Effect and Feasibility of Controlled Rewarming After Moderate Hypothermia in Stroke Patients With Malignant Infarction of the Middle Cerebral Artery

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Background and Purpose—Moderate hypothermia has been found to reduce intracranial pressure (ICP) significantly in patients who have severe middle cerebral artery infarction. However, during passive rewarming, ICP continuously rises and some patients suffer transtentorial herniation.

Methods—We investigated the question of whether slower rewarming leads to slower increase in ICP and slower decrease in cerebral perfusion pressure (CPP). Furthermore, we studied feasibility of slow, controlled rewarming. ICP, CPP, and core body temperature were monitored continuously. Achievement of rewarming protocol was assessed by hit rate of temperature target intervals. Side effects of hypothermia were assessed.

Results—Rates of change of both ICP and CPP were correlated significantly with increase in temperature (ICP $r=0.62$, $P=0.002$; CPP $r=-0.50$, $P=0.017$). In feasibility analysis of 13 controlled rewarmed patients, hit rate of temperature target intervals was 63% (median; range 48% to 81%); hit rate within the target interval or below was 79% (median; range 62% to 94%).

Conclusions—Slow, controlled rewarming is feasible and may be used for ICP and CPP control after moderate hypothermia for space-occupying infarction. (Stroke. 2001;32:2833-2835.)

Key Words: stroke, ischemic ▪ brain edema ▪ intracranial pressure ▪ hypothermia

About 3% to 10% of patients with middle cerebral artery (MCA) territory infarction develop space-occupying hemispheric edema with increases in intracranial pressure (ICP), subsequent transtentorial herniation, and brain stem compression.¹ Moderate hypothermia (body temperature 32°C to 33°C for 48 to 72 hours) has been found to reduce ICP significantly in these patients.² However, during rewarming, ICP continuously rises and some patients suffer transtentorial herniation.

Until 1998, rewarming took place in a passive manner; ie, after hypothermia, the cooling system was stopped and the rewarming process ensued without induction of any cooling or rewarming device within the next 17 to 24 hours (median 18 hours).³ We refer to this rewarming protocol as “passive rewarming.” To address the question of whether prolonged and controlled rewarming would lower risk of critical rewarming, we studied modified controlled rewarming. Feasibility of the protocol was analyzed by hit rates of the target interval (HTI) for the temperature.

Subjects and Methods
We studied a consecutive series of 15 patients with malignant MCA infarction who underwent therapeutic hypothermia for 72 hours. Patients with any previous disabling neurological diseases or terminal illness were excluded from the protocol, which was approved by the local ethics committee. “Controlled rewarming” was defined as an increase in temperature of 0.1°C to 0.2°C over 2 to 4 hours (Figure 1) and was achieved by actively slowing down the process of passive rewarming. The cooling blanket (Polar Bair, Augustine Medical) or mattress (Hico-Variotherm 530, Hirtz) was switched on and off to achieve the planned increase in temperature. ICP, cerebral perfusion pressure (CPP), and core temperature were evaluated continuously. Technical procedures to measure these parameters were identical to those used in our previous study.² Side effects were documented. To increase number of patients for the correlation analysis, we added 10 patients from our previous study who underwent the same hypothermia protocol except for the passive rewarming protocol within 24 hours.² An additional 15 patients from that previous study could not be included because at least 1 of the parameters was not recorded continuously.

Statistical Methods
For each patient, hourly measurements of temperature, ICP, and CPP during the rewarming phase were summarized by rates of change.³ To investigate whether rates of change of ICP and CPP during the rewarming phase depend on rewarming velocity, we calculated nonparametric Spearman correlation coefficients. To analyze compliance with and feasibility of the protocol, we introduce the concept of target areas for the temperature and measured the hit rate within
these target areas, which we explain by a constructed example (Figure 2).

**Results**

Fifteen patients were treated after the controlled rewarming protocol. Of these, 2 died during the cooling phase of hypothermia; therefore, these patients had to be excluded from the rewarming analysis. One patient was excluded because ICP/CPP values were not recorded as a result of logistic problems. However, because temperature had been measured, feasibility analysis could be performed for this patient. Three of 13 controlled rewarmed patients died during and after the rewarming phase: 2 from herniation and 1 of septic complications. The following nonfatal complications during the rewarming phase were registered (numbers indicate numbers of patients): pulmonary infections 12, septic syndrome 3, arrhythmia 2, coagulatory disturbances 3, and pancreatitis during hypothermia (which improved after rewarming) 2.

Time between onset of symptoms and start of hypothermia was 4 to 84 hours (median 17 hours). Time to reach target cooling temperature was from 2 to 7 hours. Duration of controlled rewarming was 26 to 88 hours (median 59 hours).

Correlation analyses of slopes including 12 controlled rewarmed and 10 passively rewarmed patients reveal significant correlations of temperature with both ICP and CPP, for which $r_s = 0.62$ ($P = 0.002$) and $r_s = -0.50$ ($P = 0.017$), respectively. Correlation analyses alone from 12 controlled rewarmed patients already had shown a significant correlation for CPP ($r_s = -0.67$, $P = 0.02$) but not ICP ($r_s = 0.35$, $P = 0.27$).

HTI for the controlled rewarming protocol was 63% median (range 48% to 81%, $n = 13$). In half of the patients, HTI was between 53% and 68% (first and third quartiles, respectively). Because fast rewarming might harm the patient, we considered it reasonable to calculate hits within and below the target interval. Hit rates within and below the target interval came to 79% median (range 62% to 94%).

**Discussion**

Hypothermia may control ICP during the cooling phase in patients with malignant MCA infarction. However, the

![Figure 1](image1.png)

**Figure 1.** Example from a patient with controlled rewarming. Core temperature (dashed line), ICP (gray), and CPP (solid) during rewarming phase are fitted by regression lines. Slopes can be interpreted as rates of change.

![Figure 2](image2.png)

**Figure 2.** Constructed example illustrates concept of target areas for core temperature. At time point 1 (a), core temperature is 33.0°C (●). According to the rewarming protocol (see Subjects and Methods), rectangular target area (shaded area) is defined by its lower left corner at 33.1°C (33.0 + 0.1°C) at time point 3 and its upper right corner at 33.2°C (33.0 + 0.2°C) at time point 5. At time point 2 (b), another target area is calculated in the same manner. A third target area is computed at time point 3 (c). Now 3 target areas exist to define target interval for time point 5, which is given by lowest and highest temperature of shaded area at time point 3. HTI (d) is calculated as proportion of number of measurements in shaded area (starting with measurement 3). Both measurements (time points 3 and 4) lie within shaded area, which leads to a hit rate of 100%.
rewarming period seems to be a critical phase, as has been observed in clinical studies and animal experiments. In the present study, slower rewarming correlated with slower increase in ICP elevations and slower decrease in CPP. Several studies suggest that metabolic mechanisms, which occur along the ischemic cascade and lead to edema formation, are interrupted or at least slowed down by moderate hypothermia. However, during rewarming, these mechanisms may restart. Therefore, slowing the speed of rewarming may decrease the metabolic changes to a degree that can be handled by cellular and metabolic compensating mechanisms of the brain.

Although hypothermia can lead to several complications, experiences with the occurrence of complications and a prolonged rewarming seem to vary among studies. Controlled rewarming in the present study consists of an active slowing down of passive rewarming by intermittent surface cooling with the use of cooling blankets and mattresses. Because controlling the temperature deviation around the target increase in temperature is important, this procedure needs to be performed by a well-trained nursing staff. However, our results show that controlled rewarming can be achieved.

In conclusion, controlled rewarming after moderate hypothermia in space-occupying infarctions is feasible and improves CPP and ICP control during the critical period of rewarming. Because the number of patients in the present study is small, the present results should be verified by additional larger studies.

**Acknowledgments**

We are grateful to Renzo Manara (Department of Neurology, University of Padua, Padua, Italy) and Sally Hollis (Medical Statistics Unit, Lancaster University, Lancaster, UK) for their support. We thank the personnel of the Heidelberg Neurologic Intensive Care Unit without whose efforts the present work would not have been possible.

**References**

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Stroke. 2001;32:2833-2835
doi: 10.1161/hs1201.99511

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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