SUMMARY In a previous study occlusion of a middle cerebral artery (MCA) followed by 48 h of hypothermia (29°C) was lethal in 5 of 5 monkeys as compared to only 3 of 9 normothermic animals. The present study extended these observations in monkeys and cats with or without MCA occlusion. In monkeys MCA occlusion plus 48 h of hypothermia was consistently lethal. Without MCA occlusion 2 of 3 monkeys survived, but were comatose the first 12 h post-hypothermia. In normothermic cats, MCA occlusion was lethal in only one of 5 animals whereas hypothermia was lethal in 20 of 21 cats with or without MCA occlusion. The detrimental effects of hypothermia were not favorably influenced either by hemodilution or by deliberate alterations in Paco₂. The effect of 48 h of hypothermia and rewarming on cerebral blood flow (CBF) and cerebral metabolites was evaluated in 6 normal monkeys. CBF was reduced 60 to 70 percent at 29°C and returned to only a maximum of 50 percent of control with re-warming. Prior to re-warming distribution of CBF was inhomogeneous. Cerebral metabolites were borderline normal prior to re-warming but energy stores decreased while lactate increased with re-warming.

MANY MEASURES have been proposed as potentially efficacious in the treatment of acute regional cerebral ischemia; few of these have been found to favorably influence the outcome for patients suffering from acute stroke.¹ The cerebral protective effect of hypothermia is well established, particularly as a technique for prolonging the brain's tolerance to periods of complete cerebral ischemia.²⁻⁴ Rosomoff⁵ also reported a beneficial effect of hypothermia in an acute canine stroke model produced by occlusion of a middle cerebral artery (MCA). A study from this laboratory⁶ did not confirm these findings in monkeys with MCA occlusion subjected to 48 h of hypothermia; a detrimental effect was observed instead. It was speculated that hypothermia might ultimately diminish oxygen delivery to the region of ischemia by an effect on blood viscosity with a resulting decrease in collateral flow. Decreased oxygen delivery could also result from a temperature effect on oxygen-hemoglobin dissociation resulting in decreased release of oxygen to the tissues. The present study was designed to examine these possibilities as well as the effect of hypothermia and rewarming on cerebral blood flow and cerebral metabolites.

Materials and Methods

Twelve Macaca Java or Macaca Phillipina (3–5 kg) and 26 cats (2.5–5 kg) of both sexes, unmedicated and
fastering, were studied. In all animals anesthetics was induced and maintained during surgery with halothane 1 percent in nitrous oxide 70 percent and oxygen. Pancuronium 0.3 mg/kg was given to produce muscle paralysis and to facilitate intubation of the trachea with a cuffed endotracheal tube; ventilation was controlled with a Harvard pump. A femoral artery and vein were exposed and cannulated for pressure measurements, blood sampling, and drug and fluid administration. A urinary catheter and esophageal thermometer were inserted and secured.

Survival Studies. Six monkeys and all cats were used for survival studies. Previously reported survival studies in 14 monkeys (Macaca Java) were included for comparison purposes and comprised groups I and II.* The 6 new monkeys were divided into 2 groups (Monkeys III and IV) and the cats were divided into 6 groups (Cats I-VI). For detailed breakdown of the groups see table 1. In 3 monkeys (III) and 23 cats (I-V), the right middle cerebral artery (MCA) was exposed via a transorbital approach using the operating microscope. A miniaturized Mayfield clip was placed across the MCA distal to the first anterior branch which supplies an anterior-inferior portion of the frontal lobe, except for 5 cats (V) where the clip was placed on the dura (sham operation). The body of the clip remained extradurally. After placement of the clip (or at an equivalent time in animals not subjected to MCA occlusion) halothane was discontinued in all monkeys and in cats, groups II-VI. In animals subjected to operation this was initiated 30 min after MCA occlusion (table 1). The temperature was controlled with ice-packs or heat lamps as needed. Ventilation was initially controlled with oxygen 40 percent, and nitrogen 60 percent (humidified) and adjusted according to blood gases. PaCO2 was kept at 35 ± 2 mm Hg (temperature corrected) in monkey group IV, and cat groups I, IV-VI. Monkey group III and cat groups II and III were ventilated to maintain a PaCO2 35 ± 2 mm Hg, uncorrected for temperature. The trachea was suctioned as needed. The extremities were wrapped and the animals were turned every 4 h.

One monkey group (III) and 2 cat groups (III, IV) were hemodiluted during cooling in order to counteract the known effects of temperature on viscosity. Assuming near Newtonian behavior and a normal hematocrit of 40, dilution to a hematocrit of 30-31 should result in near normal viscosity at 29°C.*

In humans and temperate zone animals, viscosity increases 2-3 percent/°C; thus at 29°C viscosity should be increased approximately 23 percent at all shear rates from 1 to 100 sec^-1. The relative viscosity is also constant at shear rates above 1 sec^-1, indicating that plasma is the only part of the system affected by temperature, and blood with an hematocrit of 30 or less displays near Newtonian behavior at all rates of shear. A change in hematocrit should, therefore, not affect the effect upon viscosity of a change in temperature. For Newtonian behavior, viscosity can be expressed as a function of hematocrit (hct) according to Vand by: 

\[
\eta = \text{plasma}\eta (1 + 0.025 \text{hct} + 7.3 \times 10^{-4} \text{hct}^2)
\]

---

### TABLE 1 Management of Animals in Survival Studies

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MCA Occlusion</th>
<th>Hemodilution</th>
<th>Hypothermia</th>
<th>PaCO2 (35 mm Hg)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monkeys I*</td>
<td>9</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Monkeys II*</td>
<td>5</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Uncorrected</td>
</tr>
<tr>
<td>Monkeys III</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Uncorrected</td>
</tr>
<tr>
<td>Monkeys IV</td>
<td>3</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Corrected</td>
</tr>
<tr>
<td>Cats I</td>
<td>5</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Cats II</td>
<td>5</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Uncorrected</td>
</tr>
<tr>
<td>Cats III</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Uncorrected</td>
</tr>
<tr>
<td>Cats IV</td>
<td>6</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Corrected</td>
</tr>
<tr>
<td>Cats V</td>
<td>5</td>
<td>Sham</td>
<td>No</td>
<td>Yes</td>
<td>Corrected</td>
</tr>
<tr>
<td>Cats VI</td>
<td>3</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Corrected</td>
</tr>
</tbody>
</table>

*Monkey Groups I and II were reported previously.*
†A PaCO2 of 35 mm Hg was considered to be normal for normothermic animals. In hypothermic animals ventilation was varied among groups so as to produce either temperature corrected (see table 2) or uncorrected values of PaCO2 near 35 mm Hg (see text).
Dilution was achieved by infusion of albumin and blood withdrawal as needed.

One sham operated cat was re-warmed after 24 h, one after 36 h. All other hypothermic animals were re-warmed after 48 h with heat lamps and warming blankets. Drugs and fluids were discontinued after 48 h in all animals. If spontaneous ventilation was judged adequate, the endotracheal tube and all catheters were removed, monitoring was discontinued, and the animals were returned to their cages for observation for 5 days. If spontaneous ventilation remained inadequate (despite reversal of muscle relaxants), the animals were allowed to die.

**CBF and Cerebral Metabolite Studies.** These were done in 6 monkeys. Cerebral blood flow was measured with a modified Kety-Schmidt technique. A catheter was inserted retrograde into the common carotid artery via the sublingual artery for injection of $^{133}$Xe; the external carotid artery was tied off immediately distal to the catheter. The soft tissue around the ipsilateral orbit was incised to avoid extracerebral contamination with $^{133}$Xe via possible anastomoses between the ophthalmic artery and extracerebral vessels. For measurement of CBF 0.5 mc; $^{133}$Xe in 0.2 ml saline was injected, and CBF calculated from the initial one minute slope of the washout curve using a tissue/blood partition coefficient of 0.87. After completion of surgery, halothane was discontinued and diazepam 0.1 mg/kg was given. Control measurements of CBF were taken 30 min later. Hypothermia, 29°C, was then induced by surface cooling. Thereafter the monkeys were maintained for 48 h using the same protocol as in the survival studies. No blood chemical analyses were performed in order to minimize blood loss. CBF was measured every 4 h.

In 3 monkeys a craniotomy was done at the end of the 48 h period. The dura overlying the parietal cortex was excised and biopsies of the parietal cortex were taken using a technique that deposits a sample of brain (200-400 mg) into liquid nitrogen within one sec. The tissue was stored at −76°C and prepared for analysis in a refrigerated box (−25°C) as described by Folbergrova et al. Tissue extracts were analyzed with enzymatic fluorometric methods for phosphocreatine (PCr), ATP, ADP, AMP, and glucose, lactate and pyruvate. The sum of the adenine nucleotides was calculated as $\Sigma Ad = [ATP] + [ADP] + [AMP]$. The energy state of the tissues was expressed as the energy charge potential of the adenine nucleotide pool according to Atkinson: ECP = $[ATP]/([ATP] + 0.5 [ADP])/\Sigma Ad$.

In these same 3 monkeys the distribution of CBF was assessed at the conclusion of the experiment by autoradiography using $^{14}$C-antipyrine. Seventy-five $\mu$Ci/kg of the isotope was infused at a constant rate over the last minute prior to the taking of brain biopsies; immediately following biopsy the monkeys were killed with KCl intravenously. The whole brain was rapidly removed and frozen in acetone-dry ice. Twenty micron sections were cut coronally every 8 mm in a cryostate at −15°C. The sections were immediately dried on a hot plate at 60°C. Immediately adjacent sections were prepared for histology (H & E stain) or autoradiographs. The latter were placed in contact with a high resolution, single emulsion x-ray film, and following a 14-day exposure, the films were developed.

In the 3 other monkeys re-warming was instituted as in the survival studies. CBF and the other variables were recorded with every 2 degrees increase in temperature. At 37°C brain biopsies were taken and analyzed as described above.

All blood gases are reported corrected for temperature. All values are presented as mean ± SEM. Student's t-test for paired data was used for statistical comparison of data obtained from the same animals. Student's t-test for unpaired data was used for comparison of different groups of animals, p < 0.05 was regarded as significant. No statistical comparisons were done between animal groups with n < 5.

**Results**

**Survival Studies.** Six of 9 normothermic monkeys with MCA occlusion (Group 1) survived 7 days while all 8 hypothermic monkeys with MCA occlusion (Groups II, III) died (with or without hemodilution) (table 2). One of the 3 hypothermic monkeys without MCA occlusion (Group IV) died, while the remaining 2 survived without any apparent deficit, although both remained comatose for the first 12 hours post-hypothermia. All deaths in the hypothermic monkeys occurred during or shortly after re-warming.

Four of 5 normothermic cats with MCA occlusion (Group 1) survived 7 days, while 20 of 21 hypothermic cats (Groups II–VI) died (table 2). MCA occlusion, hemodilution, or level of PaCO$_2$ had no effect on survival. Three cats required inotrope support at some point during hypothermia. Two cats (Group III) died at 32 and 33 hours of hypothermia. One cat died 2 days post-hypothermia, all other non-survivors died during or shortly after re-warming.

There were no significant changes from controls in plasma lactate, pyruvate, L/P ratio, potassium, osmolality or corticosteroid levels when measured after 48 h (not tabulated). There was a decrease in plasma sodium in all groups, from 154 ± 1 to 140 ± 2 meqv/l (mean ± SEM for all groups combined). Mean 48 h values for other variables are presented in table 2. Differences between groups are largely accounted for by the expected effects of the various physiologic interventions used (hypothermia, hemodilution, and/or controlled ventilation). A mild metabolic acidosis was evident in many of the animals at the end of the 48 h. CBF and Metabolite Studies.

As in the survival studies, hypothermia in this group resulted in a modest reduction in blood pressure and a significant decrease in heart rate (table 3). With re-warming, heart rate returned toward control while blood pressure remained below control. PaO$_2$ and PaCO$_2$ remained steady throughout the study, but a metabolic acidosis developed with significant decreases in pH and buffer base (BB⁺).

With cooling, mean CBF decreased immediately to 40 percent of control (fig. 1), and after 16 hours to ap-
proximately 30 percent of control. Thereafter CBF remained relatively stable. With re-warming, CBF initially increased to about 50 percent of control (at 33°C) but with continued re-warming to 37°C, CBF again decreased to 30 percent of control.

In the monkeys not re-warmed, autoradiographic studies showed non-homogeneous distribution of CBF in 2 of 3 animals after 48 h of hypothermia (fig. 2). In 4 of the combined 10 coronal sections taken from these 2 monkeys there were areas of cerebral cortex with very poor perfusion adjacent to well perfused areas. In the third monkey, CBF distribution was normal in all 5 sections. Histologic study of these sections showed no apparent abnormalities in any of the monkeys. There were no histologic differences between adjacent regions of well perfused and poorly perfused cortex (fig. 3).

The metabolic measurements (table 4) were consistent with the CBF and histologic findings. Prior to re-warming the cerebral energy state was near normal (primarily as reflected by the ECP) although a degree of lactate accumulation is evident. After re-warming the cerebral metabolic state was clearly abnormal with loss of energy stores and further accumulation of lactate.

**Discussion**

It is readily apparent from these results that a prolonged period (48 h) of moderate hypothermia (29°C) has severe deleterious effects in both monkeys and cats. In monkeys, these effects were exaggerated by, but not dependent upon, the prior creation of a regional cerebral ischemic lesion (by MCA occlusion). In cats, prolonged hypothermia was almost uniformly lethal (upon re-warming) whether or not a regional ischemic lesion had been created. This confirms the results of a previous study in which 48 h of hypothermia was found to aggravate rather than ameliorate the effects of regional cerebral ischemia in monkeys. Combining the results of that study with the present

### TABLE 2

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>7 day survival</th>
<th>MAPB (mm Hg)</th>
<th>CVP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>Temp (°C)</th>
<th>Het (%)</th>
<th>PaO₂* (mm Hg)</th>
<th>PaCO₂* (mm Hg)</th>
<th>pH</th>
<th>BB+ (meq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monkeys I</td>
<td>5</td>
<td>6</td>
<td>98</td>
<td>2</td>
<td>196</td>
<td>37.1</td>
<td>±4</td>
<td>160</td>
<td>35</td>
<td>7.55</td>
<td>±3</td>
</tr>
<tr>
<td>Monkeys II</td>
<td>5</td>
<td>0</td>
<td>91</td>
<td>2</td>
<td>128</td>
<td>29.4</td>
<td>±3</td>
<td>116</td>
<td>24</td>
<td>7.55</td>
<td>±1</td>
</tr>
<tr>
<td>Monkeys III</td>
<td>5</td>
<td>0</td>
<td>94</td>
<td>2</td>
<td>126</td>
<td>28.9</td>
<td>±4</td>
<td>182</td>
<td>24</td>
<td>7.52</td>
<td>±1</td>
</tr>
<tr>
<td>Monkeys IV</td>
<td>5</td>
<td>2</td>
<td>115</td>
<td>3</td>
<td>113</td>
<td>29.2</td>
<td>±6</td>
<td>218</td>
<td>37</td>
<td>7.37</td>
<td>±2</td>
</tr>
<tr>
<td>Cats I</td>
<td>5</td>
<td>4</td>
<td>114</td>
<td>4</td>
<td>196</td>
<td>37.0</td>
<td>±9</td>
<td>145</td>
<td>35</td>
<td>7.39</td>
<td>±1</td>
</tr>
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<td>5</td>
<td>0</td>
<td>111</td>
<td>3</td>
<td>120</td>
<td>29.2</td>
<td>±8</td>
<td>170</td>
<td>24</td>
<td>7.48</td>
<td>±0</td>
</tr>
<tr>
<td>Cats III</td>
<td>5</td>
<td>0</td>
<td>60</td>
<td>2</td>
<td>121</td>
<td>29.0</td>
<td>±11</td>
<td>145</td>
<td>23</td>
<td>7.47</td>
<td>±1</td>
</tr>
<tr>
<td>Cats IV</td>
<td>5</td>
<td>0</td>
<td>106</td>
<td>4</td>
<td>114</td>
<td>29.3</td>
<td>±4</td>
<td>181</td>
<td>36</td>
<td>7.30</td>
<td>±1</td>
</tr>
<tr>
<td>Cats V</td>
<td>5</td>
<td>0</td>
<td>93</td>
<td>5</td>
<td>117</td>
<td>28.1</td>
<td>±7</td>
<td>195</td>
<td>35</td>
<td>7.24</td>
<td>±2</td>
</tr>
<tr>
<td>Cats VI</td>
<td>3</td>
<td>0</td>
<td>122</td>
<td>3</td>
<td>120</td>
<td>28.1</td>
<td>±15</td>
<td>201</td>
<td>36</td>
<td>7.28</td>
<td>±1</td>
</tr>
</tbody>
</table>

*Estimated from hemoglobin concentration.

---

**TABLE 3**

<table>
<thead>
<tr>
<th>Time</th>
<th>n</th>
<th>MAPB (mm Hg)</th>
<th>HR (beats/min)</th>
<th>Het (%)</th>
<th>PaO₂* (mm Hg)</th>
<th>PaCO₂* (mm Hg)</th>
<th>pH</th>
<th>BB+ (meq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 37°C</td>
<td>6</td>
<td>101</td>
<td>199</td>
<td>40</td>
<td>185</td>
<td>38</td>
<td>7.46</td>
<td>49</td>
</tr>
<tr>
<td>24 hr 29°C</td>
<td>6</td>
<td>98</td>
<td>118</td>
<td>48</td>
<td>163</td>
<td>38</td>
<td>7.33</td>
<td>40</td>
</tr>
<tr>
<td>48 hr 29°C</td>
<td>6</td>
<td>71</td>
<td>98</td>
<td>42</td>
<td>159</td>
<td>39</td>
<td>7.30</td>
<td>40</td>
</tr>
<tr>
<td>Rewarmed 37°C</td>
<td>3</td>
<td>74</td>
<td>167</td>
<td>~35*</td>
<td>150</td>
<td>40</td>
<td>7.28</td>
<td>39</td>
</tr>
</tbody>
</table>

*Estimated from hemoglobin concentration.
CBF Before, During And After 48 Hours Of Hypothermia

FIGURE 1. CBF before and during 48 h of hypothermia, 29°C, in 6 monkeys, and during subsequent re-warming in 3 of them. The values at 48 h were the same in monkeys re-warmed (3 animals) and not re-warmed. The data are therefore presented as one continuous graph.

The results reveals that MCA occlusion was lethal (at 48 h) in 8 of 8 hypothermic monkeys as compared to only 3 of 9 normothermic monkeys.

These results would seem to conflict with the many favorable reports, both experimental and clinical, describing the beneficial effects of hypothermia. To our knowledge, all of these reports have been concerned with short term application of hypothermia only (up to a few hours). Results following hypothermia of longer duration have been equivocal or even negative. Rosomoff reported that one hour of hypothermia (24°C) in dogs reduced the neurologic deficit resulting from MCA occlusion while others have consistently found that hypothermia acutely increases the tolerance of the brain to periods of complete global ischemia. The presumed basis for such protection is the known direct effect of temperature on metabolic rates. Thus, in complete ischemia, a temperature induced reduction in metabolism should prolong brain viability by reducing the rates of energy utilization and lactate production. In incomplete ischemia, as produced by MCA occlusion, a reduction in brain O₂ requirements should increase the brain's tolerance for a reduction in O₂ delivery. That Rosomoff was able to demonstrate protection in an acute model of MCA occlusion, whereas we observed an opposite effect in a chronic model, suggests that the duration of hypothermia per se may be a critical factor. In addition to an effect of time, we considered and tested for the possible deleterious effects of reduced temperature on blood viscosity, acid-base balance, and oxygen-hemoglobin dissociation.

In both monkeys and cats, hemodilution of a degree calculated to result in normal viscosity at 29°C did not alter the lethality of MCA occlusion followed by 48 h of hypothermia. Possibly any beneficial effect of hemodilution was countered by the detrimental effect of reduced O₂ carrying capacity. In normal dogs Koster et al. reported that the increase in CBF resulting from hemodilution during hypothermia was balanced by the reduced O₂ carrying capacity such that O₂ delivery was unaltered. Whether this would also be true in regional ischemia as produced by MCA occlusion is not known.

FIGURE 2. Coronal sections of monkey brain showing autoradiographs (top) and adjacent sections stained with H & E (bottom). Arrow indicates a gyrus of cortical gray which is grossly underperfused compared to remainder of cortex.
DETRIMENTAL EFFECT OF HYPOTHERMIA/Steen et al.

At temperatures other than 37°C, the optimum level of ventilation, and hence \( P_{\text{aco}} \) and \( \text{pH} \), for nonhibernating homeotherms is unknown. It has been established that poikilotherms do not adjust ventilation with a decrease in temperature and thus \( P_{\text{aco}} \) remains constant (uncorrected for temperature). If this is appropriate for homeotherms (with a normal \( P_{\text{aco}} \) of 35 mm Hg) then at 29°C the appropriate corrected \( P_{\text{aco}} \) would be 24 mm Hg. Such a relative respiratory alkalosis would further shift the oxygen-hemoglobin dissociation curve to the left (hypothermia per se results in a leftward shift of the curve) and might aggravate tissue hypoxia by limiting off-loading of oxygen. On the other hand, hibernating animals tend to maintain a constant \( \text{pH} \) with reduction in body temperature. If this is appropriate for homeotherms then corrected \( P_{\text{aco}} \) at 29°C should remain close to 35 mm Hg (equivalent to a \( P_{\text{aco}} \) of about 50 mm Hg uncorrected) and the leftward shift of oxygen hemoglobin dissociation would be reduced. An additional important variable altered by \( \text{CO}_2 \) is the cerebral blood flow. In normal hypothermic rats, CBF remains responsive to \( \text{CO}_2 \). Hägerdal et al. reported that CBF was reduced to 15 percent of control at a \( P_{\text{aco}} \) of 15 mm Hg (corrected) and a temperature of 22°C. They observed no adverse metabolic effects resulting from this low CBF state. Again the possible effects on CBF in areas of regional ischemia is unknown. We speculated that maintenance of a constant uncorrected \( P_{\text{aco}} \) (as in poikilotherms) might, by the combined effect on oxygen-hemoglobin dissociation and CBF, aggravate regional ischemia, thus accounting for the untoward effects of hypothermia. However, survival in animals maintained at a corrected \( P_{\text{aco}} \) of 35 mm Hg was not improved. In these latter animals, we did not completely normalize the effect of temperature on oxygen-hemoglobin dissociation. This would have required deliberate production of a degree of metabolic acidosis or a further reduction in ventilation. Still, in most of the animals maintained at a corrected \( P_{\text{aco}} \) of 35 mm Hg, a modest metabolic acidosis did develop with time. Thus, any leftward shift in oxygen-hemoglobin dissociation would be further reduced.

A nearly uniform observation in both the monkey and cat survival studies was the apparent unmasking of a deleterious effect of hypothermia only upon re-warming. Prior to re-warming, most animals appeared stable as judged by vital signs, electrolyte balance, acid-base status, and blood gases. This has been previously reported. Blair et al. described acute circulatory collapse during re-warming in spontaneously ventilating hypothermic dogs. Popovic reported that rats would survive maximally 5.5 hours of hypothermia (15°C) if re-warmed, but for 9 hours if not re-warmed. He suggested that hypothermia was protecting against its own potentially injurious effects and that re-warming unmasks these effects.

In order to determine whether injurious effects existed prior to re-warming as well as during and following re-warming, we carried out additional studies to determine the effect of both hypothermia and re-warming on CBF and cerebral metabolites. With the onset of hypothermia, the reduction in CBF was

<table>
<thead>
<tr>
<th>Temp</th>
<th>n</th>
<th>( P_{\text{aco}} ) (( \mu \text{mol/g} ))</th>
<th>ATP (( \mu \text{mol/g} ))</th>
<th>ADP (( \mu \text{mol/g} ))</th>
<th>AMP (( \mu \text{mol/g} ))</th>
<th>ECP (( \mu \text{mol/g} ))</th>
<th>Glucose (( \mu \text{mol/g} ))</th>
<th>Lactate (( \mu \text{mol/g} ))</th>
<th>L/P ratio (#)</th>
</tr>
</thead>
<tbody>
<tr>
<td>29°C</td>
<td>3</td>
<td>2.76 ± 0.04</td>
<td>1.87 ± 0.03</td>
<td>0.31 ± 0.01</td>
<td>0.039 ± 0.004</td>
<td>0.914 ± 0.005</td>
<td>9.24 ± 0.60</td>
<td>2.70 ± 0.27</td>
<td>44</td>
</tr>
<tr>
<td>37°C</td>
<td>3</td>
<td>2.28 ± 0.20</td>
<td>1.73 ± 0.11</td>
<td>0.40 ± 0.02</td>
<td>0.067 ± 0.004</td>
<td>0.878 ± 0.007</td>
<td>9.05 ± 0.06</td>
<td>5.46 ± 0.69</td>
<td>69</td>
</tr>
</tbody>
</table>

*Normal primate (Saimiri sciureus) values, this laboratory: ATP = 2.00 ± 0.07; Lactate = 2.14 ± 0.16; L/P = 9.0 ± 1.8.*

*Normal canine values, this laboratory: \( P_{\text{aco}} = 3.04 ± 0.17; \) ATP = 2.14 ± 0.10; ADP = 0.30 ± 0.01; AMP = 0.06 ± 0.01; ECP = 0.92 ± 0.01; Glucose = 2.21 ± 0.18; Lactate = 1.04 ± 0.14; L/P = 17 ± 1.*

Table 4. Cerebral Metabolites after 48 h of Hypothermia and after Re-warming.
nearly appropriate for the expected reduction in metabolic rate (approximately 50 percent). By 16 h, CBF stabilized at a moderately reduced level (30 percent of control) but, assuming homogeneous distribution, adequate for metabolic needs. With re-warming, CBF initially increased but could not be maintained at temperatures greater than 35°C. From the autoradiographic studies done prior to re-warming, it is evident that distribution of CBF was not homogeneous in at least 2 of 3 animals. Inhomogeneity of flow during hypothermia has been found in other vascular beds such as the mesentery of rats and dogs. The brain metabolites prior to re-warming were consistent with a marginally abnormal cerebral status. Following re-warming, these abnormalities were clearly magnified presumably as a reflection of an inadequate CBF, both regionally and globally.

These findings are consistent with and perhaps sufficient to explain the deleterious effects of hypothermia encountered in the survival studies. Although the underlying mechanism remains undefined, it is probable that such effects are a function of both time and temperature. Whether there is a "critical" time for a given temperature is unknown. Possibly the technique of re-warming may also be critical. Our animals were progressively re-warmed over a 2–3 h period. Perhaps if re-warming was instead "staged" with deliberate pauses at 2–3°C increments, the deleterious effects might be minimized. It is apparent, too, that species differences exist. Cats are extremely sensitive such that even in the absence of regional cerebral ischemia, hypothermia was lethal upon re-warming. Normal monkeys were less sensitive, but the detrimental effects of hypothermia were easily demonstrated in monkeys with regional cerebral ischemia. In man, with normal cerebral function, prolonged periods of hypothermia (28–30°C) are generally assumed to be well tolerated. However, it is interesting to note that in Fay's pioneer human studies done in 1940 of prolonged hypothermia for treatment of metastatic carcinoma, the mortality rate in 169 "treatments" (administered to 124 patients) was 11.2 percent. Of these, only 2 patients died while hypothermic, 4 died during re-warming and 13 died within 24 h of re-warming. We are unaware of any published reports concerning the effects of hypothermia in patients suffering from acute stroke. In one unreported series, 12 acute stroke patients were cooled to 28–30°C for 4–7 days; following re-warming 10 of these died. The once common use of prolonged hypothermia as a therapeutic tool in head injured and post-cardiac arrest patients has been largely abandoned. A review of the literature does not provide a satisfactory explanation for this change in practice. It is reasonable to conclude that morbidity and mortality were not improved by hypothermia. The present study supports such a conclusion and suggests, in addition, a possible detrimental effect.

References

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Prognosis in Patients With Infarction and TIA in Carotid Territory During and After Anticoagulant Therapy

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SUMMARY One hundred seventeen patients, 31 with TIA and 86 with cerebral infarction, had angiographically verified atherosclerosis within the relevant carotid artery territory and normal CSF. They were treated with anticoagulants for a mean of 11.1 months. No TIA but 1 cerebral infarction, appearing during inadequate anticoagulant therapy, was registered. Seventy-six of the patients, 20 with TIA and 56 with infarction, were followed for a mean of 4.4 months after cessation of anticoagulants or during inadequate anticoagulant treatment. Ten patients, 1 with initial TIA and 9 with initial infarction, developed cerebral infarction necessitating re-institution of anticoagulant therapy.

Long-term, anticoagulant treatment can be recommended in carefully selected patients with TIA, and also with infarction in the carotid territory.

EVIDENCE has been reported that patients with transient ischemic attacks (TIA) in the carotid territory benefit from treatment with anticoagulant drugs.1, 2 Patients with cerebral infarction are commonly not treated in the same way because of the risk of cerebral hemorrhage. Studies have shown that, in unselected cases, the risks of anticoagulant therapy can exceed the benefits.4

A careful selection of patients with cerebral infarction seems warranted in order to study the effect of anticoagulant treatment in this patient category. This study describes the outcome in a selected group of patients with cerebral infarction or TIA in the part of the brain supplied by the carotid artery. All patients were investigated by cerebral angiography and were followed during and after anticoagulant therapy.

Materials and Methods

Patients

One hundred sixty-two consecutive patients, 47 females and 115 males, 36 patients with TIA, and 126 with cerebral infarction were included. The age distribution is given in table 1. In patients with cerebral infarction, neurological signs and symptoms had persisted for more than 24 h, and the neurological examination usually revealed persistent, though often only slightly disabling, symptoms. TIA was defined as an attack with symptoms and signs of neurological dysfunction of less than 24 h duration. The patients were admitted to the neurology department during a 2 year period (Oct. 1, 1973 to Sept. 30, 1975). Only those patients who were included who were considered candidates for carotid endarterectomy and/or anticoagulant treatment, i.e. the biological age was acceptably low, the patients were considered able to manage treatment with anticoagulants, and they were not living too far from facilities for control of treatment. Patients with disorders which contraindicated anticoagulant therapy were excluded. High blood pressure was not considered a contraindication, but was always lowered to a value below 160/100 mm Hg before anticoagulant therapy was started. Electrocardiograms and determinations of serum transaminases were performed in all 162 patients on day 1 and 3 after admission. Patients with a probable source of embolism other than the carotid artery or its branches were excluded. These included patients with recent myocardial infarction or atrial fibrillation. CSF studies and cerebral angiography was carried out in all patients.

CSF Investigations

In all patients lumbar puncture was performed on
Deterimental effect of prolonged hypothermia in cats and monkeys with and without regional cerebral ischemia.

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