.89±0.30*</td>
<td>0.26±0.04*</td>
<td>0.96±0.18</td>
</tr>
<tr>
<td>16</td>
<td>0.88±0.15*</td>
<td>0.87±0.03*</td>
<td>1.71±0.26*</td>
<td>0.53±0.10*</td>
<td>1.00±0.18</td>
</tr>
<tr>
<td>32</td>
<td>0.93±0.07</td>
<td>0.97±0.04</td>
<td>1.27±0.18</td>
<td>0.78±0.12*</td>
<td>1.04±0.11</td>
</tr>
<tr>
<td>48</td>
<td>0.91±0.11</td>
<td>1.03±0.07</td>
<td>1.23±0.26</td>
<td>0.88±0.18</td>
<td>1.14±0.13</td>
</tr>
<tr>
<td>64</td>
<td>0.87±0.04*</td>
<td>0.97±0.06</td>
<td>1.11±0.08</td>
<td>0.89±0.10</td>
<td>1.12±0.10</td>
</tr>
<tr>
<td>96</td>
<td>0.93±0.06</td>
<td>0.96±0.06</td>
<td>1.21±0.14</td>
<td>0.82±0.15</td>
<td>1.02±0.10</td>
</tr>
<tr>
<td></td>
<td>Preischemic hyperthermia (n=9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.61±0.13*</td>
<td>0.59±0.10</td>
<td>4.62±1.29†</td>
<td>0.14±0.05†</td>
<td>1.00±0.28</td>
</tr>
<tr>
<td>16</td>
<td>0.73±0.11*</td>
<td>0.72±0.10†</td>
<td>3.33±1.13†</td>
<td>0.24±0.09†</td>
<td>1.00±0.18</td>
</tr>
<tr>
<td>32</td>
<td>0.81±0.10*</td>
<td>0.78±0.09**</td>
<td>2.57±0.95*</td>
<td>0.36±0.20†</td>
<td>0.99±0.14</td>
</tr>
<tr>
<td>48</td>
<td>0.83±0.09*</td>
<td>0.83±0.14†</td>
<td>1.92±0.89</td>
<td>0.55±0.29*</td>
<td>1.00±0.17</td>
</tr>
<tr>
<td>64</td>
<td>0.85±0.11*</td>
<td>0.81±0.17</td>
<td>1.78±0.94</td>
<td>0.59±0.35</td>
<td>0.96±0.16</td>
</tr>
<tr>
<td>96</td>
<td>0.74±0.09†</td>
<td>0.72±0.16†</td>
<td>2.19±1.28</td>
<td>0.49±0.34*</td>
<td>0.98±0.18</td>
</tr>
</tbody>
</table>

Data are mean±SD ratio of peak height at indicated time to peak height before ischemia. β-ATP, β-adenosine 5'-triphosphate; PCR, phosphocreatine; Pi, inorganic phosphate.

*p<0.008 different from 1.0.
†p<0.008 different from normothermia.
aggressive efforts should be made to control body temperature to perhaps even subnormal levels.

The mechanisms whereby mild hyperthermia prolongs ischemic cerebral acidosis are unclear. Under nonischemic conditions in our study, hyperthermia did not cause changes in intracellular pH. The 4.7% decrease in β-ATP concentrations with hyperthermia before ischemia is consistent with data reported by Nilsson et al,14 though a significant decline was not reported in that study. A more recent study15 using microwave-induced cerebral hyperthermia reported 6.9% and 10.8% declines in ATP concentrations at temperatures elevated 1.4° and 3.4°C respectively, in rats. Carlsson et al,2 using a heating bulb to induce hyperthermia, noted no change in cerebral ATP concentrations from normothermic values at 42°C in cats. The temperatures achieved in our experiments are therefore unlikely to cause direct metabolic damage. Hyperthermia stimulates the cerebral metabolic rate for oxygen (CMRO₂) and increases cerebral blood flow (CBF) 5–6%/°C in normal brain; an effect on CMRO₂ and CBF has not been studied during cerebral ischemia. Even if CMRO₂ were identical in ischemic and nonischemic hyperthermia, it is unlikely that hyperthermia would cause the degree of intracellular acidosis we observed. Furthermore, if the increased metabolic activity were totally anaerobic during recirculation, a proportional change in intracellular acidosis might be expected. Thus, for example, a 10% change in metabolic activity is inconsistent with the threefold increase in hydrogen ion concentration, that is, the pH change from 6.9 to 6.3 after 48 minutes of recirculation. Further studies are necessary to elucidate the mechanism by which hyperthermia prolongs postischemic brain acidosis and metabolic dysfunction.

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References


Key Words: cerebral ischemia • hyperthermia, induced • metabolism • cats
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