Changes in cerebral blood flow and oxygen metabolism during moderate hypothermia in patients with severe middle cerebral artery infarction

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Object. Moderate hypothermia has been reported to be effective in the treatment of postischemic brain edema. The effect of hypothermia on cerebral hemodynamics is a matter of controversial discussion in literature. Clinical studies have yet to be performed in patients with ischemic stroke after induction of hypothermia.

Methods. Measurements during mild hypothermia (33–34°C) were made in six patients with severe ischemic stroke involving the middle cerebral artery territory. Hypothermia was induced as soon as possible and maintained for 48 to 72 hours. Cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO₂) were estimated by a new double-indicator dilution method. Measurements of CBF were made during normothermia, immediately after induction of hypothermia, and during hypothermia at the end of hypothermia, and after rewarming. A total of 19 measurements of CBF and jugular bulb O₂ saturation were made. Immediately after induction of hypothermia, CBF decreased in all patients. During late hypothermia, CBF improved in patients who survived but remained diminished in the two patients who died. Reduced CMRO₂ levels were observed during all phases of hypothermia in all but one case.

Conclusions. Preliminary observations indicate that moderate hypothermia seems to reduce CMRO₂. Immediately after induction of hypothermia, CBF may decrease in all patients. During late hypothermia, CBF seems to recover in patients with good outcome but remains diminished in patients who die. Serial bedside CBF measurements with the new double-indicator dilution technique may be useful to describe cerebral hemodynamic characteristics in patients with severe ischemic stroke during hypothermia.

Key Words: • hypothermia • stroke • ischemia • cerebral blood flow • cerebral metabolic rate of oxygen

Clinical Material and Methods

Patient Population

Six patients (two women and four men) ranging in age from 28 to 66 years with severe ischemic stroke in the MCA territory were studied. The protocol was part of a project (hypothermia in acute hemispheric stroke) approved by the Ethics Committee of the University of Heidelberg (AZ 217-96). Written informed consent was obtained from the next of kin or legal representatives. The inclusion criteria were as follows: clinical and computerized tomography scanning evidence of space-occupying MCA territory infarction, no previous disabling neurologic disease, and no signs of cardiac insufficiency or peripheral arterial occlusive disease. Therapy was performed according to a standardized protocol for treatment of post-ischemic brain edema in space-occupying infarction. In the procedures, the patients were sedated with a 5- to 8-μg/kg/hr fentanyl infusion and 0.1- to 0.4-mg/kg/hr
midazolam, and they received a neuromuscular block (atracurium 0.3–0.6 mg/kg/hr).

**Measurement Parameters**

The following data were prospectively recorded: ICP was monitored ipsilaterally to the affected hemisphere by using intraparenchymatous sensors and transducers (Codman microsensor; Johnson & Johnson, Raynham, MA). The mean arterial blood pressure, ICP, and cerebral perfusion pressure, as the difference between mean arterial blood pressure and ICP, were monitored continuously. With each CBF measurement blood gas level analysis and dye dilution curves were rejected if the following artifacts were identified: thermal drift in the baseline, wall artifacts by the jugular bulb catheter, or insufficient result of curve fitting because of respiratory artifacts induced by mechanical ventilation. Values of CBF less than 25 ml/100g/min were calculated from a corresponding long mean transit time of more than 240 seconds, which cannot be measured precisely for the highly diffusible indicator negative heat. The CMRO₂ was calculated from the product of CBF and AVDO₂. The series of CBF measurements were made to baseline value during normothermia, immediately before hypothermia was induced, after induction of hypothermia when the target body core temperature of 33 to 34°C was reached, at the end of hypothermia before rewarming, and after rewarming during normothermia.

**Induction of Hypothermia**

Moderate hypothermia was induced using cooling blankets (Bair Hugger; Augustine Medical, St Prairie; Minnesota) with cool ventilator air to fanning the patient’s body surface. The core body temperature was kept between 33°C and 34°C for 48 to 96 hours. After a decrease in the signs of brain edema, patients were rewarmed passively. Foley catheters with a temperature resolution of 0.1°C were used for monitoring core body temperature in the bladder (Mon-a-therm; Mallinckrodt, Hennet/Sieg, Germany). The room temperature in the intensive care unit was maintained between 18°C and 20°C.

**RESULTS**

Moderate hypothermia was induced in six patients during a mean period of 63.5 hours (range 49–86 hours). Table 1 gives the intervals in hours between onset of symptoms and the series of CBF measurements. In six patients, 19 CBF measurements and jugular bulb O₂ saturation values were obtained (Table 2). Absolute values for CBF varied from less than 25 (below the methodological limit of measurement) to 84 ml/100g/min and for CMRO₂ from less than 1.13 (below the methodologic limit of measurement) to 3.45 ml/100g/min. In two patients with pupillary disturbances hypothermia was initiated as quickly as possible. Therefore baseline ICP, CBF, AVDO₂, and CMRO₂ were not measured in these two patients during

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**TABLE 1**

<table>
<thead>
<tr>
<th>Interval From Onset of Symptoms</th>
<th>Mean (hrs)</th>
<th>Range (hrs)</th>
</tr>
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<tr>
<td>therapeutic hypothermia (33–34°C)</td>
<td>73.5</td>
<td>27–170.5</td>
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<tr>
<td>first CBF measurement</td>
<td>68.5</td>
<td>26–162</td>
</tr>
<tr>
<td>second CBF measurement (early hypothermia)</td>
<td>83</td>
<td>55.5–179.5</td>
</tr>
<tr>
<td>third CBF measurement (late hypothermia)</td>
<td>139.5</td>
<td>76–229.5</td>
</tr>
<tr>
<td>fourth CBF measurement (after rewarming, normothermia)</td>
<td>158</td>
<td>100–237</td>
</tr>
</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Normothermia (ml/100g/min)</th>
<th>Early (% change)</th>
<th>Late (% change)</th>
<th>Normothermia (ml/100g/min)</th>
<th>Early (% change)</th>
<th>Late (% change)</th>
<th>Normothermia (ml/100g/min)</th>
<th>Early (% change)</th>
<th>Late (% change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
<td>&lt;25 (~64)</td>
<td>3.45</td>
<td>1.65 (~52)</td>
<td>1.20 (~65)</td>
<td>4.95</td>
<td>6.61 (~34)</td>
<td>6.6 (~33)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NA</td>
<td>52</td>
<td>NA</td>
<td>3.38</td>
<td>2.18</td>
<td>NA</td>
<td>6.52</td>
<td>6.02</td>
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<tr>
<td>3</td>
<td>58</td>
<td>&lt;25 (~57)</td>
<td>2.45</td>
<td>1.13 (~54)</td>
<td>1.87 (~24)</td>
<td>4.21</td>
<td>4.44 (~5.7)</td>
<td>2.8 (~33)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>&lt;25 (~19)</td>
<td>1.57</td>
<td>1.6 (~2)</td>
<td>2.71 (~73)</td>
<td>5.20</td>
<td>6.42 (~23)</td>
<td>4.82 (~7)</td>
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<tr>
<td>5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.05</td>
<td>2.90</td>
<td>4.11</td>
<td>4.29 (~10)</td>
<td>2.56 (~34)</td>
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</tr>
<tr>
<td>6</td>
<td>84</td>
<td>54 (~35)</td>
<td>3.44</td>
<td>2.07 (~40)</td>
<td>1.91 (~44)</td>
<td>4.11</td>
<td>3.82 (~7)</td>
<td>2.67 (~35)</td>
<td></td>
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</tbody>
</table>

* Only the patients in Cases 3 to 6 survived. Abbreviation: NA = not available.
† Values for CBF less than 25 ml/100g/min were below the methodological limit of the measurement technique.
Hypothermia in severe cerebral artery infarction

In this preliminary study, only a small number of patients were studied in whom there were high interindividual variabilities in the time intervals to initiation of hypothermia as well as in absolute CBF and CMRO₂ values. Median values for these patients were not calculated. Therefore the measurements obtained during the different phases of hypothermia are given for each patient separately in Table 2 and in Fig. 1.

After induction of hypothermia, elevated ICP could be controlled in all patients. During early hypothermia, CBF decreased in all patients (Fig. 1). During late hypothermia, CBF recovered in the three patients who survived but remained diminished in those two patients who eventually died. In all but one patient, CMRO₂ was reduced during all phases of hypothermia (Fig. 1). The diminished CMRO₂, as the product of CBF and AVDO₂, can be explained during early hypothermia by the drop in CBF and during late hypothermia by the reduction in AVDO₂ (five of six patients). The AVDO₂ increased in four of five patients during early hypothermia and decreased markedly in all but those two patients who died during late hypothermia (Fig. 1).

DISCUSSION

The results of animal and clinical studies have shown that hypothermia has the potential to limit the extent of secondary brain damage. The protective effects of hypothermia have been described to be a consequence of lowering high ICP, suppressing the extracellular concentrations of excitatory neurotransmitters, stabilizing cell membranes, slowing the depletion of brain energy stores, and improving the O₂ supply and demand relationship by reducing cerebral metabolism. Maher and Hachinski concluded that one of the most important mechanisms of hypothermia is that the decrease in cerebral O₂ consumption is more pronounced than the decline in CBF, resulting in apparent luxury perfusion. Hypothermia may also lower the minimum amount of CBF necessary to maintain cell viability and, by this and other mechanisms, expand the ischemic penumbra surrounding the infarct.

In animals the effect of artificial hypothermia on cerebral O₂ metabolism and CBF were investigated more than 40 years ago. In uninjured dogs, Rosomoff demonstrated that CBF decreased 6.7% with a similar decrease in CMRO₂ by reducing body temperature by 1°C. The author further assessed the protective effect of hypothermia in a canine model of permanent MCA occlusion and evaluated the beneficial effects of preinjury or immediate postinjury hypothermia. Busto, et al., assessed hypothermia-induced changes in the microvascular blood flow during global ischemia. The authors demonstrated in rats that local CBF was not affected during mild to moderate intraischemic hypothermia in any group. On the other hand, in a rabbit model of focal cerebral ischemia, Lo and Steinberg demonstrated that moderate hypothermia (30°C) decreases significantly cortical blood flow but not blood flow in other brain areas. This effect was not seen at either 37 or 33°C.

To our knowledge no studies of CBF and CMRO₂ measurements have been performed in patients with ischemic infarction during hypothermia treatment. Our preliminary observations in six patients with severe hemispheric infarction indicate that CBF may decrease immediately after induction of hypothermia. During late hypothermia CBF seems to recover in patients who survive but remains diminished in patients who die. In addition, AVDO₂ increased in most patients during early hypothermia and decreased in all but those patients who died during late hypothermia. The CMRO₂ level is diminished during early hypothermia as a consequence of CBF reduction and during late hypothermia by the diminished AVDO₂.

Metz, et al., reported a significant decrease in CMRO₂ in 10 patients with severe brain injury which was caused
by reduced cerebral $O_2$ extraction. In contrast to our measurements, the authors observed no CBF changes during early hypothermia. Marion, et al., measured CBF by using the $^{133}$Xe technique in 20 hypothermia-treated patients; they described a decline in CBF by approximately 5.2 ml/100g/min per 1°C reduction in body temperature. Shiozaki, et al., performed CBF measurements using the hydrogen clearance method in five patients with severe head injury and found a mean decrease of 15.4 ml/100g/min in CBF and 1 ml/100 ml in AVDO$_2$ 2 hours after induction of hypothermia.

It is possible that CBF may be influenced by different causes of primary brain damage and timing of induction of hypothermia. Furthermore, initial experience with CBF monitoring in patients with severe hemispheric infarction showed that critical rises in ICP were accompanied by decreased CBF values as well. Positron emission tomography findings showed that severe partial ischemia with impaired neuronal function without causing irreversible neuronal damage frequently persists for up to 24 hours and occasionally even up to 72 hours. This was demonstrated by an elevated regional $O_2$ extraction in the presence of a relative preservation of the rate of regional $O_2$ metabolism and a low regional CBF. According to our experience CBF measurements during early hypothermia were performed 83 hours in the mean after onset of symptoms of ischemic stroke. Therefore, increased AVDO$_2$ and decreased CBF during early hypothermia could be a consequence of changes in cerebral hemodynamics during ischemic stroke itself and may not be induced by hypothermia. Additionally, different methods of CBF measurement may contribute to the discrepancies in the literature. The double-indicator dilution technique used in our studies allowed global CBF measurements, whereas the $^{133}$Xe technique, applied in the study by Metz, et al., estimates cortical CBF.

**CONCLUSIONS**

Moderate hypothermia in severe MCA infarction reduced CMRO$_2$, during all phases and CBF during early hypothermia. During late hypothermia, CBF recovered in patients who eventually had good outcomes but remained diminished in those patients who died. Further studies in which the results from a normothermia group are compared are needed to clarify the influence of hypothermia independent from the CBF measurement technique and from other factors characterizing the course of the illness of ischemic stroke.

**References**


