The Effect of Graded Hypothermia on Hypoxic-Ischemic Brain Damage: A Neuropathologic Study in the Neonatal Rat

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SUMMARY To investigate the relationship between neuropathologic damage and cerebral metabolic alterations during hypothermia in the neonatal animal, 7 day old Sprague-Dawley rats were subjected to unilateral common carotid artery ligation and hypoxia at 37°C, 29°C, and 21°C. At 37°C, animals had extensive infarction of tectum and ipsilateral cerebral hemisphere, and marked depletion of brain ATP. At 29°C, there was no significant change in brain ATP; neuropathologic damage was limited to a few areas of necrosis in the deeper layers of cerebral cortex. No histologic injury was seen in the 21°C group of rats. Profound hypothermia may prevent cerebral edema and visible neuropathologic damage associated with hypoxic-ischemic injury by decreasing cerebral metabolic demands. Moderate hypothermia confers a partial, but incomplete degree of protection; whereas during normothermia, the full extent of hypoxic-ischemic injury is manifest.

HYPOTHERMIA significantly prolongs the survival time of young animals of many species subjected to hypoxic-ischemic injury.1-3 Nonetheless, it remains uncertain what degree of hypothermia is necessary to prevent brain damage in the surviving animals. Moreover, although the physiologic, metabolic, and neuropathologic effects of hypothermia on hypoxic-ischemic brain injury have been extensively studied in the adult experimental animal,4-8 similar observations in the neonatal experimental animal are few.9

There is also controversy regarding the protective effects of hypothermia in young humans who suffer hypoxic-ischemic injury. Neurologic deficits in children drowning in cold water may be manifest either transiently10 or permanently.11 Neuropathologic dysfunction in the form of seizures, movement disorders, and altered personality may occur in children undergoing circulatory arrest during profound hypothermia (19-21°C) for open heart surgery.12,13

Our purpose was to compare the morphologic changes in the central nervous system of the neonatal rat produced by hypoxic-ischemic injury during normothermia (37°C), moderate hypothermia (29°C), and profound hypothermia (21°C). The neuropathologic findings were correlated with levels of brain lactate, glucose, adenosine triphosphate (ATP), and phosphocreatine (PCr), and with alterations in brain water content.14,15

Methods

The Levine procedure (unilateral common carotid occlusion and hypoxia) as modified for the neonatal rat by Rice et al16 was employed. Seven day old Sprague-Dawley rats (Charles River Laboratories) of both sexes were anesthetized with halothane (1.5-3.5%) in oxygen by mask inhalation. Under microscopic guidance, the right common carotid artery was exposed and ligated with 4-0 surgical silk. The wound was sutured with 3-0 silk and the animal returned to its dam and permitted to suckle for a 3-hour recovery period. Following the recovery period, the animals were placed in airtight 500 ml jars with a continuous flow of humidified gas (8% O₂, 92% N₂) for 3.5 hours. During the hypoxic exposure, hypothermia was induced (or normothermia maintained) by immersing the jars in a water bath thermostatically regulated to maintain a temperature of 37°C, 29°C, or 21°C. The skin temperature of some of the rats was recorded with a cutaneous sensor (Yellow Springs Telethermometer). Two types of studies were carried out: (A) Metabolic and brain water determinations, and (B) Survival studies with neuropathologic examination. Separate groups of animals were used for each study. Animals studied neuropathologically were returned to their dams immediately after removal from the hypoxic chambers until time of sacrifice, five days later.

Control animals consisted of seven day old rats who were subjected neither to hypoxia-ischemia nor to hypothermia. These normoxic, non-ligated control animals were allowed to suckle ad lib from their dams until time of sacrifice. The skin temperature of these control animals was 32 ± 0.5°C.

A. Metabolic and Brain Water Determinations

The animals were decapitated immediately after removal from the hypoxic chambers. Samples of mixed arterial and venous blood (approximately 50 μl) were drawn into heparinized capillary tubes from the blood that welled from the severed vessels. The amount of base deficit was calculated from measurements of pH and pCO₂ (Blood gas analyzer, Radiometer BMS Mk II). Plasma glucose and lactate levels were determined enzymatically17 in a spectrophotometer (Beckman, Model 25) using the highest quality reagents available (Sigma).

The decapitated heads of some of the animals were...
immediately immersed in liquid nitrogen and stored at
-80°C for later determination of cerebral metabolites.
The hemispheres ipsilateral to the ligation were then
dissected from the calvaria in a cold room (-20°C),
powdered under continuous irrigation with liquid ni­
trogen, extracted into perchloric acid, and spectropho­
tometrically assayed for concentrations of glucose,
lactate, adenosine triphosphate and phosphocreatine,
using standard enzymatic analyses.\textsuperscript{17} Brain metabo­
"lites were not measured in the contralateral (left) hemi­
sphere because we noted little neuropathologic injury
in the contralateral hemisphere. Moreover, these data
have been previously reported,\textsuperscript{18} and do not provide
substantially more information.

In other animals, the brains were removed from the
calvaria for brain water determinations. The olfactory
bulb and brainstem (distal to the quadrigeminal plate)
were discarded. The cerebral hemispheres were bi­
sected and placed in separate, tared weighing vessels.
The hemispheres were then dessicated at 100°C for 48
hours and reweighed. Brain water in each hemisphere
was determined according to the formula:

\[
\text{Brain water} = \frac{\text{wet weight} - \text{dry weight}}{\text{wet weight}} \times 100
\]

B. Survival Studies and Neuropathologic Examination

Survival studies were conducted by noting the num­
ber of animals in each of the three experimental groups
who were alive at the end of the 3.5 hour period of
hypoxia. Neuropathologic examination of the surviv­
"ing animals’ brains was carried out five days after
exposure to hypoxia-ischemia. After an intraperitoneal
injection of pentobarbital (25 mg/kg), a perfusion nee­
dle was introduced into the ascending aorta by means
of a midline thoracotomy incision. The brain was then
perfused for 30 seconds with normal saline and for 20
minutes with a mixture of formalin-acetic acid-metha­
nol in a ratio of 1:1:8. The perfused brain was re­
moved, further fixed for 24 hours, and then sectioned,
embedded in paraffin and stained (hematoxylin and
eosin; cresyl violet). Stained sections (taken at the
level of the anterior commissure, the thalamus, and the
cerebellum — brainstem) were examined (without
knowledge of the animal’s experimental status) by
light microscopy by two observers (RSKY, JT). Neuronal
damage was graded according to the following
scale: normal, mild (a few cells damaged), moderate
(small groups of cells damaged), severe (gross infar­
ction).

Results

A. Metabolic Alterations and Brain Water Changes

Statistical analysis of two types were performed on a
Tektronix 4051 computer using analysis of variance.
First, metabolic changes in the ligated, hypoxic ani­
mals at 21°C, 29°C and 37°C were compared to the
normoxic, non-ligated control animals. In addition,
animals exposed to hypoxia-ischemia at 21°C and
29°C were compared to those subjected to hypoxia-
ischemia at 37°C (table 1).

There was no significant \( p < 0.05 \) difference in
base deficit between normoxic control animals and
animals exposed to hypoxia-ischemia at 21°C. In con­
trast, animals at 29°C and 37°C had significant base
deficits compared to the normoxic, control animals.
Moreover, the hypoxic-ischemic animals at 37°C had
significantly greater base deficits than did animals at
29°C or animals at 21°C.

Plasma lactate levels were significantly increased in
all three ligated, hypoxic groups compared to nor­
moxic, non-ligated controls. Plasma lactate concen­
trations were significantly higher in the 37°C animals
than in the 29°C animals or the 21°C animals. Al­

<p>| Table 1 Systemic and Cerebral Metabolic Changes in Hypoxic, Ligated Animals |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Normothermic    | Ligated hypoxic  | Ligated hypoxic  |</p>
<table>
<thead>
<tr>
<th></th>
<th>normoxic control</th>
<th>animals 21°C</th>
<th>animals 29°C</th>
<th>animals 37°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base excess (mMole/L)</td>
<td>5.2±1.4</td>
<td>-2.0±1.4**</td>
<td>-9.4±1.7†</td>
<td>-15.8±1.3‡</td>
</tr>
<tr>
<td>Plasma lactate (mMole/L)</td>
<td>1.5±0.6</td>
<td>4.9±0.5‡**</td>
<td>6.4±0.7‡**</td>
<td>11.9±0.8‡</td>
</tr>
<tr>
<td>Plasma glucose (mMole/L)</td>
<td>8.8±0.8</td>
<td>10.9±0.6***</td>
<td>8.7±1.0†**</td>
<td>4.3±0.9‡</td>
</tr>
<tr>
<td>Brain lactate (mMole/kg)</td>
<td>1.3±0.5</td>
<td>3.2±0.7***</td>
<td>4.3±0.5‡**</td>
<td>9.4±0.4‡</td>
</tr>
<tr>
<td>Brain glucose (mMole/kg)</td>
<td>1.5±0.9</td>
<td>2.7±0.1†***</td>
<td>1.0±0.1‡§</td>
<td>0.4±0.1‡</td>
</tr>
<tr>
<td>Brain ATP (mMole/kg)</td>
<td>2.1±0.1</td>
<td>2.9±0.2*</td>
<td>2.0±0.1</td>
<td>0.3±0.2‡</td>
</tr>
<tr>
<td>Brain PCr (mMole/kg)</td>
<td>2.4±0.2</td>
<td>3.7±0.3†</td>
<td>2.3±0.2</td>
<td>0.5±0.3‡</td>
</tr>
</tbody>
</table>

All values are mean ± SE; mean no. of animals per group = 8.
Significance (analysis of variance):
*Significantly different from normoxic control group \( p < 0.05 \).
†Significantly different from normoxic control group \( p < 0.01 \).
‡Significantly different from normoxic control group \( p < 0.001 \).
§Significantly different from hypoxic-ischemic 37°C group \( p < 0.05 \).
| Significantly different from hypoxic-ischemic 37°C group \( p < 0.01 \).
**Significantly different from hypoxic-ischemic 37°C group \( p < 0.001 \).
though made hypoxic and ischemic, animals at 21°C had significantly higher plasma glucose levels than did normoxic, non-ligated controls. Plasma glucose was significantly depressed in the ligated, hypoxic animals at 37°C compared to normoxic, non-ligated animals. Glucose levels in the hypoxic, ligated animals at 21°C and the animals at 29°C were significantly greater than those in the animals made hypoxic-ischemic at 37°C.

Brain glucose concentrations in the hypoxic-ischemic rats at 21°C were significantly greater than that of control, normoxic animals. Brain glucose levels in the hypoxic-ischemic animals at both 29°C and 37°C were significantly lower than those of controls. However, brain glucose concentrations in the 21°C and 29°C hypoxic-ischemic animals were significantly greater than those of animals in the 37°C hypoxic-ligated group.

Brain lactate was significantly increased in all hypoxic-ischemic animals at 21°C, 29°C, and 37°C compared to normoxic, non-ligated controls. However, brain lactate was significantly higher ($p < 0.001$) in the 37°C hypoxic-ligated animals compared to those made hypoxic-ischemic at 21°C or 29°C.

Measurements of cerebral high energy phosphates revealed significant differences between the normoxic control and the hypoxic-ligated animals. Significant differences also existed between hypoxic-ligated animals at 37°C vs. those at 21°C and 29°C. ATP and PCR levels were significantly elevated in the 21°C hypoxic-ischemic animals and significantly depressed in the 37°C hypoxic-ischemic animals compared to normoxic, non-ligated controls. In addition, ATP and PCR levels were significantly lower in the 37°C hypoxic-ischemic animals compared to those at 21°C and 29°C.

A significant degree of cerebral edema (the increase in brain water content in the hemisphere ipsilateral to the ligation versus that in the hemisphere contralateral to the ligation, table 2) developed only in the animals exposed to hypoxia-ischemia at 37°C (student's $t$ test; $p < 0.001$). Animals in the 29°C group developed minimal (non-significant) increases in brain water in the ipsilateral compared to the contralateral hemisphere. There was no difference in brain water content between the right and left cerebral hemispheres in the animals in the 21°C hypoxic-ischemic group or the normoxic controls.

### Table 2 Brain Water Determinations in Hypoxic, Ligated Animals

<table>
<thead>
<tr>
<th>Temp. hemisphere</th>
<th>% Water</th>
<th>% Water</th>
<th>% Water</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-ligated (right)</td>
<td>Non-ligated (left)</td>
<td>right-left hemispheres</td>
<td>(student's $t$ test)</td>
</tr>
<tr>
<td>21°</td>
<td>88.16 ± 0.03</td>
<td>88.20 ± 0.04</td>
<td>-0.04 ± 0.02</td>
<td>NS</td>
</tr>
<tr>
<td>29°</td>
<td>88.58 ± 0.03</td>
<td>88.45 ± 0.07</td>
<td>0.13 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>37°</td>
<td>89.38 ± 0.23</td>
<td>88.25 ± 0.12</td>
<td>1.13 ± 0.32</td>
<td>$p &lt; 0.001$</td>
</tr>
</tbody>
</table>

All values are mean ± SE; each group represents 7–20 brains.

Control (normoxic, non-ligated) animals had no significant difference in brain water content between right and left hemispheres.

**B. Survival Data and Neuropathologic Changes**

When separated from their dams, the animals' skin temperature was initially 32 ± 0.5°C. One hour after placement in the water bath, skin temperature of the animals in the 37°C group was 33 ± 1°C; of the animals in the 29°C group, 29 ± 1°C; of the animals in the 21°C group, 23 ± 1°C. Hypothermia significantly (Chi square analysis) increased the survival of the ligated animals during hypoxia. There was no mortality in the groups of animals exposed to 3.5 hours of hypoxia at temperatures of either 29°C (40/40 animals survived) or 21°C (48/48 survived). In contrast, mortality was significantly increased (9/43 died; mortality = 21%) in the group of animals exposed to hypoxia at 37°C (Chi square, 16.64; one tail probability, $p < 0.0001$).

Light-microscopic examination of the brains of the animals (mean number of animals per group = 15) exposed to hypoxia-ischemia at 37°C showed that approximately one-half of them sustained moderate to severe damage in the ipsilateral cerebral cortex, white matter, hippocampus, caudate, thalamus and brainstem (Fig. 1, 2). Cerebral cortical damage occurred primarily in the territory supplied by the right middle cerebral artery. In a few cases, right pyriform cortex and paramedian cortex (supplied respectively by right posterior cerebral and by the anterior cerebral arteries) were involved. Damage ranged from large groups of necrotic cells to frank infarction. The contralateral (non-ligated) hemisphere showed no evidence of cellular damage except in rare instances when necrosis was present in the contralateral (left) paramedian cortex. The brains of animals sustaining massive cerebral hemispheric infarction frequently showed clusters of necrotic cells in the superior and inferior colliculi (Fig. 3) as well.

In contrast to the 37°C group, neuropathologic injury in the animals exposed to hypoxia-ischemia at 29°C was much less (Fig. 2, 4). Damage was usually

**Figure 1. Hypoxia-Ischemia, 37°C: There is complete infarction in the territory supplied by the right middle cerebral artery. Note sparing of the paramedian cerebral cortex and pyriform cortex (supplied respectively by anterior cerebral and posterior cerebral arteries, arrows). The ipsilateral hippocampus, corpus callosum and periventricular white matter are necrotic. H & E, × 16.**
mild and was limited to the deeper layers of cerebral cortex (layers 4–6) and occasionally, the thalamus. There was no light microscopically visible damage present in white matter, hippocampus, basal ganglia or brainstem in the 29°C group. Animals exposed to hypoxia-ischemia at 21°C (Fig. 2) showed no evidence of neuropathologic damage.

**Discussion**

This study demonstrates that the Levine procedure as adapted by Rice et al. is a reliable method for producing neuropathologic damage in a neonatal animal which is inexpensive and readily available. More importantly, the Levine procedure allows the use of a degree of hypoxia which is less likely to cause cardiac fatalities. Our mortality rate of 21% in the group of animals exposed to hypoxia-ischemia at 37°C is comparable to that reported by Rice et al. We further observed that there was no mortality in the groups of animals exposed to hypoxia-ischemia during moderate or severe hypothermia.

The severity and distribution of neuropathologic damage in our 37°C hypoxic, ligated animals paralleled that reported by Rice et al. Infarction occurred primarily in the territory supplied by the middle cerebral artery including cerebral cortex, hippocampus, sub-cortical white matter, basal ganglia and thalamus. A columnar pattern of injury in the cerebral cortex was not noted. Although brainstem lesions were not observed by Rice et al., we noted that many of the severely injured animals in the 37°C group sustained injury to the tectum of the midbrain. Similar lesions in the quadrigeminal plate were also noted by Levine in his original description of the method. Since the midbrain is nourished by the intact posterior circulation, collicular damage possibly results from the effects of hypoxia.

**Figure 2.** Distribution and Severity of Neuropathologic Lesions in Animals Exposed to Hypoxia-Ischemia at 21°C, 29°C, and 37°C.

**Figure 3.** Hypoxia-Ischemia, 37°C: There are scattered groups of necrotic neurons in both the superior and the inferior colliculi (arrows). H & E, × 90.

**Figure 4.** Hypoxia-Ischemia, 29°C: Scattered clusters of necrotic neurons are present in the deeper layers of the cerebral cortex (arrowheads). The hippocampus and adjacent white matter are unaffected. H & E, × 90.
Asphyxiated fetal rhesus monkeys show prominent lesions in the inferior colliculus. DeCourten et al has recently demonstrated in the rat that hypoxia (with attendant hypotension) produces lesions in the inferior colliculus. Necrosis of brainstem nuclei is often seen in asphyxiated human infants in association with widespread cerebral injury and resembles the lesions seen in experimental animals. Brain ATP and PCr levels were the most depressed and brain lactate the most elevated in the animals made hypoxic-ischemic at 37°C. Animals in the 29°C group showed a unique pattern of neuropathologic injury, viz. deeper layers of cerebral cortex and the thalamus. Metabolic correlations showed that neither ATP nor PCr declined significantly in this group of animals (compared to normoxic, non-ligated controls). Thus, the demand for high energy phosphates was probably reduced by the moderate degree of hypothermia. Finally, brain water was not significantly increased in the ipsilateral hemisphere in the 29°C hypoxia-ischemia group.

Because animals made hypoxic-ischemic at 21°C had no visible brain injury, plasma and brain metabolic findings are also of interest. In this group of animals, plasma and brain glucose were elevated above that of normoxic, non-ligated control animals. Blood glucose rises due to hemocconcentration, decreased insulin release and decreased glucose consumption. Brain glucose concentrations increase as a result of hyperglycemia and decreased cerebral utilization of glucose. Brain ATP and PCr were significantly elevated in the 21°C group of animals compared to normoxic, non-ligated controls. The same phenomenon was noted in Levine-operated adult rats by Keykhah et al and can be partially attributed to the method of the bulk brain freezing. Since a finite amount of time is necessary to arrest cerebral metabolism during either funnel freezing or decapitation and immersion freezing, the autolytic degeneration of metabolites occurs more rapidly in the normoxic, non-ligated controls than it does in the hypothermic animals. Thus, a more appropriate reference group for future metabolic investigations would be normoxic, hypothermic animals.

Brain lactate was elevated in the 21°C group of rats compared to normoxic, non-ligated controls. The same phenomenon was noted in Levine-operated adult rats by Keykhah et al and can be partially attributed to the method of the bulk brain freezing. Since a finite amount of time is necessary to arrest cerebral metabolism during either funnel freezing or decapitation and immersion freezing, the autolytic degeneration of metabolites occurs more rapidly in the normoxic, non-ligated controls than it does in the hypothermic animals. Thus, a more appropriate reference group for future metabolic investigations would be normoxic, hypothermic animals.

Brain lactate was elevated in the 21°C group of rats compared to normoxic, non-ligated controls. However, since lactate readily enters the neonatal brain, the increase in brain lactate may reflect systemic (body) hypoxia as well as cerebral hypoxia.

This study demonstrates that moderate hypothermia is effective in significantly increasing survival during conditions of hypoxia-ischemia. Nonetheless, moderate hypothermia provides only partial protection from neuropathologic damage and alters the pattern of "vulnerable areas". Profound hypothermia ameliorates the systemic and cerebral metabolic derangements and prevents the neuropathologic changes caused by hypoxic-ischemic injury in the neonatal rat. It would be inaccurate to equate the absence of visible cell damage with lack of brain injury. Subtle disturbances in neuronal growth or dendritic branching may occur which elude detection with light microscopy. Further studies of DNA content, dendritic branching, and brain metabolism are necessary to resolve these questions.

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References
Cerebrovascular Diseases and Their Underlying Vascular Lesions in Hisayama, Japan — A Pathological Study of Autopsy Cases

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SUMMARY Frequency of cerebrovascular diseases (CVD) and their underlying vascular lesions were analyzed in 724 autopsy cases, aged 40 years and over, in the community of Hisayama, Japan during the period 1961 to 1981. Cerebral infarction (CI) was more frequently found at autopsy than cerebral hemorrhage (CH) with a ratio of infarction and hemorrhage of 4.4. Small CI occupied 75.7% of the cases with CI. The cases with any type of CVD showed more severe atherosclerosis of the major cerebral arteries than did those without CI or CH. Cerebral atherosclerosis of those with large and medium CI was the greatest, and with decreasing severity in those with small CI and with CH sequentially. Fibrinoid necrosis of the intracerebral small arteries was frequently found in cases with hypertension and particularly associated with CH.

The decline in frequency of CH was confirmed; however, changes in frequency of CI were not evident. Fibrinoid necrosis was also reduced, although the severity of cerebral atherosclerosis showed no definite change. The decline of CH seemed to be ascribed to the reduction of fibrinoid necrosis of the intracerebral small arteries.

CEREBROVASCULAR DISEASES are the leading causes of death in many countries.1 However, a declining trend in death rates from cerebrovascular diseases and changing pattern of types of cerebrovascular diseases in various countries have been reported.2-8 Most reports describe a particularly large decline in cerebral hemorrhage.5 6 These reports, however, show no data concerning the changing of underlying vascular lesions responsible for the changing pattern of the types of cerebrovascular diseases. We also reported a declining trend in incidence both of cerebral hemorrhage and cerebral infarction. Mortality from cerebral hemorrhage showed a decline but mortality from cerebral infarction increased during the period from 1961 to 1976 in the community of Hisayama, Japan, where an autopsy-based population survey has been conducted since 1961. 8 This provides us a unique opportunity to study whether the declining trend of cerebrovascular diseases in recent years can be explained by the changing pattern of the underlying vascular lesions. In this study, we investigate the correlation between various types of cerebrovascular diseases and their underlying vascular lesions in the autopsy cases within the same community during the period of 20 years.

Materials and Methods

Autopsied cases of 724 Japanese people (397 males and 327 females), about 80% of the deceased persons in the town of Hisayama during the period from November 1961 to October 1981, were subjected to this study. The age and sex distribution of the cases is shown in table 1.

A prospective community study on cerebrovascular diseases was started in November 1961 in the town of Hisayama, a farming community adjoining Fukuoka City in Kyushu Island, Japan. According to the 1960 census, the number of residents aged 40 years and over was 1851 or 27.6% of the population, identical to the average of Japan (28%). Details of the method of the epidemiological study in this community have been published elsewhere.9 The characteristic of this community study is that the causes of death were verified by autopsy at a high rate (80%).

Atherosclerotic brain infarction (cerebral infarction, CI) was classified into three groups according to the size of the infarcted area. Large cerebral infarction (large CI) was defined as that considered to be caused by the occlusion of the major cerebral arteries at the base of the brain. Small cerebral infarction (small CI) was infarction less than one centimeter in diameter.
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