Reduction of the Cerebral Protective Effect of Hypothermia by Oligemic Hypotension During Hypoxia in the Rat

M. MEHDI KEYKHAH, M.D.,* FRANK A. WELSH, Ph.D.,† MAGNUS HAGERDAL, M.D.,‡ and JAMES R. HARP, M.D.§

SUMMARY The effect of arterial hypotension on cerebral cortical tissue levels of adenosine triphosphate (ATP), phosphocreatine (PC\textsubscript{r}), lactate, and reduced nicotinamide adenine dinucleotide (NADH) was studied in male Wistar rats with unilateral carotid ligation exposed to arterial hypoxia (Pa\textsubscript{O\textsubscript{2}} 25 torr) for 20 min. while the body temperature was maintained at 32°C and 27°C. Brain metabolite levels were normal in normotensive hypothermic animals exposed to hypoxia, but reduction in arterial pressure to 75 torr caused a significant (p < 0.05) decrease in ATP and PC\textsubscript{r} values and a significant increase in lactate and NADH levels. These changes were comparable to those of normothermic normotensive, hypoxic animals. Furthermore, there was no significant difference in the brain metabolite levels between the two hypotensive hypothermic groups.

These results indicate that arterial hypotension severely alters the cerebral protective effect of hypothermia against injury caused by hypoxia, and that further reduction in body temperature (from 32°C to 27°C) will not prevent the harmful effect of hypoxia upon the brain in hypotensive rats.

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Cerebral cortical tissue metabolites

For purposes of reference the metabolite values presented in group 6 are considered normal in our laboratory. The values for ATP and P<sub>C</sub> from the right cortices (hemolateral to the ligated carotid artery) and that of lactate and NADH from both cortices in group I (normothermic-hypoxia) were significantly (p < 0.05) different from group 6. These low values for high energy phosphate and the high levels of lactate and NADH are evidence of presence of hypoxic injury in the cerebral cortex in group 1 animals. Compared with group 1, the values for ATP from the right cortices was significantly (p < 0.05) higher in hypothermic-hypotensive groups (groups 4 and 5) indicating injury due to hypoxia. The metabolic acidosis was more severe in group 4 and comparable with group 1.

The effect of hypoxic metabolic acidosis upon oxygen transport is seen by comparing arterial oxygen content (C<sub>ao2</sub>) in groups 2 and 3 with that of groups 4 and 5. Group 4 has higher C<sub>ao2</sub> than group 1, and this difference relates to the effect of hypothermia upon oxyhemoglobin dissociation. Hemoglobin values were similar in all groups.

Results

Physiologic parameters

All other groups are compared with group 1, the normothermic, hypoxic series which defines the standard stress. Values for all parameters in this control group are comparable to results of previous studies from this laboratory. In experimental groups 4 and 5 MAP was well controlled at 75 torr.

The third dependent variable, P<sub>ao2</sub> was identical in groups 1-5; P<sub>aco2</sub> adjusted to 35 torr during normoxia was markedly reduced in group 1 in association with metabolic acidosis. The level of metabolic acidosis is lower in groups 2 and 3 (hypothermic-hypoxia) in accordance with results of earlier studies. However, when MAP was 75 torr (groups 4 and 5), metabolic acidosis was more severe in group 4 and comparable with group 1.

<table>
<thead>
<tr>
<th>Rectal temperature (°C)</th>
<th>MAP (torr)</th>
<th>Pa&lt;sub&gt;O2&lt;/sub&gt; (torr)</th>
<th>Pa&lt;sub&gt;CO2&lt;/sub&gt; (torr)</th>
<th>pH&lt;sub&gt;a&lt;/sub&gt;</th>
<th>Ca&lt;sub&gt;O2&lt;/sub&gt; (m/dl)</th>
<th>Hemoglobin (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>37.1 ± 0.1</td>
<td>122 ± 5</td>
<td>25.7 ± 0.6</td>
<td>26.6 ± 1.4</td>
<td>7.27 ± 0.2</td>
<td>3.97 ± 0.1</td>
</tr>
<tr>
<td>Group 2</td>
<td>31.8 ± 0.008</td>
<td>134.1 ± 5</td>
<td>26.7 ± 0.6</td>
<td>23.6 ± 1.1</td>
<td>7.42 ± 0.2</td>
<td>8.4 ± 0.2</td>
</tr>
<tr>
<td>Group 3</td>
<td>26.5 ± 0.2</td>
<td>151 ± 7</td>
<td>26.5 ± 0.9</td>
<td>32.8 ± 2.6</td>
<td>7.41 ± 0.1</td>
<td>12.6 ± 0.3</td>
</tr>
<tr>
<td>Group 4</td>
<td>31.9 ± 0.7</td>
<td>75 ± 1.3</td>
<td>26.3 ± 0.4</td>
<td>29.4 ± 2.1</td>
<td>7.28 ± 0.2</td>
<td>5.4 ± 0.2</td>
</tr>
<tr>
<td>Group 5</td>
<td>26.9 ± 0.1</td>
<td>75 ± 0.6</td>
<td>25.1 ± 0.6</td>
<td>35.2 ± 1.9</td>
<td>7.30 ± 0.2</td>
<td>8.2 ± 0.5</td>
</tr>
<tr>
<td>Group 6</td>
<td>37.0 ± 0.1</td>
<td>174 ± 5</td>
<td>162 ± 8</td>
<td>34.7 ± 1.5</td>
<td>7.41 ± 0.2</td>
<td>19.8 ± 0.7</td>
</tr>
</tbody>
</table>

Values are mean ± sem.

*Significantly different from Group 1, p < 0.05.
Table 2. Cerebral Cortical Tissue Concentrations of Adenosine Triphosphate (ATP) Phosphocreatinine (PCr), Lactate, and NADH from Right and Left Cortices (Right Cortex Homolateral to Carotid Ligation)

<table>
<thead>
<tr>
<th></th>
<th>ATP (µmol/g)</th>
<th>PCr (µmol/g)</th>
<th>Lactate (µmol/g)</th>
<th>NADH (µmol/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right cortex</td>
<td>Left cortex</td>
<td>Right cortex</td>
<td>Left cortex</td>
</tr>
<tr>
<td>Group 1</td>
<td>2.42</td>
<td>2.82</td>
<td>2.51±0.6</td>
<td>4.23±0.2</td>
</tr>
<tr>
<td>Group 2</td>
<td>2.95*±0.05</td>
<td>2.88</td>
<td>4.88±0.3</td>
<td>5.09±0.2</td>
</tr>
<tr>
<td>Group 3</td>
<td>2.86±0.04</td>
<td>2.82</td>
<td>5.34±0.2</td>
<td>5.05±0.2</td>
</tr>
<tr>
<td>Group 4</td>
<td>2.19±0.4</td>
<td>2.41</td>
<td>2.11±0.6</td>
<td>3.57±0.6</td>
</tr>
<tr>
<td>Group 5</td>
<td>2.41±0.2</td>
<td>2.76</td>
<td>3.4±0.7</td>
<td>4.3±0.2</td>
</tr>
<tr>
<td>Group 6</td>
<td>2.79±0.03</td>
<td>2.76</td>
<td>4.65±0.1</td>
<td>4.37±0.1</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
*Significantly different from Group 1, p < 0.05.

Changes in the cerebral energy state indicative of cerebral tissue injury in normothermic animals. Thus while the levels of NADH and lactate increased, PCr and ATP values decreased significantly in group 1 in comparison with normothermic animals in group 6. These changes were more profound in the cortices on the side of the ligated carotid artery than in the controlateral cortices in group 1 (table 2). These results are in agreement with those reported by Salford et al, using similar experimental protocol and may indicate the same degree of neuronal damage in this group.

Reduction in body temperature by 5°C in group 2 prevented the harmful effect of hypoxia on the cerebral metabolite levels which occurred in normothermic animals. These results are comparable to those of normothermic-normoxic animals in group 6, demonstrating the cerebral protective effect of hypothermia from hypoxia. Further reduction in body temperature to 27°C produced the same degree of protection against hypoxia with regard to brain tissue metabolite levels.

These results are in agreement with those of Carlsson et al demonstrating complete cerebral protection from hypoxia with hypothermia at 27°C using rat model with no carotid ligations and with earlier studies from this laboratory using the Levine model rats with unilateral carotid ligation.

However, in the present study when the arterial pressure was lowered to 75 torr, hypothermia, 32°C, failed to protect the brain tissue from hypoxia, and further reduction in body temperature to 27°C did not improve the situation. Thus in both groups 4 and 5 changes which occurred in cerebral tissue metabolites were similar to those of normothermic-hypoxic animals in group 1.

It is quite possible that lack of cerebral blood flow (CBF) autoregulation caused by hypoxia makes the systemic arterial pressure the prime determining factor for maintaining cerebral perfusion. Thus oligemic hypotension would decrease CBF below the critical value needed to maintain brain tissue metabolism in groups 4 and 5.

It has been assumed that hypothermia protects the brain tissue from hypoxic stress by reducing the tissue demand for oxygen. We have shown in previous studies that hypothermia reduces the cerebral meta-
bolic rate for oxygen (CMR_{O2}) in Wistar rat by 5 percent for each degree centigrade,\textsuperscript{21-22} thus at 32°C CMR_{O2} decreases by 25 percent. An impressive brain protection from hypoxia was achieved at this body temperature in group 2 in the present study. The mild elevation of lactate should not be associated to any neuronal injury in this group.\textsuperscript{18}

Hypothermia also greatly increases arterial oxygen content (\text{CaO}_2) during hypoxia.\textsuperscript{2-18} This increase is due to the leftward shift of the oxyhemoglobin dissociation curve and the absence of systemic acidosis in hypothermic animals during hypoxia and has been assumed to be one of the causes of hypothermic protection of brain tissue from hypoxia.\textsuperscript{2}

Carlsson et al examined the role of increased \text{CaO}_2 during hypothermia in hypoxic rats. They exposed one group of animals to P_{aO}_2 of 12 torr at 27°C body temperature producing \text{CaO}_2 of 4.48 volumes percent. Metabolite values in that group were similar to those in 32°C normotensive animals in the present study. Furthermore, although similar values for \text{CaO}_2 were obtained in 32°C normotensive and 27°C hypotensive groups in the present study (table I) there were persistent changes in metabolite levels compatible with hypoxic injury in the hypotensive group. These results are in support of our previous study\textsuperscript{16} indicating that the cerebral protective effect of hypothermia from hypoxic injury does not depend solely on increases in \text{CaO}_2 in hypoxic animals.

Our results thus indicate that an impressive degree of cerebral protection can be achieved at 32°C, and while reduction in \text{CaO}_2 due to systemic acidosis may have a role in reducing the hypothermic protection during hypotension, changes in cerebral blood flow due to fall in systemic blood pressure must be a more important factor.

Maintenance of MAP during hypoxia which is characteristic of hypothermic animals (see groups 2 and 3, table I) may be a very important element of the “protective” effect of hypothermia. This suggests that hypothermia might not be helpful in ischemic stress.

References

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