Effects of Arterial Hypotension on Brain Metabolism in Normotensive and Spontaneously Hypertensive Rats

YASUO NAKATOMI, M.D., MASATOSHI FUJISHIMA, M.D., TAKAO ISHITSUKA, M.D., KINYA TAMAKI, M.D., AND TERUO OMAE, M.D.

SUMMARY The effects of graded systemic hypotension induced by the combination of bleeding and trimethaphan camsylate infusion on brain metabolism were studied in normotensive rats (NTR) and spontaneously hypertensive rats (SHR). Metabolites such as lactate, pyruvate and adenosine triphosphate (ATP) of the brain frozen in situ were measured at the end of 1 hour of hypotension. In SHR, either cerebral lactate or the lactate/pyruvate (L/P) ratio increased rapidly and progressively with a concomitant decrease in ATP, controlled by a Harvard respirator after immobilization with tubocurarine chloride. Paco₂ was maintained between 35 and 45 mm Hg as constantly as possible by adjusting respiration rate or tidal volume, and Pao₂ was kept above 80 mm Hg by addition of oxygen as needed. Both femoral arteries were cannulated, one for continuous blood pressure recording with an electromanometer, and the other for blood withdrawal to induce graded hypotension and for anaerobic blood sampling to determine pH, Pco₂ and Po₂ with an IL meter (Model 113). A femoral vein was also cannulated for trimethaphan camsylate infusion. The arterial blood samples were taken before and during hypotension, after which the head was frozen in situ by pouring liquid nitrogen into a plastic funnel previously placed on the skull. The whole brain was chiselled out and separated grossly into the supra- and infratentorial portions. The cortical part of the brain was weighed, ground in the frozen state, and homogenized after the addition of 12 ml of ice cold 1.0 N perchloric acid. The tissue homogenate, maintained at 0° to 4°C, was centrifuged and neutralized with 3 N potassium hydroxide at a pH of between 4.5 and 5.0. The supernatants were added to 0.5 M triethanolamine buffer, pH 7.6, for ATP. Substrates were determined by the enzymatic methods as follows: lactate and pyruvate by the lactate dehydrogenase reaction, and ATP by phosphoglycerate kinase, glyceraldehyde-3-phosphate dehydrogenase, triose phosphate isomerase and glycerol-1-phosphate dehydrogenase reaction.

Materials and Methods

Male SHR (Okamoto and Aoki) and NTR of the Wistar strain, weighing 250 to 340 g, aged 4 to 7 months, were anesthetized with intraperitoneal amobarbital (10 mg/100 g of body weight). The animal was tracheotomized and respiration was artificially controlled by a Harvard respirator after immobilization with tubocurarine chloride. Paco₂ was maintained between 35 and 45 mm Hg as constantly as possible by adjusting respiration rate or tidal volume, and Pao₂ was kept above 80 mm Hg by addition of oxygen as needed. Both femoral arteries were cannulated, one for continuous blood pressure recording with an electromanometer, and the other for blood withdrawal to induce graded hypotension and for anaerobic blood sampling to determine pH, Pco₂ and Po₂ with an IL meter (Model 113). A femoral vein was also cannulated for trimethaphan camsylate infusion. The arterial blood samples were taken before and during hypotension, after which the head was frozen in situ by pouring liquid nitrogen into a plastic funnel previously placed on the skull. The whole brain was chiselled out and separated grossly into the supra- and infratentorial portions. The cortical part of the brain was weighed, ground in the frozen state, and homogenized after the addition of 12 ml of ice cold 1.0 N perchloric acid. The tissue homogenate, maintained at 0° to 4°C, was centrifuged and neutralized with 3 N potassium hydroxide at a pH of between 4.5 and 5.0. The supernatants were added to 0.5 M triethanolamine buffer, pH 7.6, for ATP. Substrates were determined by the enzymatic methods as follows: lactate and pyruvate by the lactate dehydrogenase reaction, and ATP by phosphoglycerate kinase, glyceraldehyde-3-phosphate dehydrogenase, triose phosphate isomerase and glycerol-1-phosphate dehydrogenase reaction.

From the Second Department of Internal Medicine, The Faculty of Medicine, Kyushu University, Fukuoka, Japan.
In control animals, cerebral metabolites and acid-base parameters were measured in a similar manner after 1 hour controlled respiration without induced hypotension.

**Results**

MAP in SHR was lowered from 176 ± 19 (SD) mm Hg to 93–32 mm Hg, and in NTR from 134 ± 13 mm Hg to 84–25 mm Hg. In the former group, however, it was difficult to maintain MAP below 30 mm Hg for 1 hour without death of the animals.

Arterial acid-base parameters in the control group and at the end of 1 hour of hypotension are summarized in Table 1. Either arterial pH or PCO₂ decreased during the hypotensive period despite an effort to keep the respiration constant by artificial ventilation, whereas PaO₂ was adequately maintained. Such a tendency was more marked either in the animals with severe hypotension than in those with mild hypotension or in SHR than NTR.

The figure shows the relationship between MAP and cortical metabolites in SHR and NTR. In SHR, there were no remarkable changes in lactate, lactate/pyruvate (L/P) ratio and ATP until MAP fell to about 50 mm Hg. Below this level, however, both lactate and the L/P ratio increased progressively with a concomitant decrease in ATP. The statistical differences between 2 MAP levels, above and below 50 mm Hg of MAP, were significant for lactate \((p < 0.005)\), the L/P ratio \((p < 0.05)\) and ATP \((p < 0.05)\) as shown in Table 2.

In NTR, as shown in the figure, lactate, the L/P ratio and ATP did not change markedly until MAP fell to about 40 mm Hg, below which lactate and the L/P ratio increased and ATP tended to decrease. Comparing the 2 groups at severe hypotension below 50 mm Hg, SHR had a tendency to increase lactate and the L/P ratio more markedly, and to decrease ATP.

**Discussion**

In the present experiment, a large increase in ischemic metabolites of the brain was observed when MAP was lowered below about 50 mm Hg in SHR and 40 mm Hg in NTR. Such ischemic changes were more marked in SHR than in NTR. Siesjö and Zwetnow have shown that a derangement of the energy metabolism of the brain did not occur in normo-

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**Table 1** Arterial Acid–Base Parameters During Graded Hypotension in Spontaneously Hypertensive Rats (SHR) and Normotensive Rats (NTR)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>≥50 mm Hg</th>
<th>&lt;50 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SHR</strong> No. of rats</td>
<td>11</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>176 ± 19</td>
<td>67 ± 14</td>
<td>39 ± 6</td>
</tr>
<tr>
<td>pH</td>
<td>7.383 ± 0.044</td>
<td>7.172 ± 0.117**</td>
<td>7.090 ± 0.064**</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>38.4 ± 3.8</td>
<td>36.1 ± 11.1</td>
<td>25.4 ± 11.4*</td>
</tr>
<tr>
<td>PO₂ (mm Hg)</td>
<td>120.7 ± 50.3</td>
<td>105.2 ± 40.1</td>
<td>132.1 ± 29.9</td>
</tr>
<tr>
<td><strong>NTR</strong> No. of rats</td>
<td>9</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>134 ± 13</td>
<td>67 ± 12</td>
<td>36 ± 9</td>
</tr>
<tr>
<td>pH</td>
<td>7.353 ± 0.079</td>
<td>7.318 ± 0.068</td>
<td>7.186 ± 0.108*</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>38.5 ± 3.4</td>
<td>37.0 ± 5.3</td>
<td>29.9 ± 6.8*</td>
</tr>
<tr>
<td>PO₂ (mm Hg)</td>
<td>161.6 ± 61.2</td>
<td>198.6 ± 55.1</td>
<td>127.5 ± 24.3</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Statistical significance (vs control) = *p < 0.001; **p < 0.001.

**Table 2** Cortical Metabolites During Hypotension in SHR and NTR

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>≥50 mm Hg</th>
<th>&lt;50 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SHR</strong> No. of rats</td>
<td>11</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Lactate (mM/Kg)</td>
<td>2.42 ± 0.37</td>
<td>3.49 ± 1.44*</td>
<td>11.23 ± 7.89**</td>
</tr>
<tr>
<td>L/P ratio</td>
<td>18.5 ± 5.8</td>
<td>24.0 ± 8.6</td>
<td>75.7 ± 85.8**</td>
</tr>
<tr>
<td>ATP (mM/Kg)</td>
<td>2.70 ± 0.20</td>
<td>2.67 ± 0.22</td>
<td>2.32 ± 0.44**</td>
</tr>
<tr>
<td>(n = 9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NTR</strong> No. of rats</td>
<td>9</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Lactate (mM/Kg)</td>
<td>2.21 ± 0.45</td>
<td>3.50 ± 1.08*</td>
<td>6.07 ± 2.72*</td>
</tr>
<tr>
<td>L/P ratio</td>
<td>18.9 ± 8.8</td>
<td>33.1 ± 5.9*</td>
<td>33.3 ± 12.4*</td>
</tr>
<tr>
<td>ATP (mM/Kg)</td>
<td>2.60 ± 0.19</td>
<td>2.47 ± 0.19</td>
<td>2.58 ± 0.34</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Statistical significance (vs control) = a: p < 0.001, b: p < 0.01, c: p < 0.02, d: p < 0.05, e: p < 0.001, (vs hypotension ≥ 50 mm Hg) f: p < 0.05, **p < 0.001. Number in parentheses denotes number of animals.
Figure. Relationships between mean arterial pressure (MAP) and brain metabolites such as lactate, the L/P ratio and ATP in spontaneously hypertensive rats (SHR) and normotensive rats (NTR). Lactate and the L/P ratio started to increase with a concomitant decrease in ATP when MAP fell below 50 mm Hg in SHR, whereas these changes occurred, but less markedly, below 40 mm Hg of MAP in NTR. Open circles express mean values ± SEM in control animals of either SHR or NTR.

Cerebral circulation is constant despite a wide range of cerebral perfusion pressure, a phenomenon known as cerebral autoregulation. A decline of the cerebral perfusion pressure does not affect CBF when cerebrovascular resistance reduces proportionally, but CBF decreases when blood pressure falls below the lower limit of the autoregulatory range. Despite a decrease in CBF, however, cerebral oxygen consumption is maintained as long as the oxygen is extracted more completely from the blood flowing through the brain. This compensation becomes inadequate when blood pressure falls to a further extent, resulting in reduced oxygen consumption.\(^1\) From our experience,\(^2\) the critical CBF in anesthetized rats was approximately 40% of normal; below that the brain became hypoxic. This was compatible with the findings by Eklof and Siesjö.\(^3\)

The lower limit of cerebral autoregulation and the lowest tolerable blood pressure (mild, transient symptoms of brain hypofunction) in the normotensive human are stated to be 50–70 mm Hg and 35–40 mm Hg, respectively. In severely hypertensive patients, however, these limits are shifted to higher levels such as to 85–150 mm Hg and 50–85 mm Hg, respectively.\(^4\) Considering these observations together with our previous findings in rats,\(^5\) one might expect the present study to show a more severe derangement of brain metabolism when exposed to profound hypotension in SHR.

Arterial pH during severe hypotension decreased to the acidic side and PCO\(_2\) became low despite controlling the animal's respiration. This was probably due to systemic hypotension-induced lactic acidemia with compensatory hypocapnia. According to Eklof et al.,\(^6\) a significant decrease in arterial pH and PCO\(_2\) during hemorrhagic hypotension leads to no changes in cerebrospinal fluid pH and PCO\(_2\), suggesting that acidosis per se does not change tissue pH. The present results also showed no relation between cortical lactate level and arterial pH. Based on these findings, in addition to others,\(^7\) it is less likely that the increased brain lactate is simply the result of lactic acidosis, namely, movement of lactate from the circulation into the brain.

From the present results we concluded that hypertensive animals, as well as humans, are less tolerant of acutely induced profound hypotension. Our findings are not only important for treating hypertensive patients with drugs, but also for elucidating the etiology of cerebral infarction in hypertension.

Acknowledgment

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Y Nakatomi, M Fujishima, T Ishitsuka, K Tamaki and T Omae

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